PRODUCT MONOGRAPH

[Pr]NABUMETONE

Nabumetone Tablets BP

500 mg

Nonsteroidal Anti-Inflammatory Agent

APOTEX INC.
150 Signet Drive
Toronto, Ontario
M9L 1T9

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	All Non-medicinal Ingredients (in alphabetical order)
Oral	Tablet; 500 mg	croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, polyethylene glycol, sodium lauryl sulphate and titanium dioxide

INDICATIONS AND CLINICAL USE

NABUMETONE (Nabumetone Tablets) is indicated for acute and chronic relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

For patients with an increased risk of developing cardiovascular (CV) and/or gastrointestinal (GI) adverse events, other management strategies that do NOT include the use of non-steroidal anti-inflammatory drugs (NSAIDs) should be considered first (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Use of NABUMETONE should be limited to the lowest effective dose for the shortest possible duration of treatment in order to minimize the potential risk for cardiovascular or gastrointestinal adverse events (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

NABUMETONE, as a NSAID, does NOT treat clinical disease or prevent its progression.

NABUMETONE, as a NSAID, only relieves symptoms and decreases inflammation for as long as the patient continues to take it.

Geriatrics (≥65 years of age)

Evidence from clinical studies and postmarket experience suggests that use in the geriatric population is associated with differences in safety (see **WARNINGS AND PRECAUTIONS**, **General** and **Special populations, Geriatrics**).

Patients older than 65 years and frail or debilitated patients are most susceptible to a variety of adverse reactions from NSAIDs and a brief discussion can be found under **WARNINGS AND PRECAUTIONS**.

Pediatrics (<18 years of age)

Safety and efficacy have not been established in the pediatric population (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Special populations**, **Pediatrics**).

CONTRAINDICATIONS

NABUMETONE is contraindicated in:

- Patients with known hypersensitivity to nabumetone or who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing of ingredients, see the **DOSAGE FORMS**, **COMPOSITION AND PACKAGING** section of the product monograph.
- The peri-operative setting of coronary artery bypass graft surgery (CABG). Although NABUMETONE has NOT been studied in this patient population, a selective COX-2 inhibitor NSAID studied in such a setting has led to an increased incidence of cardiovascular/thromboembolic events, deep surgical infections, and sternal wound complications.
- During the third trimester of pregnancy, because of risk of premature closure of the ductus arteriosus, and prolonged parturition.
- Women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants.
- Severe uncontrolled heart failure.
- History of asthma, urticaria, or allergic-type reactions after taking acetylsalicylic acid (ASA) or other NSAIDs (i.e. complete or partial syndrome of ASA-intolerance - rhinosinusitis, urticaria/ angioedema, nasal polyps, asthma). Fatal anaphylactoid reactions have occurred in such individuals. Individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction. The potential for cross-reactivity between different NSAIDs must be kept in mind (see **WARNINGS AND PRECAUTIONS - Hypersensitivity Reactions - Anaphylactoid Reactions**).
- Active gastric / duodenal / peptic ulcer, active GI bleeding.
- Cerebrovascular bleeding or other bleeding disorders.
- Inflammatory bowel disease.
- Severe liver impairment or active liver disease.
- Severe renal impairment (creatinine clearance <30 mL/min or 0.5 mL/sec) or deteriorating renal disease (individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored) (see **WARNINGS AND PRECAUTIONS, Renal)**.
- Known hyperkalemia (see **WARNINGS AND PRECAUTIONS - Renal - Fluid and Electrolyte Balance**).

- Children and adolescents less than 18 years of age.
- NABUMETONE is not recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Risk of Cardiovascular (CV) Adverse Events: Ischemic Heart Disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV) (see WARNINGS AND PRECAUTIONS - Cardiovascular).

NABUMETONE is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke, or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Caution should be exercised in prescribing NABUMETONE to any patient with ischemic heart disease (including but NOT limited to acute myocardial infarction, history of myocardial infarction, and/or angina), cerebrovascular disease (including but NOT limited to stroke, cerebrovascular accident, transient ischemic attacks, and/or amaurosis fugax), and/or congestive heart failure (NYHA II-IV).

Use of NSAIDs, such as NABUMETONE, can promote sodium retention in a dose dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of congestive heart failure (see also WARNINGS AND PRECAUTIONS - Renal - Fluid and Electrolyte Balance).

Randomized clinical trials with NABUMETONE have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing NABUMETONE.

Risk of Gastrointestinal (GI) Adverse Events (see WARNINGS AND PRECAUTIONS – Gastrointestinal).

Use of NSAIDs, such as NABUMETONE, is associated with an increased incidence of gastrointestinal adverse events (such as peptic/duodenal ulceration, perforation, obstruction, and gastrointestinal bleeding).

Risk in Pregnancy: Caution should be exercised in prescribing NABUMETONE during the first and second trimesters of pregnancy. Use of NSAIDS at approximately 20 weeks of gestation or later may cause fetal renal dysfunction leading to oligohydramnios and neonatal renal impairment or failure (see **WARNINGS AND PRECAUTIONS**). NABUMETONE is contraindicated for use during the third

trimester because of risk of premature closure of the ductus arteriosus and uterine inertia (prolonged parturition) (see **CONTRAINDICATIONS**).

General

Frail or debilitated patients may tolerate side effects less well and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse event, the lowest effective dose should be used for the shortest possible duration.** As with other NSAIDs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic, or cardiac function. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

NABUMETONE is NOT recommended for use with other NSAIDs, with the exception of low-dose ASA for cardiovascular prophylaxis, because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions (see **DRUG INTERACTIONS - Drug/Drug Interactions - Acetylsalicylic acid (ASA) or other NSAIDs**).

Carcinogenesis and Mutagenesis

See **PART II: SCIENTIFIC INFORMATION**, **TOXICOLOGY**, **Mutagenicity/Carcinogenicity**.

Cardiovascular

NABUMETONE is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke, or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Caution should be exercised in prescribing NABUMETONE to patients with risk factors for cardiovascular disease, cerebrovascular disease, or renal disease, such as any of the following (NOT an exhaustive list):

- **Hypertension**
- **Dyslipidemia / Hyperlipidemia**
- **Diabetes Mellitus**
- **Congestive Heart Failure (NYHA I)**
- **Coronary Artery Disease (Atherosclerosis)**
- **Peripheral Arterial Disease**
- **Smoking**
- **Creatinine Clearance < 60 mL/min or 1 mL/sec**

Use of NSAIDs, such as NABUMETONE, can lead to new hypertension or can worsen pre-existing hypertension, either of which may increase the risk of cardiovascular events as described above. Thus, blood pressure should be monitored regularly. Consideration should be given to discontinuing NABUMETONE should hypertension either develop or worsen with its use.

Use of NSAIDs, such as NABUMETONE, can induce fluid retention and edema, and may exacerbate congestive heart failure, through a renally-mediated mechanism (see **WARNINGS AND PRECAUTIONS - Renal - Fluid and Electrolyte Balance**).

For patients with a high risk of developing an adverse CV event, other management strategies that do NOT include the use of NSAIDs should be considered first. **To minimize the potential risk for an adverse CV event, the lowest effective dose should be used for the shortest possible duration.**

In long-term clinical trials (up to 8 years) in patients treated with nabumentone (over 300 patients treated for five years or longer), hypertension and palpitations were reported with an incidence of more than or equal to 1% each, angina, arrhythmia, myocardial infarction, syncope, thrombophlebitis, and vasculitis were reported with an incidence of less than 1% each (see **ADVERSE REACTIONS**, **Clinical Trial Adverse Drug Reactions**, **Table 1**, and **Less Common Clinical Trial Adverse Drug Reactions**, **Cardiovascular**).

Endocrine and Metabolism

Corticosteroids
NABUMETONE (Nabumetone Tablets) is NOT a substitute for corticosteroids. It does NOT treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids (see **DRUG INTERACTIONS - Drug-Drug Interactions - Glucocorticoids**).

Gastrointestinal

Serious GI toxicity (sometimes fatal), such as peptic / duodenal ulceration, inflammation, perforation, obstruction, and gastrointestinal bleeding, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs such as NABUMETONE. Minor upper GI problems, such as dyspepsia, commonly occur at any time. Health care providers should remain alert for ulceration and bleeding in patients treated with NABUMETONE, even in the absence of previous GI tract symptoms. 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, the lowest effective dose should be used for the shortest possible duration**. For high risk patients, alternate therapies that do not involve NSAIDs should be considered (see **WARNINGS AND PRECAUTIONS - Special Populations - Geriatrics**).

