PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] NABUMETONE

Nabumetone Tablets

Tablet, 500 mg, Oral

BP

Nonsteroidal Anti-Inflammatory Agent

AA Pharma Inc.
1165 Creditstone Road, Unit #1
Vaughan, Ontario
L4K 4N7

Date of Initial Authorization:
NOV 29, 2017

Date of Revision:
MAR 24, 2023

Submission Control Number: 272841

RECENT MAJOR LABEL CHANGES

1 INDICATIONS	10/2022
1 INDICATIONS, 1.1 Pediatrics	10/2022
1 INDICATIONS, 1.2 Geriatrics	10/2022
2 CONTRAINDICATIONS	10/2022
3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risk of Cardiovascular (CV) Adverse Events	10/2022
3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risk of Gastrointestinal (GI) Adverse Events	10/2022
3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risk in Pregnancy	10/2022
4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations	03/2023
4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	03/2023
7 WARNINGS AND PRECAUTIONS, General	10/2022
7 WARNINGS AND PRECAUTIONS, Cardiovascular	10/2022
7 WARNINGS AND PRECAUTIONS, Driving and Operating Machinery	03/2023
7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism	10/2022
7 WARNINGS AND PRECAUTIONS, Gastrointestinal	10/2022
7 WARNINGS AND PRECAUTIONS, Hematologic	10/2022
7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic	10/2022
7 WARNINGS AND PRECAUTIONS, Immune	10/2022
7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests	10/2022
7 WARNINGS AND PRECAUTIONS, Neurologic	10/2022
7 WARNINGS AND PRECAUTIONS, Psychiatric	10/2022
7 WARNINGS AND PRECAUTIONS, Renal	10/2022
7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential, Fertility	10/2022
7 WARNINGS AND PRECAUTIONS, Reproductive Health: Teratogenic Risk	03/2023

7 WARNINGS AND PRECAUTIONS, Respiratory	10/2022
7 WARNINGS AND PRECAUTIONS, Skin	10/2022
7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant women	10/2022
7 WARNINGS AND PRECAUTIONS, 7.1.2 Breast-feeding	10/2022
7 WARNINGS AND PRECAUTIONS, 7.1.4 Geriatrics	10/2022

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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 2 CONTRAINDICATIONS and Cardiovascular, and Gastrointestinal).

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 2 CONTRAINDICATIONS and Cardiovascular, and Gastrointestinal).

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.

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of NABUMETONE in pediatric patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 2 CONTRAINDICATIONS and 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (≥65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see 4.2 Recommended Dose and Dosage Adjustment, 7 WARNINGS AND PRECAUTIONS, General, 7.1.4 Geriatrics and 10.3 Pharmacokinetics, Geriatrics).

Patients older than 65 years are most susceptible to a variety of adverse reactions from NSAIDs, such as NABUMETONE (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

Nabumetone is contraindicated in:

- Patients with a known hypersensitivity to nabumetone or to other NSAIDs, patients who are hypersensitive to nabumetone or to any ingredient in the formulation or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- 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 (see 7.1.1 Pregnant women).
- Women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants (see 7.1.2 Breast-feeding).
- Severe uncontrolled heart failure (see Cardiovascular).
- 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 7 WARNINGS AND PRECAUTIONS -— Immune - Anaphylactoid Reactions).
- Active gastric / duodenal / peptic ulcer, active GI bleeding (see Gastrointestinal).
- Cerebrovascular bleeding or other bleeding disorders.
- Inflammatory bowel disease.
- Severe liver impairment or active liver disease (see Hepatic/Biliary/Pancreatic).
- 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 7 WARNINGS AND PRECAUTIONS, Renal).
- Known hyperkalemia (see 7 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.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Risk of Cardiovascular (CV) Adverse Events: Ischemic Heart Disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV)** (see 7 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 7 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 7 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 7.1.1 Pregnant Women). 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 2 CONTRAINDICATIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Use of NABUMETONE should be limited to the lowest effective dose for the shortest possible duration of treatment (see 1 INDICATIONS).
- A lower dose should be considered in patients with renal or hepatic impairment or in elderly patients (see 4.2 Recommended Dose and Dosage Adjustment).

4.2 Recommended Dose and Dosage Adjustment

Osteoarthritis and Rheumatoid Arthritis

Adults

The starting and usual dose is 1000 mg daily taken as a single dose. 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 its principal active metabolite 6-methoxy-2-naphthylacetic acid (6-MNA) will approximate steady-state within one week of dosing (see 10.3 Pharmacokinetics, Table 4). 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.