Patients should be informed about the signs and/or symptoms of serious GI toxicity and instructed to discontinue using NABUMETONE and seek emergency medical attention if they experience any such symptoms. The utility of periodic laboratory monitoring has NOT been demonstrated, nor has it been adequately assessed. Most patients who develop a serious upper GI adverse event on NSAID therapy have no symptoms. Upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for one year. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. Even short-term therapy has its risks.

NABUMETONE should be given under close medical supervision to patients prone to gastrointestinal irritation particularly those with a history of peptic ulcer, diverticulosis, or other inflammatory disease of the gastrointestinal tract such as ulcerative colitis and Crohn's disease. In these cases, the physician must weigh the benefits of treatment against the possible hazards.

In controlled and open label extension 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/or symptoms of serious GI toxicity and instruct them to contact a physician immediately if they experience persistent dyspepsia or other symptoms or signs suggestive of gastrointestinal ulceration or bleeding.

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients by checking their hemoglobin periodically and by being vigilant for the signs and symptoms of ulceration and bleeding and should inform the patient of the importance of this follow-up.

If ulceration is suspected or confirmed, or if GI bleeding occurs, nabumetone should be discontinued immediately, appropriate treatment should be instituted, and the patient should be monitored closely.

Studies to date have identified that there is no group of patients not at risk of developing ulceration and bleeding. A prior history of serious GI events and other factors such as excess alcohol intake, smoking, age, female gender, and anticoagulant use have been associated with increased risk. Caution should be used when administering to patients with other therapies known to increase the risk of gastrointestinal ulcer (e.g., oral corticosteroids).

High doses of any NSAID may carry a 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 GI toxicity.

Older patients are also at risk of lower esophageal ulceration and bleeding. However, data from controlled clinical studies with nabumetone (where 24% of 1677 patients were ≥65 years of age) have indicated that there were no overall differences in efficacy or safety between older patients and younger ones.

As with other NSAIDs, the lowest dose should be sought for each patient. Therefore, after observing the response to initial therapy, the dose should be adjusted to meet individual patients' requirements.

Caution should be taken if prescribing NABUMETONE to patients with a prior history of peptic / duodenal ulcer disease, or gastrointestinal bleeding, as these individuals have a greater than 10-fold higher risk for developing a GI bleed when taking a NSAID than patients with neither of these risk factors. Other risk factors for GI ulceration and bleeding include the following: *Helicobacter pylori* infection, increased age, prolonged use of NSAID therapy, excess alcohol intake, smoking, poor general health status, or concomitant therapy with any of the following:

- Anti-coagulants (e.g. warfarin)
- Anti-platelet agents (e.g. ASA, clopidogrel)
- Oral corticosteroids (e.g. prednisone)
- Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. citalopram, fluoxetine, paroxetine, sertraline)

For available data from studies for the concomitant use of nabumetone with warfarin, ASA, or corticosteroids, see **DRUG INTERACTIONS**, **Drug-Drug Interactions**.

There is no definitive evidence that the concomitant administration of histamine H_2 receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow continuation of nabumetone therapy when and if these adverse reactions occur.

In long-term clinical trial follow-up involving treatment with nabumetone for up to 8 years and/or from spontaneous reports from worldwide marketing experience, the following GI related adverse events were reported with an incidence of more than 10% each: Diarrhea, dyspepsia, and abdominal pain. Nausea and flatulence were reported with an incidence of more than 5% each, constipation was reported with an incidence of 4%, positive stool guaiac and dry mouth were reported with an incidence of 2% each, and gastritis, vomiting, and melena were reported with an incidence of 1% each. Eructation, gastroenteritis, anorexia, rectal bleeding, gastric ulcer, duodenal ulcer, stomatitis, dysphagia, increased appetite, glossitis, gingivitis, duodenitis, gastrointestinal bleeding were all reported with an incidence of less than 1% each (see **ADVERSE REACTIONS**, **Clinical Trial Adverse Drug Reactions**, **Table 1**, and **Less Common Clinical Trial Adverse Drug Reactions**, **Gastrointestinal** and **Other**).

Genitourinary

Some NSAIDs are associated with persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria, or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with a NSAID. Some cases have become severe on continued treatment. Should urinary symptoms occur, in the absence of an alternate explanation, treatment with NABUMETONE should be stopped to ascertain if symptoms disappear. This should be done before urological investigations or treatments are carried out.

In long-term clinical trial follow-up involving treatment with nabumetone for up to 8 years and/or from spontaneous reports from worldwide marketing experience, impotence and vaginal bleeding were reported with an incidence of less than 1% each (see **ADVERSE REACTIONS**, **Less Common Clinical Trial Adverse Drug Reactions**, **Renal/Genitourinary**).

Hematologic

NSAIDs inhibiting prostaglandin biosynthesis do interfere with platelet function to varying degrees; patients who may be adversely affected by such an action, such as those on anti-coagulants or suffering from haemophilia or platelet disorders should be carefully observed when NABUMETONE is administered.

In one 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 (see **ACTION AND CLINICAL PHARMACOLOGY**, **Mechanism of Action**). NABUMETONE cannot be used as a substitute for low dose aspirin therapy in patients requiring such therapy.

Anti-coagulants
Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding. Concurrent therapy of NABUMETONE with warfarin requires close monitoring of the international normalized ratio (INR).

Even with therapeutic INR monitoring, increased bleeding may occur.

Anti-platelet Effects
NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike acetylsalicylic acid (ASA), their effect on platelet function is quantitatively less, or of shorter duration, and is reversible.

NABUMETONE and other NSAIDs have no proven efficacy as anti-platelet agents and should NOT be used as a substitute for ASA or other anti-platelet agents for prophylaxis of cardiovascular thromboembolic diseases. Anti-platelet therapies (e.g. ASA) should NOT be discontinued. There is some evidence that use of NSAIDs with ASA can markedly attenuate the cardioprotective effects of ASA (see **DRUG INTERACTIONS - Drug-Drug Interactions - Acetylsalicylic Acid (ASA) or other NSAIDs**).

Concomitant administration of NABUMETONE with low dose ASA increases the risk of GI ulceration and associated complications.

Blood dyscrasias
Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anemia, and agranulocytosis) associated with the use of NSAIDs are rare, but could occur with severe consequences.

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

In long-term clinical trial follow-up involving treatment with nabumetone for up to 8 years and/or from spontaneous reports from worldwide marketing experience, anemia, leucopenia, thrombocytopenia, granulocytopenia, and aplastic anemia were reported with an incidence of less than 1% each (see **ADVERSE REACTIONS**, **Less Common Clinical Trial Adverse Drug Reactions**, **Hematologic/Lymphatic**).

Hepatic/Biliary/Pancreatic

As with other NSAIDs, borderline elevations of one or more liver enzyme tests (AST, ALT, alkaline phosphatase) may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient 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.

In long-term clinical trial follow-up involving treatment with nabumetone for up to 8 years and/or from spontaneous reports from worldwide marketing experience, liver function abnormalities, elevated liver function tests, hepatic failure, jaundice, cholestatic jaundice, gallstones, bilirubinuria, and pancreatitis were reported with an incidence of less than 1% each (see **ADVERSE REACTIONS**, **Less Common Clinical Trial Adverse Drug Reactions**, **Hepatic** and **Gastrointestinal**).

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 this drug. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported with NSAIDs.

Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop (e.g. jaundice), or if systemic manifestations occur (e.g., eosinophilia, associated with rash, etc.), this drug should be discontinued.

During long-term therapy, liver function tests should be monitored periodically. If there is a need to prescribe this drug in the presence of impaired liver function, it must be done under strict observation.

Immune

Infection
NABUMETONE, in common with other NSAIDs, may mask signs and symptoms of an underlying infectious disease.

Aseptic Meningitis: Rarely, with some NSAIDs, the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever, or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissue diseases, etc.) seem to be pre-disposed. Although aseptic meningitis has not been reported for nabumetone tablets, in such patients, the physician must be vigilant to the potential development of this complication.

Hypersensitivity Reactions
Anaphylactoid Reactions: As with other NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to NABUMETONE. In post-marketing experience, rare cases of anaphylactic/ anaphylactoid reactions and angioedema have been reported in patients receiving NABUMETONE (see **ADVERSE REACTIONS**, **Less Common Clinical Trial Adverse Drug**

Reactions, **Allergic/hypersensitivity**). NABUMETONE should NOT be given to patients with the ASA-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 ASA or other NSAIDs (see **CONTRAINDICATIONS**).