Pediatrics (<18 years of age): Health Canada has not authorized an indication for pediatric patients (see 2 CONTRAINDICATIONS and 7.1.3 Pediatrics).

Geriatrics (≥65 years of age): In the elderly, frail and debilitated, the dosage should be reduced to the lowest level providing control of symptoms, and adjusted when necessary under close supervision (see 7.1.4 Geriatrics).

Renal impairment: In patients with impaired renal function, lower doses should be considered, patients should be closely monitored, and dosage level adjustments should be made on an individual basis. In moderate renal impairment dose reduction may be warranted (see 7 WARNINGS AND PRECAUTIONS, Renal and 9.4 Drug-Drug Interactions). NABUMETONE is contraindicated in patients with 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 2 CONTRAINDICATIONS).

Hepatic impairment: Patients with impaired hepatic function should be carefully monitored and kept at the minimal effective daily dosage. In patients with hepatic impairment, dosage level adjustments should be made on an individual basis (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic and 9.4 Drug-Drug Interactions). NABUMETONE is contraindicated in

patients with severe hepatic impairment or active liver disease (see 2 CONTRAINDICATIONS).

4.4 Administration

NABUMETONE should be taken immediately after a meal or with food or milk. Tablets should be swallowed whole, not crushed or chewed.

4.5 Missed Dose

If the patient misses a dose, instruct the patient to take the dose as soon as they remember. If it is almost time for the next dose, inform the patient to skip the missed dose and continue the regular dosing schedule. The patient should be instructed not to take 2 doses at the same time.

5 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1–Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
oral	tablet; 500 mg of nabumetone	croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, polyethylene glycol, sodium lauryl sulphate and titanium dioxide

Description

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

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

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 9.4 Drug-Drug Interactions - Acetylsalicylic acid (ASA) or other NSAIDs).

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity and 16 NON-CLINICAL TOXICOLOGY, Genotoxicity.

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 7 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.**

CV adverse events were reported with the use of NABUMETONE (see 8.2 Clinical Trial Adverse Reactions, Table 2, 8.3 Less Common Clinical Trial Adverse Reactions, Cardiac disorders, and 8.3 Less Common Clinical Trial Adverse Reactions, Vascular disorders).

Driving and Operating Machinery

Some patients may experience dizziness, drowsiness, insomnia, visual disturbances, vertigo, or depression with the use of NABUMETONE (see Neurologic). Therefore, patients should exercise caution in carrying out potentially hazardous activities that require alertness.

Endocrine and Metabolism

Corticosteroids: NABUMETONE 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 9.4 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. Healthcare professionals 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 7.1.4 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.

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.

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.

Healthcare professionals 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 or perforation occur, 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 times 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 9.4 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.

Gastrointestinal adverse events were frequently reported with the use of NABUMETONE (see 8.2 Clinical Trial Adverse Reactions, Table 2, 8.3 Less Common Clinical Trial Adverse Reactions, Gastrointestinal disorders, and 8.3 Less Common Clinical Trial Adverse Reactions, Metabolism and nutrition disorders).

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 8.3 Less Common Clinical Trial Adverse Reactions, Reproductive system and breast disorders).

Hematologic

NSAIDs inhibiting prostaglandin biosynthesis 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 10.2 Pharmacodynamics).

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 (see 9.4 Drug-Drug Interactions, Oral Anticoagulants).

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 9.4 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.

Anemia, leucopenia, thrombocytopenia, granulocytopenia, and aplastic anemia were reported with the use of NABUMETONE (see 8.3 Less Common Clinical Trial Adverse Reactions, Blood and lymphatic system disorders).

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. 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.

Hepatic, biliary, and pancreatic adverse events were reported with the use of NABUMETONE (see 8.3 Less Common Clinical Trial Adverse Reactions, Hepatobiliary disorders and 8.3 Less Common Clinical Trial Adverse Reactions, Investigations).

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 NABUMETONE. 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.), NABUMETONE should be discontinued.

During long-term therapy, liver function tests should be monitored periodically. If there is a need to prescribe NABUMETONE 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, in such patients, the healthcare professional must be vigilant to the potential development of this complication.

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 8.3 Less Common Clinical Trial Adverse Reactions, Immune system disorders). 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 2 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 2 CONTRAINDICATIONS).

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

Monitoring and Laboratory Tests

The following testing or monitoring is recommended for various populations of patients taking NABUMETONE. This is not an exhaustive list.

Cardiovascular: Blood pressure should be monitored regularly (see 2 CONTRAINDICATIONS, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risk of CV Adverse Events, Cardiovascular and 9.4 Drug-Drug Interactions).