ASA-Intolerance: NABUMETONE should NOT be given to patients with complete or partial syndrome of ASA-intolerance (rhinosinusitis, urticaria/angioedema, nasal polyps, asthma), in whom asthma, anaphylaxis, urticaria/angioedema, rhinitis, or other allergic manifestations are precipitated by ASA or other NSAIDs. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction (see **CONTRAINDICATIONS**).

Cross-Sensitivity: Patients sensitive to one NSAID may be sensitive to any of the other NSAIDs as well.

Serious skin reactions: (See **WARNINGS AND PRECAUTIONS - Skin**).

Monitoring and Laboratory Tests

Pregnancy
If NABUMETONE is administered in the middle (approximately 20 weeks) to the end of the second trimester, it is recommended that pregnant women on NABUMETONE be closely monitored for amniotic fluid volume since NABUMETONE may result in reduction of amniotic fluid volume and even oligohydramnios (see **WARNINGS AND PRECAUTIONS**, **Special Populations**). NABUMETONE is contraindicated for use in the third trimester of pregnancy.

Neurologic

Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss, insomnia, or depression with the use of NSAIDs, such as NABUMETONE. If patients experience such adverse reaction(s), they should exercise caution in carrying out activities that require alertness.

In long-term clinical trial follow-up involving treatment with nabumetone for up to 8 years and/or from spontaneous reports from worldwide marketing experience, headache and dizziness were reported with an incidence of more than 5% each, insomnia was reported with an incidence of 3%, fatigue and somnolence were reported with an incidence of 2% each, increased sweating and nervousness were reported with an incidence of 1% each, tinnitus was reported with an incidence of 4%, abnormal vision was reported with an incidence of 2%, and the following adverse events were reported with an incidence of less than 1% each: Depression, vertigo, malaise, paresthesia, asthenia, anxiety, confusion, agitation, tremor, and nightmares (see **ADVERSE REACTIONS**, **Clinical Trial Adverse Drug Reactions**, **Table 1**, and **Less Common Clinical Trial Adverse Drug Reactions**, **Central Nervous System**).

Ophthalmologic

Blurred and/or diminished vision has been reported with the use of NSAIDs. If such symptoms develop, NABUMETONE should be discontinued and an ophthalmologic examination should be performed. Ophthalmologic examination should be carried out at periodic intervals in any patient receiving NABUMETONE for an extended period of time.

Peri-Operative Considerations

(See **CONTRAINDICATIONS - Coronary Artery Bypass Graft Surgery**).

Psychiatric

(See **WARNINGS AND PRECAUTIONS – Neurologic**).

Renal

Long-term administration of NSAIDs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis, hematuria, low grade proteinuria, and occasionally nephrotic syndrome.

Renal insufficiency due to NSAID use is seen in patients with pre-renal conditions leading to reduction in renal blood flow or blood volume. Under these circumstances, renal prostaglandins help maintain renal perfusion and glomerular filtration rate (GFR). In these patients, administration of a NSAID may cause a reduction in prostaglandin synthesis leading to impaired renal function. Patients at greatest risk of this reaction are those with pre-existing renal insufficiency (GFR < 60 mL/min or 1 mL/s), dehydrated patients, patients on salt restricted diets, those with congestive heart failure, cirrhosis, liver dysfunction, taking angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, cyclosporin, diuretics, and those who are elderly. Serious or life-threatening renal failure has been reported in patients with normal or impaired renal function after short term therapy with NSAIDs. Even patients at risk who demonstrate the ability to tolerate a NSAID under stable conditions may decompensate during periods of added stress (e.g. dehydration due to gastroenteritis). Discontinuation of NSAIDs is usually followed by recovery to the pre-treatment state.

Caution should be used when initiating treatment with NSAIDs, such as NABUMETONE, in patients with considerable dehydration. Such patients should be rehydrated prior to initiation of therapy. Caution is also recommended in patients with pre-existing kidney disease.

Nabumetone and its metabolites are eliminated primarily by the kidneys, therefore the drug should be used with caution in patients with impaired renal function.

As with other NSAIDs, in patients with severely impaired renal function (creatinine clearance <30 mL/min or <0.5 mL/sec), lower doses of nabumetone should be considered and patients should be monitored more closely than patients with normal renal function. Laboratory tests should be performed at baseline and within weeks of starting therapy. Further tests should be carried out as necessary; if the impairment worsens, discontinuation of therapy may be warranted.

In moderate renal impairment (creatinine clearance 30 to 49 mL/min), there is a 50% increase in unbound plasma 6-methoxy-2-naphthylacetic acid (6-MNA; the principal active metabolite of nabumetone), and dose reduction may be warranted (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Renal insufficiency**).

During long-term therapy, kidney function should be monitored periodically.

Advanced Renal Disease
(See **CONTRAINDICATIONS**).

Fluid and Electrolyte Balance
Use of NSAIDs, such as NABUMETONE, can promote sodium retention in a dose-dependent manner, which can lead to fluid retention and edema, and consequences of increased blood pressure and exacerbation of congestive heart failure. Thus, caution should be exercised in prescribing NABUMETONE in patients with a history of congestive heart failure, compromised cardiac function, hypertension, increased age, or other conditions predisposing to fluid retention (see **WARNINGS AND PRECAUTIONS - Cardiovascular**).

Use of NSAIDs, such as NABUMETONE, can increase the risk of hyperkalemia, especially in patients with diabetes mellitus, renal failure, increased age, or those receiving concomitant therapy with adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, cyclosporin, or some diuretics.

Electrolytes should be monitored periodically (see **CONTRAINDICATIONS**).

In long-term clinical trial follow-up involving treatment with nabumetone for up to 8 years and/or from spontaneous reports from worldwide marketing experience, the following adverse events were reported with an incidence of less than 1% each: Dysuria, hematuria, hyperuricemia, albuminuria, azotemia, edema, hypokalemia, renal stones, interstitial nephritis, nephrotic syndrome, and renal failure (see **ADVERSE REACTIONS**, **Less Common Clinical Trial Adverse Drug Reactions**, **Renal/Genitourinary** and **Other**).

In studies of patients with renal insufficiency, the mean terminal half-life of 6-MNA was increased in patients with severe renal dysfunction (creatinine clearance <30 mL/min/1.73 m^2 or <0.5 mL/sec/1.73 m^2). In patients undergoing hemodialysis, steady state plasma concentrations of the active metabolite were similar to those observed in healthy subjects (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Renal insufficiency**).

Respiratory

ASA-induced asthma is an uncommon but very important indication of ASA and NSAID sensitivity. It occurs more frequently in patients with asthma who have nasal polyps.

Sexual Function / Reproduction

The use of NABUMETONE, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of NABUMETONE should be considered.

Skin

Serious skin reactions: Use of some NSAIDs, such as NABUMETONE, have been associated with rare post-market cases of serious, fatal, or otherwise life-threatening skin reactions, including:

- Drug reaction with eosinophilia and systemic symptoms (DRESS),
- Stevens-Johnson syndrome,
- Toxic epidermal necrolysis,
- Exfoliative dermatitis, and
- Erythema multiforme.

Patients appear to be at higher risk for these events early in the course of therapy, with the onset of cases usually occurring within the first month of treatment. These reactions may be reversible if the causative agent is discontinued and appropriate treatment instituted. Patients should be advised that they should discontinue their NSAID at the first appearance of a skin rash, mucosal lesions, or any other sign of hypersensitivity, and contact their physician immediately for assessment and advice, including which therapies to discontinue.

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, and 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.

In long-term clinical trial follow-up involving treatment with nabumetone for up to 8 years and/or from spontaneous reports from worldwide marketing experience, rash was reported with an incidence of 7%, pruritus was reported with an incidence of 3%, whereas alopecia, urticaria, acne, bullous eruptions, photosensitivity, pseudoporphyria cutanea tarda, erythema multiforme, Stevens Johnson syndrome, and toxic epidermal necrolysis were reported with an incidence of less than 1% each (see **ADVERSE REACTIONS**, **Clinical Trial Adverse Drug Reactions**, **Table 1**, and **Less Common Clinical Trial Adverse Drug Reactions**, **Dermatologic**).

Special Populations

Pregnant Women
There is no clinical trial experience with the use of nabumetone during human pregnancy.

Use of nabumetone during the first two trimesters of pregnancy should be restricted to situations where the potential benefit to the mother justifies the potential risk to the fetus or nursing infant.

The known effects of drugs of this class on the human fetus during the third trimester of pregnancy include constriction of the ductus arteriosis, pulmonary and cardiac changes. Therefore, use of nabumetone during the third trimester of pregnancy is contraindicated (see **CONTRAINDICATIONS**).