Hematology: Hemoglobin, hematocrit, red blood cells (RBCs), white blood cells (WBCs), and platelets should be checked in patients on long-term treatment with NABUMETONE. Concurrent therapy with anticoagulants requires close monitoring of the international normalized ratio (INR) (see Hematologic and 9.4 Drug-Drug Interactions).

Lithium plasma concentration (in case of lithium co-prescription) should be monitored (see 9.4 Drug-Drug Interactions, Lithium).

Hepatic: Serum transaminase and bilirubin should be monitored regularly during NABUMETONE treatment (see Hepatic/Biliary/Pancreatic).

Ophthalmologic: An ophthalmologic examination should be carried out at periodic intervals (see Ophthalmologic).

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 7.1.1 Pregnant Women). NABUMETONE is contraindicated for use in the third trimester of pregnancy (see 2 CONTRAINDICATIONS, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risk in Pregnancy, and 7.1.1 Pregnant women).

Renal: Serum creatinine, creatinine clearance, and serum urea should be monitored in patients during NABUMETONE treatment. Electrolytes including serum potassium should be monitored (see Renal and 9.4 Drug-Drug Interactions).

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 reactions, they should exercise caution in carrying out activities that require alertness.

Neurological adverse events were reported with the use of NABUMETONE (see 8.2 Clinical Trial Adverse Reactions, Table 2, 8.3 Less Common Clinical Trial Adverse Reactions, Nervous system disorders; 8.3 Less Common Clinical Trials Adverse Reactions, Psychiatric disorders, and 8.3 Less Common Clinical Trials Adverse Reactions, General disorders and administration site conditions).

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 2 CONTRAINDICATIONS - Coronary Artery Bypass Graft Surgery.

Psychiatric

Some patients may experience depression with the use of NSAIDs, such as NABUMETONE (see 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 impaired renal function, 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-MNA (the principal active metabolite of nabumetone), and dose reduction may be warranted (see 10.3 Pharmacokinetics, Renal insufficiency). NABUMETONE is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min or 0.5 mL/sec) (see 2 CONTRAINDICATIONS).

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

Advanced Renal Disease: See 2 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 7 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 2 CONTRAINDICATIONS).

Renal adverse events were reported with the use of NABUMETONE (see 8.3 Less Common Clinical Trial Adverse Reactions, Renal and urinary disorders, and 8.3 Less Common Clinical Trial Adverse Reactions, General disorders and administration site conditions).

Reproductive Health: Female and Male Potential

- **Fertility**

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.

- **Teratogenic Risk**

In animal studies, dystocia leading to maternal and fetal/neonatal death, delayed parturition, and reduced maternal weight gain were frequently observed (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology). Drugs of this class may cause dystocia and delayed parturition in pregnant animals (see 7.1.1 Pregnant Women).

Because of the known effect of drugs of this class on the human fetal cardiovascular system (closure of ductus arteriosus), use of NABUMETONE during the third trimester of pregnancy is contraindicated (see 2 CONTRAINDICATIONS).

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.

Skin

Serious skin reactions: Use of some NSAIDs, such as NABUMETONE, has 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 healthcare professional 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.

Skin adverse events and serious skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) were reported with the use of NABUMETONE (see 8.2 Clinical Trial Adverse Reactions, Table 2, and 8.3 Less Common Clinical Trial Adverse Reactions, Skin and subcutaneous tissue disorders).

7.1 Special Populations

7.1.1 Pregnant Women

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

Nabumetone and/or its active metabolites have been shown to cross the placental barrier of rats (see 10.3 Pharmacokinetics, Distribution).

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 2 CONTRAINDICATIONS and 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental 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.

7.1.2 Breast-feeding

There is no clinical trial experience with the use of nabumetone during breastfeeding. NABUMETONE is contraindicated in women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of NABUMETONE in pediatric patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 2 CONTRAINDICATIONS).

7.1.4 Geriatrics

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 (see 4.2 Recommended Dose and Dosage Adjustment, Geriatrics, 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Gastrointestinal, and 7 WARNINGS AND PRECAUTIONS, Renal).