Teratogenic effects were not observed in rats or rabbits. Postnatal development was not affected even though the active metabolite of nabumetone (6-MNA) is found in the milk of lactating rats. Nabumetone and/or its active metabolites have been shown to cross the placental barrier of rats (see **TOXICOLOGY** and **DETAILED PHARMACOLOGY**, **Animal**).

NABUMETONE is contraindicated for use during the third trimester of pregnancy because of risks of premature closure of the ductus arteriosus and the potential to prolong parturition (see **TOXICOLOGY**). Caution is recommended in prescribing NABUMETONE during the first and second trimesters of pregnancy, particularly from the middle to end of the second trimester of pregnancy (onset at approximately 20 weeks) due to possible fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment or failure.

Published studies and postmarketing reports describe maternal NSAID use at approximately 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment or failure. NSAIDs were shown to cause significant reduction in fetal urine production prior to reduction of amniotic fluid volume. There have also been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction and renal impairment without oligohydramnios, some of which were irreversible, even after treatment discontinuation.

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. 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 after careful consideration of the benefit-risk, NSAID treatment is considered necessary to be administered anywhere from the middle (onset at approximately 20 weeks) to the end of the second trimester of pregnancy, the use should be limited to the lowest effective dose and shortest duration possible. It is also recommended that ultrasound monitoring of amniotic fluid be considered if NABUMETONE treatment extends beyond 48 hours and that NSAIDs treatment be discontinued if oligohydramnios occurs, followed by appropriate medical follow up.

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo-fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-fetal lethality. In addition, increased incidences of various

malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenesis period.

Breastfeeding
There is no clinical trial experience with the use of nabumetone during breastfeeding. As the safety and efficacy of nabumetone in breastfeeding women have not been established, its use is therefore contraindicated (see **CONTRAINDICATIONS**).

Pediatrics (<18 years of age)
Nabumetone is contraindicated for use in children and adolescents less than 18 years of age because the safety and efficacy in this pediatric population have not been established (see **CONTRAINDICATIONS**).

Geriatrics (≥65 years of age)
Patients older than 65 years (referred to in this document as older or elderly) and frail or debilitated patients are more susceptible to a variety of adverse reactions from NSAIDs. The incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal injury including ulceration and bleeding. For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision.

Use in the elderly and debilitated patient should be monitored more closely as NSAID use in this population is known to be associated with a higher risk of adverse events. Data from controlled clinical studies (where 24% of 1677 patients were ≥65 years of age) and UK post marketing studies with nabumetone (where 43% of 10,800 patients were ≥65 years of age) indicate that there were no differences in efficacy or safety between older and younger patients (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular**, **Gastrointestinal**, and **Renal**).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The most common adverse reactions encountered with NSAIDs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred particularly in the elderly.

Adverse reaction information was derived from blinded controlled and open-labelled clinical trials and from worldwide marketing experience. Over 6,000 patients have been treated with nabumetone in clinical trials, and over 49,000 patients included in post-marketing surveillance studies and

nabumetone has been prescribed extensively in those countries where the drug has received registration clearance.

In large scale post-marketing studies the adverse event profile was highly consistent with the profile seen in clinical trials of nabumetone. The pattern of adverse events remained similar in patients treated with nabumetone for several years, similar in patients taking 1 to 2 g doses, and was similar in patients aged <65 or ≥65 years.

Information on adverse experiences observed in U.S. clinical studies is presented below. Of the 1,677 patients who received nabumetone during U.S. clinical trials, 1,524 were treated for at least one month, 1,327 for at least three months, 929 for at least a year and 750 for at least two years. Over 300 patients have been treated for five years or longer.

The most frequently reported adverse reactions were related to the gastrointestinal tract. They were diarrhea, dyspepsia and abdominal pain. Discontinuation of therapy due to these adverse events was 1.3% (diarrhea), 0.8% (dyspepsia) and 1.1 % (abdominal pain) during the double blind phase of the US clinical trials involving 930 patients treated with nabumetone for up to 6 months. Of 1,677 patients treated with nabumetone in controlled and open label extension clinical trials (1,140 followed for one year and 927 for two years), the cumulative incidence of peptic ulcers was 0.3% at 3 to 6 months, 0.5% at one year and 0.8% at two years.

The following table displays adverse events reported in long-term clinical trial follow-up involving treatment for up to 8 years. Where available, percentages are based upon the total number of observations, thus patients reporting multiple incidents of an adverse event have been recorded for each occurrence. Causal relationship to nabumetone has not necessarily been established for all of the events listed below.

Table 1 - Adverse Events Reported in Long-term Follow-up with Nabumetone

	Nabumetone (%)
Gastrointestinal:	
Diarrhea	14
Dyspepsia	13
Abdominal Pain	12
Nausea	9
Flatulence	6
Constipation	4
Positive Stool Guaiac	2
Dry Mouth	2
Gastritis	1
Vomiting	1
Melena	1
Central Nervous System:	
Headache	8
Dizziness	6
Insomnia	3

Table 1 - Adverse Events Reported in Long-term Follow-up with Nabumetone

	Nabumetone (%)
Fatigue	2
Somnolence	2
Increased Sweating	1
Nervousness	1
Dermatologic:	
Rash	7
Pruritus	4
Special Senses:	
Tinnitus	4
Abnormal Vision	2
Cardiovascular:	
Hypertension	1.7
Palpitations	1
Respiratory:	
Dyspnea	1

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following adverse events were reported in long-term clinical trial follow-up involving treatment for up to 8 years. Adverse events listed at an estimated incidence of ≤0.01% are based on spontaneous reports from worldwide marketing experience. Where available, percentages are based upon the total number of observations, thus patients reporting multiple incidents of an adverse event have been recorded for each occurrence. Causal relationship to nabumetone has not necessarily been established for all of the events listed below.

Gastrointestinal
Eructation (0.7%), gastroenteritis (0.7%), anorexia (0.7%), rectal bleeding (0.5%), gastric ulcer (0.4%), duodenal ulcer (0.4%), stomatitis (0.4%), dysphagia (0.3%), increased appetite (0.2%), glossitis (0.2%), pancreatitis (0.1%), gingivitis (0.1%), duodenitis (0.1%), bilirubinuria (0.1%), gastrointestinal bleeding (0.1%), cholestatic jaundice (≤0.01%), gallstones (≤0.01%).

Central Nervous System
Depression (0.9%), vertigo (0.9%), malaise (0.8%), paresthesia (0.8%), asthenia (0.7%), anxiety (0.4%), confusion (0.3%), agitation (0.1%), tremor (0.1%), nightmares (<0.01%).

Dermatologic
Alopecia (0.9%), urticaria (0.7%), acne (0.4%), bullous eruptions (0.2%), photosensitivity (0.2%), pseudoporphyria cutanea tarda (≤0.01%), erythema multiforme (≤0.01%), Stevens Johnson syndrome (≤0.01%), toxic epidermal necrolysis (≤0.01%).

Special Senses
Taste disorder (0.2%).

Cardiovascular
Syncope (0.3%), thrombophlebitis (0.2%), vasculitis (0.1%), angina (0.1%), arrhythmia (0.1%), myocardial infarction (0.1%).

Respiratory
Cough (0.6%), asthma (0.4%), eosinophilic pneumonia (≤0.01%), hypersensitivity pneumonitis (≤0.01%), interstitial pneumonitis (≤0.01%).

Renal/Genitourinary
Dysuria (0.7%), albuminuria (0.5%), hematuria (0.4%), impotence (0.2%), renal stones (0.2%), hyperuricemia (0.1%), azotemia (0.1%), interstitial nephritis (≤0.01%), nephrotic syndrome (≤0.01%), renal failure (≤0.01%), vaginal bleeding (≤0.01%).

Other
Edema (0.7%), weight gain (0.7%), weight loss (0.4%), fever (0.4%), chills (0.2%), hyperglycemia (0.2%), hypokalemia (0.1%).

Hematologic/Lymphatic
Anemia (0.5%), leucopenia (0.4%), thrombocytopenia (0.2%), granulocytopenia (0.1%), aplastic anemia (<0.01).

Hepatic
Liver function abnormalities (0.5%), elevated liver function tests (≤0.01%), jaundice (≤0.01%), hepatic failure (≤0.01%).

Allergic/Hypersensitivity
Angioneurotic edema (<0.01%), anaphylactoid reaction (<0.01%), anaphylaxis (<0.01%).

DRUG INTERACTIONS

Drug-Drug Interactions

Protein-bound drugs
In vitro studies have shown that, because of its affinity for protein, the active metabolite of nabumetone may displace other protein-bound drugs such as sulfonylureas, tolbutamide, chlorpropamide and warfarin, from their binding site. However, clinical pharmacology studies demonstrated no significant drug interaction between warfarin and nabumetone.

Anticoagulants
Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increase the risk of GI adverse events such as ulceration and bleeding. For these reasons, the concomitant administration of nabumetone and warfarin or other highly protein bound drugs should be undertaken with caution. In addition, because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function, concurrent therapy of nabumetone with warfarin requires close monitoring to be certain that no change in anticoagulant dosage is necessary (see **WARNINGS AND PRECAUTIONS – Hematologic - Anti-coagulants**).

Anti-platelet Agents (including ASA)
There is an increased risk of bleeding, via inhibition of platelet function, when antiplatelet agents are combined with NSAIDs, such as NABUMETONE (see **WARNINGS AND PRECAUTIONS – Hematologic - Anti-platelet Effects**).

Cyclosporin
No specific drug interaction studies have been conducted with nabumetone and cyclosporin.

Digoxin
Digoxin levels should be monitored, and if necessary, a dosage adjustment made when administered concomitantly with nabumetone.

Lithium
NSAIDs have been reported to increase steady-state plasma lithium concentrations. Monitoring of plasma lithium concentrations is advised when stopping or starting a NSAID, as increased lithium concentrations can occur.

Monitoring of plasma lithium concentrations is recommended when initiating, adjusting, or discontinuing treatment with nabumetone.

Methotrexate
Rare cases of fatal renal toxicity have occurred when methotrexate and NSAIDs are given concomitantly.

Oral Contraceptives
No specific drug interaction studies have been conducted with nabumetone and oral contraceptives.

Oral Hypoglycemics
No specific drug interaction studies have been conducted with nabumetone and oral hypoglycemic agents.

Antacids
Concomitant administration of an aluminum-containing antacid had no significant effect on the bioavailability of 6-MNA.

Acetylsalicylic acid (ASA) or other NSAIDs
The use of NABUMETONE in addition to any other NSAID, including over-the counter ones (such as ASA and ibuprofen) for analgesic and/or anti-inflammatory effects is NOT recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions.

The exception is the use of low dose ASA for cardiovascular protection, when another NSAID is being used for its analgesic/anti-inflammatory effect, keeping in mind that combination NSAID therapy is associated with additive adverse reactions.

Some NSAIDs (e.g. ibuprofen) may interfere with the anti-platelet effects of low dose ASA, possibly by competing with ASA for access to the active site of cyclooxygenase-1.

Concomitant administration of ASA did not affect the bioavailability of the principal circulating metabolite in volunteer subjects.

Paracetamol, cimetidine
Concomitant administration of paracetamol or cimetidine did not affect the bioavailability of the principal circulating metabolite in volunteer subjects.

Glucocorticoids
Some studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI side effects such as ulceration and bleeding. This is especially the case in older (>65 years of age) individuals.

Gold, d-penicillamine, and corticosteroids
In controlled rheumatoid arthritis trials, nabumetone has been used in combination with gold, d-penicillamine, and corticosteroids. There was no evidence of untoward effects associated with their concurrent administration.

Anti-hypertensives
NSAIDs may diminish the anti-hypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors.

Combinations of ACE inhibitors, angiotensin-II antagonists, or diuretics with NSAIDs might have an increased risk for acute renal failure and hyperkalemia. Blood pressure and renal function (including electrolytes) should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure.

Diuretics
Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce the effect of diuretics.

Selective Serotonin Reuptake Inhibitors (SSRIs)
Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal ulceration and bleeding (see **WARNINGS AND PRECAUTIONS - Gastrointestinal**).

Other
No specific drug interaction studies have been conducted with nabumetone and probenecid, aminoglycosides, or cholestyramine.

Drug-Lifestyle Interactions

No specific drug interaction studies have been conducted with nabumetone and alcohol.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Osteoarthritis and Rheumatoid Arthritis
The starting and usual adult dose is 1000 mg daily taken as a single dose with or without food. The dosage may be increased to 1500 mg or 2000 mg per day given either as a single dose or in two divided doses.

Since nabumetone has an average plasma half-life of 23 hours in healthy young subjects and 30 hours in elderly patients, plasma levels of 6-MNA will approximate steady-state within one week of dosing. For this reason, dosage adjustments during therapy should not be made more frequently than at one-week intervals, except in the case of side effects.

In patients with severe renal or hepatic impairment, dosage level adjustments should be made on an individual basis. In moderate renal impairment dose reduction may be warranted (see **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**).

OVERDOSAGE

Overdoses with nabumetone have been rarely reported. There is no specific antidote and the active metabolite 6-MNA is not dialysable. If acute overdosage occurs, it is recommended that the stomach be emptied by vomiting or lavage and institution of general supportive measures as necessary. In addition, the use of activated charcoal, up to 60 g, may effectively reduce nabumetone absorption. Co-administration of nabumetone with activated charcoal orally in man has resulted in an 80% decrease in maximum plasma concentrations of the active metabolite.

For management of a suspected drug overdose, contact your regional poison control centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Nabumetone is a non-acidic, NSAID with a naphthylalkanone structure which is virtually insoluble in water. It exhibits anti-inflammatory, analgesic, and antipyretic properties in pharmacologic studies. As with the acidic NSAIDs, its mode of action is not known. However, the ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect.

Nabumetone as the parent compound is a pro-drug which undergoes rapid hepatic biotransformation to its principal active metabolite, 6-methoxy-2-naphthylacetic acid (6-MNA), a potent inhibitor of prostaglandin biosynthesis.

Nabumetone was compared to ASA 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 three or four weeks' therapy of nabumetone 1000 mg or 2000 mg daily when compared

to either placebo-treated or non-treated subjects. In contrast, ASA 3600 mg daily produced an increase in fecal blood loss when compared to the nabumetone, placebo, or non-treated subjects.

In one 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.

Pharmacokinetics

Table 2 - Mean Pharmacokinetic Parameters of Nabumetone Active Metabolite (6-MNA) at Steady-State Following Oral Administration of 1000 mg or 2000 mg Doses of Nabumetone

Abbreviations (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)
$t_{½}$ (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

*t_{max} is reported as median (range) values.

Absorption

After oral administration, approximately 80% of a radio-labelled dose of nabumetone is found in the urine, indicating that nabumetone is well absorbed from the gastrointestinal tract.

Following oral administration, peak plasma levels of 6-MNA occur between 2.5 and 4 hours (range 1 to 12 hours).

When administered with food or milk, there is more rapid absorption; however, the total amount of 6-MNA in the plasma is unchanged.

Distribution

Preliminary *in vivo* and *in vitro* studies suggest that unlike other NSAIDs, there is no evidence of enterohepatic recirculation of the active metabolite. Steady-state is generally achieved between 3 and 6 days and the elimination half-life is variable from 23 (±3.7) hours in young healthy patients to 30 (±8.1) hours in the elderly.

The active metabolite penetrates into the synovial fluids at measurable sustained levels in osteoarthritis and rheumatoid arthritis patients. There is wide inter-individual variation in plasma concentrations of 6-MNA. A correlation between plasma 6-MNA levels and efficacy has not been established.

6-MNA is more than 99% bound to plasma proteins. The free fraction is dependent on total concentration of 6-MNA and is proportional to dose over the range of 1000 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.

Metabolism
Nabumetone itself is not quantifiable in the plasma because, after absorption, it undergoes rapid biotransformation to the principal active metabolite, 6-MNA. Approximately 35% of a 1000 mg dose of nabumetone is converted to 6-MNA and 50% is converted into unidentified metabolites which are subsequently excreted in the urine.

Excretion
After oral administration, approximately 80% of a radio-labelled dose of nabumetone is found in the urine.

Special Populations and Conditions

Geriatrics
Steady-state plasma concentrations in elderly patients were generally higher than in young healthy subjects (see **Table 2**).

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

Renal Insufficiency
In moderate renal impairment (creatinine clearance 30 to 49 mL/min), there is a 50% increase in unbound plasma 6-MNA.

In studies of patients with renal insufficiency, the mean terminal half-life of 6-MNA was increased in patients with severe renal dysfunction (creatinine clearance <30 mL/min/1.73 m^2 or <0.5 mL/sec/1.73 m^2). In patients undergoing hemodialysis, steady state plasma concentrations of the active metabolite were similar to those observed in healthy subjects. Due to extensive protein binding, 6-MNA is not dialyzable.

STORAGE AND STABILITY

NABUMETONE (Nabumetone Tablets) should be stored at room temperature (15°C to 30°C) in a dry place and dispensed in a light resistant container.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NABUMETONE (Nabumetone Tablets) is available as 500 mg tablets. Each white, modified capsule-shaped, biconvex, film-coated tablet engraved "500" on one side, contains 500 mg nabumetone. Available in bottles of 100 tablets.