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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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 (see Gastrointestinal).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 US clinical studies is presented below. Of the 1,677 patients who received nabumetone during US 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 2 - Adverse Events Reported in Long-term Follow-up with Nabumetone

	Nabumetone (%)
Cardiac Disorders	
Palpitations	1
Ear and labyrinth disorders	
Tinnitus	4
Eye Disorders	
Abnormal vision	2
Gastrointestinal disorders	
Diarrhea	14
Dyspepsia	13
Abdominal Pain	12
Nausea	9
Flatulence	6
Constipation	4
Dry Mouth	2
Gastritis	1
Vomiting	1
Melena	1

Table 2 - Adverse Events Reported in Long-term Follow-up with Nabumetone	
	Nabumetone (%)
General disorders and administration site conditions	
Fatigue	2
Increased sweating	1
Investigations	
Positive Stool Guaiac	2
Nervous system disorders	
Headache	8
Dizziness	6
Insomnia	3
Somnolence	2
Psychiatric disorders	
Nervousness	1
Respiratory, thoracic and mediastinal disorders	
Dyspnea	1
Skin and subcutaneous tissue disorders	
Rash	7
Pruritus	4
Vascular disorders	
Hypertension	1.7

8.3 Less Common Clinical Trial Adverse Reactions

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.

Blood and lymphatic system disorders: Anemia (0.5%), leucopenia (0.4%), thrombocytopenia (0.2%), granulocytopenia (0.1%), aplastic anemia (<0.01).

Cardiac disorders: Syncope (0.3%), angina (0.1%), arrhythmia (0.1%), myocardial infarction (0.1%).

Gastrointestinal disorders: Eructation (0.7%), gastroenteritis (0.7%), rectal bleeding (0.5%), gastric ulcer (0.4%), duodenal ulcer (0.4%), stomatitis (0.4%), dysphagia (0.3%), glossitis (0.2%), gingivitis (0.1%), duodenitis (0.1%), gastrointestinal bleeding (0.1%), taste disorder (0.2%).

General disorders and administration site conditions: Malaise (0.8%), asthenia (0.7%), edema (0.7%), fever (0.4%), chills (0.2%).

Hepatobiliary disorders: Cholestatic jaundice (≤0.01), gallstones (≤0.01%), liver function abnormalities (0.5%), jaundice (≤0.01%), pancreatitis (0.1%), hepatic failure (≤0.01%).

Immune system disorders: Angioneurotic edema (<0.01%), anaphylactoid reaction (<0.01%), anaphylaxis (<0.01%).

Investigations: Weight gain (0.7%), weight loss (0.4%), elevated liver function tests (≤0.01).

Metabolism and nutrition disorders: Anorexia (0.7%), increased appetite (0.2%), hyperglycemia (0.2%), hypokalemia (0.1%).

Nervous system disorders: Vertigo (0.9%), paresthesia (0.8%), confusion (0.3%), agitation (0.1%), tremor (0.1%).

Psychiatric disorders: Depression (0.9%), anxiety (0.4%), nightmares (<0.01%).

Renal and urinary disorders: Dysuria (0.7%), albuminuria (0.5%), bilirubinuria (0.1%), hematuria (0.4%), renal stones (0.2%), hyperuricemia (0.1%), azotemia (0.1%), interstitial nephritis (≤0.01%), nephrotic syndrome (≤0.01%), renal failure (≤0.01%).

Reproductive system and breast disorders: Impotence (0.2%), vaginal bleeding (≤0.01%).

Respiratory, thoracic and mediastinal disorders: Cough (0.6%), asthma (0.4%), eosinophilic pneumonia (≤0.01%), hypersensitivity pneumonitis (≤0.01%), interstitial pneumonitis (≤0.01%).

Skin and subcutaneous tissue disorders: 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%).

Vascular disorders: Thrombophlebitis (0.2%), vasculitis (0.1%).

8.5 Post-Market Adverse Reactions

Information is not available.

9 DRUG INTERACTIONS

9.3 Drug-Behavioural Interactions

There are no specific studies about the effects on the ability to drive vehicles and to use

machinery. Patients who experience visual disturbances or other central nervous system disturbances should refrain from these activities (see Driving and Operating Machinery).

No specific drug interaction studies have been conducted with nabumetone and alcohol. Concurrent use of alcohol with a NSAID may increase the risk of gastrointestinal side effects, including ulceration and hemorrhage (see Gastrointestinal).

9.4 Drug-Drug Interactions

The drugs listed in Table 3 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 - Established or Potential Drug-Drug Interactions

Proper/ Common name	Source of Evidence	Effect	Clinical comment
Acetylsalicylic acid (ASA) or other NSAIDs	T	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.	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.
Antacids	T	Concomitant administration of an aluminum-containing antacid had no significant effect on the bioavailability of 6-MNA.	