In addition to the active ingredient, NABUMETONE Tablets contain the following non-medicinal ingredients (in alphabetical order): croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, polyethylene glycol, sodium lauryl sulphate, and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

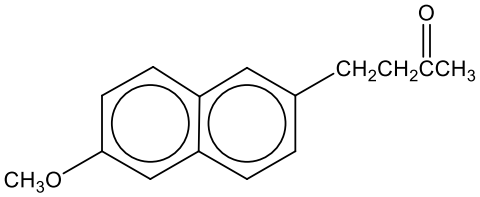
Proper Name(s): Nabumetone

Chemical Name(s): 1) 2-butanone, 4-(6-methoxy-2-naphthalenyl)-;
2) 4-(6-methoxy-2-naphthyl)-butan-2-one

Molecular Formula: $C_{15}H_{16}O_2$

Molecular Weight: 228.29 g/mol

Structural Formula:



Physicochemical Properties: Nabumetone, the active ingredient in NABUMETONE, is a nonacidic naphthylalkanone derivative. It is a white or almost white crystalline powder which is practically insoluble in water; sparingly soluble in ethanol (96%) and in methanol; freely soluble in acetone. The melting range of nabumetone is 78ºC to 82ºC.

CLINICAL TRIALS

Randomized clinical trials with NABUMETONE have NOT been designed to detect differences in cardiovascular adverse events in a chronic setting.

Comparative Bioavailability Studies

A randomized, two-treatment, two-period, two-way, single-dose, crossover comparative bioavailability study of NABUMETONE 500 mg tablets (Apotex Inc.) and Relafen® 500 mg tablets (SmithKline Beecham Pharma Inc.) was conducted in healthy adult male subjects under fasting conditions. Comparative bioavailability data, based on the active metabolite of nabumetone, 6-methoxy-2-naphthylacetic acid, from 18 subjects that were included in the statistical analysis are presented in the following table:

Table 3 SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

6-methoxy-2-naphthylacetic acid (3 x 500 mg) Geometric Least Square Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (mcg·hr/mL)	1318.60 1396.83 (34)	1438.79 1509.62 (31)	91.6	85.5 – 98.3
AUC_I (mcg·hr/mL)	1583.32 1694.62 (36)	1685.83 1779.33 (33)	93.9	87.5 – 100.8
C_{max} (mcg/mL)	32.70 34.13 (27)	33.29 33.91 (21)	98.2	88.3 – 109.3
T_{max}[3] (h)	4.50 (2.00 – 32.00)	4.00 (3.00 – 32.00)		
$T_{1/2}$[4] (h)	23.99 (16)	23.55 (10)		

[1] NABUMETONE (nabumetone) tablets, 500 mg (Apotex Inc.)
[2] Relafen® (nabumetone) tablets, 500 mg (SmithKline Beecham Pharma Inc.)
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV%) only

DETAILED PHARMACOLOGY

Clinical

Double-blind studies of up to 6 months duration in rheumatoid arthritis and osteoarthritis have demonstrated that nabumetone at a dosage of 1 to 2 g/day is at least as effective as daily doses of 3.6 g of acetylsalicylic acid (ASA), 1.6 g of ibuprofen, 75 to 150 mg of indomethacin, 100 mg of diclofenac, and 500 mg to 1 g of naproxen. Long-term follow-up studies of up to 8 years duration have shown that nabumetone is well-tolerated.

In five endoscopically-controlled studies comparing nabumetone (102 patients treated at doses of 1to 1.5 g/day) with naproxen (110 patients treated with doses of 500 mg to 1 g/day), nabumetone caused significantly fewer gastric and duodenal ulcers than naproxen. In two studies of 1 g/day nabumetone (n=78) compared with 600 mg ibuprofen q.i.d. alone (n=73) or in combination with 200 mcg misoprostol (q.i.d.) (n=60), nabumetone treatment resulted in significantly fewer gastric and duodenal ulcers than ibuprofen, and the frequency of ulcers with nabumetone was not significantly different from the incidence of ulcers in patients taking misoprostol concomitantly with ibuprofen.

In two clinical pharmacology studies conducted in healthy volunteers, it was demonstrated that nabumetone had little effect on collagen-induced platelet aggregation and no effect on bleeding time.

Additionally, there was no evidence of serious hematological findings or clinically significant trends in hematological parameters associated with the use of nabumetone in clinical trials.

Animal

Nabumetone has shown good activity in two animal models of acute inflammation, namely carrageenin-induced edema model in the rat and the ultra-violet induced erythema model in the guinea pig. It was also active in three rat models of chronic inflammation: the cotton pellet induced granuloma, adjuvant arthritis and arthritis induced by 6-sulfanilamido-indazole. Analgesic activity has been inferred from the effect of nabumetone in the mouse exposed to phenyl-p-quinone. In the rabbit, nabumetone was found to have antipyretic properties.

In the carrageenin-induced model of acute inflammation and the fasted model of gastric irritancy, both studied in the rat, the ratio of the dose producing gastric irritancy to anti-inflammatory dose was between five and fifty times greater for nabumetone than for indomethacin, ASA, piroxicam, diclofenac, or fenbufen. In this experimental situation, nabumetone exhibited a superior therapeutic index and the dose required to produce gastric irritancy was many times greater than the anti-inflammatory dose.

Nabumetone itself is a weak inhibitor of the cyclo-oxygenase system and, hence, of prostaglandin biosynthesis. Its principal metabolite in laboratory animals and in man, 6-methoxy-2-naphthylacetic acid, is a strong inhibitor of this enzyme system.

Nabumetone was well absorbed after oral administration to the rat, mouse, rabbit, and rhesus monkey. Absorption in dogs was variable. Tissue distribution measured following administration of ^{14}C-nabumetone to rats was found to be widespread except for a noteworthy absence of radioactivity in the gastric wall. Radioactive material crossed the placental barrier in the rat and also was found in rat milk.

Following its absorption from the gut, nabumetone is subject to considerable first pass biotransformation to its principal metabolite in all species (including man), 6-methoxy-2-naphthylacetic acid. Nabumetone itself can rarely be detected in the plasma, studies in the rat suggesting that its half-life is about 15 minutes. The half-life of the principal metabolite is about 20 hours in the dog and 24 hours in man. It is substantially shorter in the mouse (1 hour), the rat (2 hours), and the rhesus monkey (2 hours).

Nabumetone is metabolized in all species by three inter-related pathways: oxidative cleavage of the side chain to yield the acetic acid derivative, O-demethylation, and reduction of the ketone moiety to an alcohol.

The kidney is the major route of elimination with approximately 75% of the dose recovered in urine in the first 48 hours. Although several metabolites were observed in the urine, nabumetone itself has not been detected. Little excretion takes place in the bile except in the rat which also demonstrates enterohepatic circulation of metabolites.

TOXICOLOGY

Acute Toxicity

The oral LD_{50} was in excess of 5000 mg/kg in mice and in excess of 2000 mg/kg in rats. Neonatal rats are approximately twice as sensitive. The principal target organ in rodents is the gastrointestinal tract.

Sub-Acute Toxicity

In Beagle dogs, the maximum tolerated oral dose was 500 mg/kg, and in a 14 day study, doses of 60 and 300 mg/kg were tolerated with only minor effects which at the high dose included hematuria, fecal occult blood, and mucosal erythema in the large bowel. Apart from slight reductions in serum alkaline phosphatase and, in one of the two dogs, in red cell parameters, 60 mg/kg/day was a no effect dose.

In the rhesus monkey, doses up to 400 mg/kg were well tolerated in an oral maximum tolerated dose study. At doses of 800 mg/kg and above, weight loss, slight gastrointestinal irritancy, and, at 1600 mg/kg, prolongation of blood coagulation time were seen. Following administration of 540 mg/kg/day for 28 days, slight weight loss, slightly reduced red cell parameters, and minimal histological change in the kidney were the principal findings. Doses of 60 and 180 mg/kg/day for 14 days were without effect.

In the rat, a dose of 200 mg/kg/day for 14 days was tolerated with only a moderate decrease in bodyweight gain, gastrointestinal ulceration in 1/12 rats, increased relative kidney weight, decreased relative pituitary and thymus weights, and increased water intake. At 600 mg/kg/day, the principal effect was marked gastrointestinal irritancy with ulceration and perforation of the small bowel resulting in 25% mortality. Apart from a slight increase in kidney weight, 67 mg/kg/day was a no-effect dose. In a study of 27 days duration, a dose of 20 mg/kg/day was without effect apart from trace amounts of fecal occult blood and minimal histological change in the adrenals. Doses of 60 and 180 mg/kg/day were tolerated with only slight effects on bodyweight gain and minor histopathological changes in spleen, bladder, and adrenal. More severe gastrointestinal effects including perforation of the small bowel were seen in one rat dosed at 180 mg/kg/day which was killed *in extremis*.