Proper/ Common name	Source of Evidence	Effect	Clinical comment
Anticoagulants e.g., Warfarin	C	Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increase the risk of GI adverse events such as ulceration and bleeding.	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 7 WARNINGS AND PRECAUTIONS – Hematologic - Anti-coagulants).
Anti-hypertensives e.g., Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin Receptor Blockers (ARBs), or Beta-Blockers (including propranolol)	T	NSAIDs may diminish the anti-hypertensive effect of ACE inhibitors, ARBs, or Beta-Blockers. 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 (see 7 WARNINGS AND PRECAUTIONS, Renal, Fluid and Electrolyte Balance).
Anti-platelet Agents (including ASA)	T	There is an increased risk of bleeding, via inhibition of platelet function, when antiplatelet agents are combined with NSAIDs, such as NABUMETONE (see 7 WARNINGS AND PRECAUTIONS – Hematologic - Anti-platelet Effects).	Monitor patients for signs of bleeding (see 7 WARNINGS AND PRECAUTIONS, Hematologic).

Proper/ Common name	Source of Evidence	Effect	Clinical comment
Cyclosporin	T	Increased risk of nephrotoxicity, particularly in elderly subjects. No specific drug interaction studies have been conducted with nabumetone and cyclosporin.	Monitor for signs of worsening renal function. Monitor for dosage adjustment.
Digoxin	T	NSAIDs may exacerbate cardiac failure, reduce GFR, and increase plasma glycoside levels.	Caution is advised, in particular in patients with renal impairment, since NSAIDs may reduce renal function and decrease renal clearance of cardiac glycosides. Digoxin levels should be monitored, and if necessary, a dosage adjustment made when administered concomitantly with NABUMETONE.
Diuretics e.g., Furosemide	T	Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce the effect of diuretics.	Patients taking diuretics are at greater risk of developing renal failure secondary to a decrease in renal blood flow caused by prostaglandin inhibition (see 7 WARNINGS AND PRECAUTIONS, Renal). Observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects.
Glucocorticoids	C	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.	Monitor patients, particularly those over 65 years of age, for signs of bleeding (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal).

Proper/ Common name	Source of Evidence	Effect	Clinical comment
Gold, d-penicillamine, and corticosteroids	CT	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.	
Lithium	T	Concurrent use of NSAIDs with lithium has 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	T	NSAIDs have been reported to decrease the tubular secretion of methotrexate and potentiate its toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction). Rare cases of fatal renal toxicity have occurred when methotrexate and NSAIDs are given concomitantly.	Caution should be used if NABUMETONE is administered concomitantly with methotrexate. Monitor patients for methotrexate toxicity.
Oral Contraceptives	T	No specific drug interaction studies have been conducted with nabumetone and oral contraceptives.	

Proper/ Common name	Source of Evidence	Effect	Clinical comment
Oral Hypoglycemics e.g., Tolbutamide	T	6-MNA is more than 99% bound to plasma proteins. Therefore, nabumetone may compete for binding sites with drugs such as oral hypoglycemic agents. No specific drug interaction studies have been conducted with nabumetone and oral hypoglycemic agents.	Patients should be monitored.
Paracetamol, cimetidine	CT	Concomitant administration of paracetamol or cimetidine did not affect the bioavailability of the principal circulating metabolite in volunteer subjects.	
Probenecid, aminoglycosides, or cholestyramine	T	No specific drug interaction studies have been conducted with nabumetone and probenecid, aminoglycosides, or cholestyramine.	
Protein-bound drugs	C	*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.	Patients should be monitored.

Proper/ Common name	Source of Evidence	Effect	Clinical comment
Selective Serotonin Reuptake Inhibitors (SSRIs)	T	Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and a NSAID may potentiate the risk of bleeding more than a NSAID alone. Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal ulceration and bleeding (see 7 WARNINGS AND PRECAUTIONS - Gastrointestinal).	Monitor for signs of bleeding.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 Pharmacodynamics

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.

Clinical

Double-blind studies of up to 6 months duration in rheumatoid arthritis and osteoarthritis have demonstrated that nabumetone at a dosage of 1 g/day 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 1 to 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 four times a day (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.

10.3 Pharmacokinetics

Table 4 - 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.
t_{max} = time to maximum observed concentration; $t_{½}$ = half-life; Cl_{ss}/F = apparent total body clearance after oral administration (at steady state); Vd_{ss}/F = volume of distribution at steady-state corrected for bioavailability

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 hour 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.

Nabumetone was well absorbed after oral administration to the rat, mouse, rabbit, and rhesus monkey. Absorption in dogs was variable.

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).

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 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.

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.

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.
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.

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

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.

Special Populations and Conditions

- **Geriatrics:** Steady-state plasma concentrations in elderly patients were generally higher than in young healthy subjects (see Table 4).

- **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.

11 STORAGE, STABILITY AND DISPOSAL

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.

NABUMETONE should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

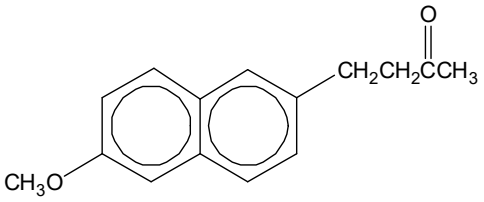
Drug Substance

Proper name: Nabumetone

Chemical name: 1) 2-butanone, 4-(6-methoxy-2-naphthalenyl)-;
2) 4-(6-methoxy-2-naphthy1)-butan-2-one

Molecular formula and molecular mass: $C_{15}H_{16}O_2$ and 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 78°C to 82°C.

14 CLINICAL TRIALS

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

14.2 Comparative Bioavailability Studies

A randomized, two-treatment, two-period, two-way, single-dose, crossover comparative bioavailability study of NABUMETONE 500 mg tablets (AA Pharma 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 who were included in the statistical analysis are presented in Table 5.

Table 5 - 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 (AA Pharma 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
CV% = high value of variability; AUC_T = Area under the curve from 0 hours to the last measureable concentration; AUC_I = Area under the curve extrapolated to infinity; T_{max} = time to maximum observed concentration; $T_{1/2}$ = half-life

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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.

Carcinogenicity

In two-year studies conducted in mice and rats, nabumetone had no statistically significant tumorigenic effect.

Genotoxicity

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).

Reproductive and Developmental Toxicology

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.

Special Toxicology

Information is not available.

Juvenile Toxicity

Information is not available.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrRELAFEN® Tablets, 500 mg and 750 mg, submission control 096377, Product Monograph, GlaxoSmithKline Inc. (OCT 31, 2005)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] NABUMETONE

Nabumetone Tablets BP

Read this carefully before you start taking **NABUMETONE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **NABUMETONE**.

Serious Warnings and Precautions

Heart and blood vessel problems:

- Nabumetone can cause heart and blood vessel problems like heart attack, stroke, blood clots, high blood pressure and heart failure. These can lead to death.
- The risk of having heart problems is higher if you take Nabumetone for long periods of time and / or at higher doses and / or in people who have heart disease.

Tell your healthcare professional if you have or had heart problems, high blood pressure or diabetes.

Stomach and intestine (gastrointestinal) problems:

- Nabumetone can cause stomach and intestine problems like ulcers, inflammation, bleeding, holes/perforation, blockage or pain.

Talk to your healthcare professional about any medical conditions you have and drugs you are taking.

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 healthcare professional.
- Medicines like NABUMETONE may cause harm to you and your baby. Your healthcare professional will need to closely monitor your health and that of your baby (including your amniotic fluid levels) if they prescribe NABUMETONE during this time.
- Tell your healthcare professional right away if you become pregnant, think you may be pregnant or want to get pregnant during your treatment with Nabumetone.

What is NABUMETONE used for?

NABUMETONE is used in adults to relieve the signs and symptoms of arthritis disorders such as:
- rheumatoid arthritis
- osteoarthritis

How does NABUMETONE work?

- NABUMETONE belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). It can reduce the chemicals produced by your body which cause pain and swelling.

NABUMETONE only treats the symptoms and relieves pain and inflammation as long as you take it. Nabumetone does not cure the illness or stop it from getting worse.

What are the ingredients in NABUMETONE?

Medicinal ingredients: Nabumetone
Non-medicinal ingredients: Croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, polyethylene glycol, sodium lauryl sulphate and titanium dioxide

NABUMETONE comes in the following dosage forms:

Tablet: 500 mg

Do not use NABUMETONE if:

- you are allergic to nabumetone or to any other ingredients in this medicine or the container.
- you have heart bypass surgery (planning to have or recently had).
- you have severe, uncontrolled heart failure.
- you have bleeding in the brain or other bleeding disorders.
- you are pregnant and in a later stage of pregnancy (28 weeks or later).
- you are currently breastfeeding (or planning to breastfeed).
- you have a history of asthma, hives, growths in your nose, sinus swelling or symptoms of an allergic reaction after taking acetylsalicylic acid (ASA) or other NSAIDs.
- you have active stomach or intestine ulcers.
- you have active bleeding from the stomach or gut.
- you have inflammatory bowel disease (Crohn’s Disease or Ulcerative Colitis).
- you have liver disease (active or severe).
- you have kidney disease (severe or worsening).
- you have high potassium in the blood.
- you are under 18 years old.
- you are taking other NSAIDs.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NABUMETONE. Talk about any health conditions or problems you may have, including if you:

- have high blood pressure, high cholesterol or diabetes
- Have or had heart attacks, chest pain, heart disease, stroke or heart failure
- have atherosclerosis. This is when fats and cholesterol build up in your arteries.
- have poor blood flow to your extremities (like your hands and feet)
- smoke or used to smoke
- have a stomach infection
- have liver or kidney problems, urine problems or are dehydrated
- have a history of ulcer or bleeding from the stomach or gut (small or large intestine)
- have other bleeding or blood problems
- drink a lot of alcohol
- have previously had ulcers, diverticulosis, ulcerative colitis or Crohn's disease or any other serious gastrointestinal problem
- are on special diet, such as low sodium diet.
- have immune system problems

Other warnings you should know about:

NABUMETONE may cause serious side effects, including:

- **Blood and bleeding problems:**
  - NABUMETONE can cause blood problems, bleeding and prolonged bleeding.
  - Taking NABUMETONE with the following medicines can increase the risk of bleeding:
    - Anticoagulants (prevent blood clots), corticosteroids (anti-inflammatory) or antidepressants like selective serotonin reuptake inhibitors (SSRIs).

- **Allergic reactions:** In rare cases, serious or life-threatening allergic reactions have been reported with some NSAIDs, such as NABUMETONE. See the Serious Side Effects and What To Do About Them table below for more information on symptoms.

  Serious Skin Reactions: In rare cases, serious, fatal, or life-threatening skin reactions have been reported with some NSAIDs such as NABUMETONE. These skin problems most often happen during the first month of treatment. Tell your healthcare professional immediately if you notice any changes in your skin both during and after treatment.

  NABUMETONE might cause you to become more sensitive to sunlight. Sunlight or sun lamps may cause sunburn, skin blisters, skin rash, redness, itching or discolouration, or vision changes. If you have a reaction from the sun, talk to your healthcare professional.

Check-ups and testing: You will have regular visits with your healthcare professional during your treatment with NABUMETONE to monitor your health. They will:

- Check your blood pressure.
- Do blood tests to check your liver, kidney and blood health.
- Check your eyes. Nabumetone can cause blurred or reduced vision.

Surgery: Tell any doctor, dentist, pharmacist or healthcare professional that you see, that you are taking this medicine. This is especially important if you are planning to have heart surgery.

Driving and Using Machines: NABUMETONE may cause eye or nervous system problems. This includes drowsiness, trouble sleeping, blurred, vision, spinning or dizziness (vertigo), hearing problems or depression. Be careful about driving or doing activities that require you to be alert. If you become drowsy, dizzy or light-headed after taking NABUMETONE, do NOT drive or operate machinery.

Fertility in women: NABUMETONE may affect your fertility. This means that it may be difficult for you to have a child. If you have trouble having a child, you might need to stop taking NABUMETONE. Talk to your healthcare professional if you have questions about this.

Adults (65 years and older): side effects like gastrointestinal problems may happen more often. Your healthcare professional might start you with a lower dose of NABUMETONE. They will monitor your health during and after treatment.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with NABUMETONE:

- Acetylsalicylic Acid (ASA) or other NSAIDs used to treat pain, fever and inflammation, like:
  - celecoxib, diclofenac, ibuprofen, naproxen
- Antacids used to treat symptoms of excess stomach acid
- Medicines used to treat depression (antidepressants) like citalopram, fluoxetine, paroxetine, sertraline, lithium
- Medicines used to treat high blood pressure like enalapril, ramipril, propranolol, candesartan, irbesartan
- Medicines used as blood thinners or to prevent blood clots like warfarin, ASA, clopidogrel
- Corticosteroids (including glucocorticoids such as prednisone) used to treat inflammation
- Medicines used to lower the risk of organ rejection, like cyclosporin
- Digoxin used to treat heart problems
- Medicines used to lower extra fluid levels (diuretics), like furosemide, hydrochlorothiazide
- A medicine used to treat different cancers called methotrexate
- Medicines used to treat diabetes including sulphonylurea, chlorpropamide and tolbutamide
- Medicines used to treat bacterial infections (antibiotics) like sulphonamide

- Alcohol

How to take NABUMETONE:

- Take NABUMETONE exactly as your healthcare professional has told you. They should recommend the lowest dose possible for your treatment for the shortest time needed.

- Take right after a meal or with food or milk to avoid an upset stomach. Take tablets at about the same time each day. Swallow tablets whole. Do not crush or chew tablets.