Chronic Toxicity

Rats received nabumetone at 20, 80, and 320 mg/kg/day for 26 weeks. At the high dose, the principal finding was of gastrointestinal irritation with evidence of ulceration of the small intestine resulting in a number of mortalities. Apart from a transient pallor in two rats, a dose of 80 mg/kg/day was without effect.

Rhesus monkeys received nabumetone for 26 weeks at oral doses of 20, 80, and 320 mg/kg. Apart from a transient effect on red cell parameters, the no-effect dose was 80 mg/kg/day. At the high dose, there was evidence of edema, blood loss from the rectum and gastric erosions in a proportion of animals.

Rhesus monkeys were also studied for 52 weeks under oral dosing regimens of 25, 75, 225, and 450 mg/kg/day. Monkeys at the highest dose showed significant gastrointestinal irritation with secondary

anemia and hypoproteinemia resulting in subcutaneous edema. Some evidence of interstitial nephritis was also seen in a proportion of animals. At the intermediate dose, gastrointestinal irritation was evident to a lesser degree and 75 mg/kg/day was a no-effect dose.

Rats received nabumetone daily for 78 weeks at doses of 37.5, 75, and 150 mg/kg in two separate studies. An additional group in one study received 300 mg/kg for 21 weeks only. The principal finding was of gastrointestinal irritancy which was severe at 300 mg/kg resulting in ulceration of the small intestine and 30% mortality before dosing was discontinued in week 21. Increases in kidney weight and decreases in urine osmolality were associated with a dose related nephropathy. There were no consistent changes in biochemical or hematological parameters. These effects in the rat are typical of nonsteroidal anti-inflammatory agents and were minimal at the low dose of 37.5 mg/kg/day. Recovery from these effects appeared to be complete in rats maintained for a further six weeks without treatment.

Except for elevations in serum sodium and chloride, no abnormalities were apparent after the surviving rats were off treatment for six weeks. All abnormalities noted appeared to be secondary to the renal and gastrointestinal effects of nabumetone at the doses employed. Mortality at the two intermediate dose levels was not different from controls but, at necropsy, decedents had findings similar to those observed at the highest dose.

Reproductive Studies

Teratology studies in rats and rabbits at doses of up to 400 and 300 mg/kg/day, respectively, resulted in some degree of maternal toxicity at the highest doses used, but no evidence for a teratogenic effect in either species was detected. In common with other NSAIDs, increased embryonic loss about the time of implantation was observed in rabbits.

In male and female rats, reproductive performance and fertility were not impaired at doses up to 320 mg/kg/day. Whilst males were unaffected, nabumetone was toxic to the pregnant and lactating dam at 320 mg/kg/day, dystocia leading to maternal and fetal/neonatal death, delayed parturition and reduced maternal weight gain being frequent observations. In general, nabumetone had no effect on embryonic or fetal development but, at the high dose, there was an indication of reduced live litter size at Cesarean section, associated with a reduced number of shed ova as assessed by corpora lutea count; there was also a reduced number of males per litter. Associated with the dystocia, perinatal pup loss was markedly increased at 320 mg/kg/day, this resulted in reduced litter size postnatally and increased pup weight consequent upon reduced intra-litter competition. However, the postnatal development and behaviour of surviving pups was normal as was their subsequent reproductive performance. At the lower doses of 20 and 80 mg/kg/day, occasional intergroup differences were considered to be of doubtful biological significance.

In a peri- and post-natal toxicity study in rats, where all females were allowed to litter, treatment at the high dose of 320 mg/kg/day was also associated with prolonged gestation, dystocia, and increased perinatal pup mortality but, as in the fertility study, there were no effects on the development of the surviving offspring. The reduced number of ova shed at ovulation leading to reduced litter size and the dystocia leading to effects on both dam and offspring during the perinatal period are likely to be due to the effect of nabumetone on prostaglandin biosynthesis. These findings are seen with other NSAIDs.

Mutagenicity/Carcinogenicity

In two-year studies conducted in mice and rats, nabumetone had no statistically significant tumorigenic effect. Nabumetone did not show mutagenic potential in the Ame's test and mouse micronucleus test *in vivo*. However, nabumetone- and 6-MNA-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).

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PART III: CONSUMER INFORMATION

[Pr]NABUMETONE
(nabumetone tablets BP)

This leaflet is part III of a three-part "Product Monograph" published when NABUMETONE (nabumetone tablets) was approved for sale in Canada and is designed specifically for Consumers.

Read this information each time you refill your prescription in case new information has been added.

This leaflet is a summary designed specifically for you to read. It will NOT tell you everything about NABUMETONE. See your health care provider and pharmacist regularly and ask them questions about your health and any medications you take.

ABOUT THIS MEDICATION

What the medication is used for:
Your health care provider has prescribed NABUMETONE for you for one or more of the following medical conditions:

- to treat arthritic symptoms such as swelling, stiffness and joint pain.

What it does:
NABUMETONE (nabumetone tablets), as a nonsteroidal anti-inflammatory drug (NSAID), can reduce the chemicals produced by your body which cause pain and swelling.

NABUMETONE, as a nonsteroidal anti-inflammatory drug (NSAID), does NOT cure your illness or prevent it from getting worse. NABUMETONE can only relieve pain and reduce swelling as long as you continue to take it.

When it should not be used:
Do not take NABUMETONE if you have any of the following medical conditions:

- Allergic to nabumetone or to any nonmedicinal ingredients of NABUMETONE.
- Heart bypass surgery (planning to have or recently had).
- Severe, uncontrolled heart failure.
- Bleeding in the brain or other bleeding disorders.
- Pregnant and in a later stage of pregnancy (28 weeks or later).
- Currently breastfeeding (or planning to breastfeed).
- Allergy to ASA (Acetylsalicylic Acid) or other NSAIDs (Nonsteroidal Anti-Inflammatory Drugs).
- Ulcer (active).
- Bleeding from the stomach or gut (active).
- Inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis).
- Liver disease (active or severe).
- Kidney disease (severe or worsening).
- High potassium in the blood.

Patients who took a drug in the same class as NABUMETONE after a type of heart surgery (coronary artery bypass grafting (CABG)) were more likely to have heart attacks, strokes, blood clots in the leg(s) or lung(s), and infections or other complications than those who did NOT take that drug.

NABUMETONE should NOT be used in patients under 18 years of age since the safety and effectiveness have NOT been established.

What the medicinal ingredient is:
nabumetone.

What the nonmedicinal ingredients are:
croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, polyethylene glycol, sodium lauryl sulphate and titanium dioxide.

What dosage forms it comes in:
500 mg tablet: white, capsule-shaped, with "500" on one side.

Check with your doctor or pharmacist if the identifying markings or colour of your tablets appear different.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

If you have, or previously had, any of the following medical conditions, see your health care provider to discuss treatment options other than NABUMETONE:

- **Heart Attack or Angina**
- **Stroke or Mini-stroke**
- **Loss of Vision**
- **Congestive Heart Failure**

Pregnancy:
DO NOT take NABUMETONE if you are pregnant and in a later stage of pregnancy (28 weeks or later).
If you are pregnant and in an earlier stage of pregnancy (less than 28 weeks) only take NABUMETONE if you are told to

do so by your doctor. Medicines like NABUMETONE may cause harm to you and your baby. Your doctor will need to closely monitor your health and that of your baby (including your amniotic fluid levels) if they prescribe NABUMETONE during this time.

BEFORE you take NABUMETONE tell your health care provider if you have any of the following:

- High blood pressure.
- High cholesterol.
- Diabetes mellitus or on a low sugar diet.
- Atherosclerosis.
- Poor circulation to your extremities.
- Smoker or ex-smoker.
- Kidney disease or urine problems.
- Previous ulcer or bleeding from the stomach or gut.
- Previous bleeding in the brain.
- Bleeding problems.
- Family history of allergy (including rash, asthma, hives, sinusitis or anaphylaxis [sudden collapse]) to NSAIDs, such as acetylsalicylic acid (ASA), celecoxib, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, rofecoxib, sulindac, tenoxicam, tiaprofenic acid, tolmetin, or valdecoxib (NOT a complete list).
- Family history of asthma, nasal polyps, long-term swelling of the sinus (chronic sinusitis) or chronic urticaria (hives).
- Family history of allergy to sulfonamide drugs
- Past history of (or current) stomach upset, or liver or heart disease.
- Blood abnormalities.
- Special diet, such as low sodium diet.
- Are pregnant, planning on becoming or become pregnant while taking NABUMETONE.
- Are breast feeding.
- Any other medical problem such as alcohol abuse etc.

Serious Skin Reactions: In rare cases, serious, fatal, or life-threatening skin reactions listed below have been reported with some NSAIDs, such as NABUMETONE.

- Drug reaction with eosinophilia and systemic symptoms (DRESS),
- Stevens-Johnson syndrome (SJS),
- toxic epidermal necrolysis (TEN),
- exfoliative dermatitis and
- erythema multiforme

You may be at a greater risk of experiencing a serious skin reaction usually during the first month of treatment. See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

While taking this medication:

- tell any other doctor, dentist, pharmacist or other health care professional that you see, that you are taking NABUMETONE, especially if you are planning to have heart surgery.
- do NOT drink alcoholic beverages while taking this medication because you would be more likely to develop stomach problems.
- fertility may be decreased. The use of NABUMETONE is not recommended in women trying to get pregnant. In women who have difficulty conceiving, stopping NABUMETONE should be considered.
- contact your doctor if you are not getting any relief of your arthritis or if you develop any unusual discomfort.
- report any untoward reactions to your doctor. This is very important as it will aid in the early detection and prevention of potential complications.
- regular medical checkups are essential.
- do not take ASA (acetylsalicylic acid) or other drugs to relieve your arthritis unless directed by your doctor.
- do not give NABUMETONE to others because it may not be suitable for them.

INTERACTIONS WITH THIS MEDICATION

Talk to your health care provider and pharmacist if you are taking any other medication (prescription or non-prescription) such as any of the following (NOT a complete list):

- Acetylsalicylic Acid (ASA) or other NSAIDs, e.g. ASA, celecoxib, diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen
- Antacids
- Antidepressants
    - Selective Serotonin Reuptake Inhibitors (SSRIs) e.g. citalopram, fluoxetine, paroxetine, sertraline
- Blood pressure medications
    - ACE (angiotensin converting enzyme) inhibitors e.g. enalapril, lisinopril, perindopril, Ramipril
    - ARBs (angiotensin II receptor blockers) e.g. candesartan, irbesartan, losartan, valsartan

- Blood thinners
  e.g. warfarin, ASA, clopidogrel
- Corticosteroids (including glucocorticoids)
  e.g. prednisone
- Cyclosporin
- Digoxin
- Diuretics
  e.g. furosemide, hydrochlorothiazide
- Lithium
- Methotrexate
- Oral contraceptives
- Oral hypoglycemics (diabetes medications)
- Tacrolimus
- Phenytoin

Your health care provider may prescribe low dose ASA (acetylsalicylic acid) as a blood thinner to reduce your risk of having a heart attack or stroke while you are taking NABUMETONE. Take only the amount of ASA prescribed by your health care provider. You are more likely to upset or damage your stomach if you take both NABUMETONE and ASA than if you took NABUMETONE alone.

It is important to tell your doctor, dentist and pharmacist if you are taking other medication, as combining drugs can sometimes result in a change from the expected drug effects, or cause harmful effects.

PROPER USE OF THIS MEDICATION

Usual Dose:

Take NABUMETONE only as directed by your health care provider. **Do NOT take more of it, do NOT take it more often and do NOT take it for a longer period of time than your health care provider recommended. If possible, you should take the lowest dose of this medication for the shortest time period.** Taking too much NABUMETONE may increase your chances of unwanted and sometimes dangerous side effects, especially if you are elderly, have other diseases or take other medications.

If you will be using NABUMETONE for more than 7 days, see your health care provider regularly to discuss whether this medicine is working for you and if it is causing you any unwanted effects.

This medication has been prescribed specifically for you. Do NOT give it to anyone else. It may harm them, even if their symptoms seem to be similar to yours.

NABUMETONE is NOT recommended for use in patients under 18 years of age since safety and effectiveness have NOT been established.

Be sure to take NABUMETONE regularly as prescribed. Try to take your tablets at the same time each day. The effect of NABUMETONE is evident early in treatment, however, in some types of arthritis, up to 1 week may pass before you feel the full relief from this medicine. It is important to keep taking NABUMETONE even after you start to feel better.

Generally, patients are instructed to take 1000 mg once a day. During treatment, your doctor may decide to increase the dosage up to 2000 mg each day, according to your response to the medication. In that case it may be divided in two doses per day.

Stomach upset is one of the common problems with NSAIDs. To lessen stomach upset, take NABUMETONE immediately after a meal or with food or milk. You should swallow the tablets whole, with water or milk. Do not chew them. You should remain standing or sitting upright (i.e., do not lie down) for about 15 to 30 minutes after taking the medicine. This helps to prevent irritation that may lead to trouble swallowing. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your doctor.

If you are prescribed this medication for use over a long period of time, your doctor will check your health during regular visits to assess your progress and to ensure that this medicine is not causing unwanted effects.

Important: Your doctor may give you different instructions better suited to your specific needs. If you need more information on how to take NABUMETONE properly, double check with your doctor or pharmacist.

Overdose:

If you think you, or a person you are caring for, have taken too much NABUMETONE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

If you take more than the prescribed dose, contact your health care provided immediately.

Missed Dose:
If you forget to take a tablet, leave out that dose completely. Take your next dose at the normal time it is due.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

NABUMETONE may cause some side effects, especially when used for a long time or in large doses. When these side effects occur, you may require medical attention. Report all symptoms or side effects to your health care provider.

Any medication can cause side effects. Most people tolerate the medicine well. Elderly, frail or debilitated patients often seem to experience more frequent or more serious side effects. The most common adverse effects associated with NABUMETONE are gastrointestinal, such as diarrhea, indigestion, abdominal pain, nausea, constipation and flatulence (i.e., large amounts of gas in the intestines). Stomach problems may be more likely to occur if you drink alcoholic beverages. Therefore, do not drink alcoholic beverages while taking this medication.

Other side effects such as headaches, tiredness, dizziness, sleepiness, insomnia (i.e., not able to sleep) have also been observed.

NABUMETONE may cause you to become drowsy or tired. Be careful about driving or participating in activities that require you to be alert. If you become drowsy, dizzy or light-headed after taking NABUMETONE, do NOT drive or operate machinery.

Consult your doctor if these symptoms become troublesome.

Check with your doctor immediately if you experience unexpected weakness while taking this medication.

NABUMETONE may cause you to become more sensitive to sunlight. Any exposure to sunlight or sunlamps, even for brief periods of time, may cause sunburn, skin blisters, skin rash, redness, itching or discoloration; or vision changes. If you have a reaction from the sun, check with your health care provider.

Check with your health care provider IMMEDIATELY if you develop chills, fever, muscle aches or pains, or other flu-like symptoms, especially if they occur before or together with, a skin rash. These symptoms may be the first signs of a SERIOUS ALLERGIC REACTION to this medication.

SERIOUS SIDE EFFECTS, AND WHAT TO DO ABOUT THEM

Symptom / effect	STOP taking NABUMETONE and talk to your doctor or pharmacist		Stop taking drug and seek immediate medical help
	Only if severe	In all cases	
Bloody or black tarry stools			✓
Shortness of breath, wheezing, any trouble breathing or chest tightness			✓
Skin rash, hives, swelling or itching			
Blurred vision, or any visual disturbance			✓
Any change in the amount or colour of your urine (red or brown)			✓
Any pain or difficulty experienced while urinating		✓	
Swelling of the feet, lower legs; weight gain		✓	
Vomiting or persistent indigestion, nausea, stomach pain or diarrhea		✓	
Yellow discolouration of the skin or eyes, with or without itchy skin		✓	
Malaise, fatigue, loss of appetite		✓	
Headaches, stiff neck		✓	
Mental confusion, depression		✓	
Dizziness, lightheadedness		✓	
Ringing in the ears or hearing problems		✓	
RARE			
Serious Skin Reactions: fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, swelling of face and/or legs, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine or dark urine			✓

This is NOT a complete list of side effects. If you develop any other symptoms while taking NABUMETONE, see your health care provider.

HOW TO STORE IT

Store your tablets in a dry place at room temperature in the original container provided by the pharmacy.

Keep this medication out of reach of children.

Do NOT keep outdated medicine or medicine no longer needed. Any outdated or unused medicine should be returned to your pharmacist.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about NABUMETONE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html). Find the Consumer Information on the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

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