- **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.**

- **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 healthcare professional recommends.** 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 taking NABUMETONE for more than 7 days, see your healthcare professional regularly. They will check if Nabumetone is working for you and if it is causing you any side effects.

Usual dose: 1000 mg once per day

You may receive a lower dose if you have kidney or liver problems. During treatment, your healthcare professional may decide to increase your dose. This will depend on how you respond to the treatment. Your healthcare professional will tell you how to take this different dose.

Your healthcare professional will decide on the right dose for you. This will be based on your condition. Your healthcare professional may change your dose, stop your treatment for a period of time or recommend that you stop taking NABUMETONE completely. This may happen if you:

- you have serious side effects, or
- your disease gets worse.

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.

Missed Dose:

- If you miss a dose of Nabumetone, take it as soon as you remember.
- If it is close to the time of your next dose, skip the missed dose. Take your next dose at the usual time.
- Do not take 2 doses at the same time to make up for a missed dose.

What are possible side effects from using NABUMETONE?

These are not all the possible side effects you may have when taking NABUMETONE. If you experience any side effects not listed here, tell your healthcare professional.

- Nausea, vomiting, diarrhea, constipation, heartburn, abdominal pain, indigestion, feeling gassy, burping
- Swelling and redness on the inside of the mouth or tongue
- Trouble swallowing
- Headache, dizziness, trouble sleeping
- Weakness
- Feeling of burning or prickling in the hands, arms, legs or feet
- Taste disorder, dry mouth
- Fatigue, drowsiness
- Increased sweating
- Confusion, nervousness
- Shortness of breath
- Skin rash
- Problems with your period (women)
- Trouble getting and keeping an erection (men)
- Hair loss
- Generally feeling unwell

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Gastrointestinal (GI) problems (bleeding, blockage, holes, ulcers or inflammation in your GI tract): blood in vomit, black tarry or bloody stool, dizziness, stomach pain, bloating,		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
loss of appetite, weight loss, nausea, vomiting, constipation or diarrhea, chills or fever			
COMMON			
Hypertension (high blood pressure): fatigue, dizziness or fainting, chest pain	✓		
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat.			✓
Coronary artery disease (condition where the heart muscle does not get enough blood and nutrients): chest pain, shortness of breath, can lead to heart attack			✓
Palpitations: heartbeat that is fast, fluttering or pounding	✓		
Tinnitus (hearing problems): includes ringing, buzzing, clicking or hissing in ears, loss of hearing		✓	
Eye problems: Blurred vision, or any visual disturbance			✓
UNCOMMON			
Liver problems (including hepatitis, liver failure, cholestasis): yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
tiredness			
Anaphylaxis / hypersensitivity (severe allergic reactions): sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat, swelling or anaphylactic reaction / shock			✓
Vertigo (a sense of severe spinning dizziness, lightheadedness)		✓	
Kidney disorder / problems (including kidney failure): nausea, vomiting, fever, swelling of extremities, fatigue, thirst, dry skin, irritability, dark urine, increased or decreased urine output, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, mental status changes (drowsiness, confusion, coma)		✓	
Depression (sad mood that will not go away): difficulty sleeping or sleeping too much, changes in appetite or weight, reduced sex drive and thoughts of death or suicide.		✓	
Lung problems, asthma: increased shortness of breath, wheezing, difficulty breathing, cough and chest tightness, irregular heartbeat			✓
Blood problems (low white and/or red blood cell or platelet count): feeling tired or weak, pale skin, bruising or bleeding for longer than usual if you hurt yourself, fever, chills		✓	
UKNOWN FREQUENCY			

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Stroke (bleeding or blood clot in the brain): sudden numbness, weakness or tingling of the face, arm, or leg, particularly on one side of the body, sudden headache, blurry vision, difficulty swallowing or speaking, or lethargy, dizziness, fainting, vomiting, trouble understanding, trouble with walking and loss of balance			✓
Congestive heart failure (heart does not pump blood as well as it should): shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise)			✓
Aseptic meningitis (inflammation of the protective lining of the brain that is not caused by infection): severe headaches, stiff neck, nausea and vomiting, fever or clouding of consciousness		✓	
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			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
dark urine			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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.

Storage:

Store at room temperature (15 to 30°C). Store in a dry place and in the original container provided by the pharmacy.

Do NOT keep expired medicine or medicine you no longer need. Return these to your pharmacist.

Keep out of reach and sight of children.

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 Patient Medication Information by visiting the Health Canada website

(https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.aapharma.ca/en/), or by calling 1-877-998-9097.

This leaflet was prepared by

AA Pharma Inc.
1165 Creditstone Road, Unit #1
Vaughan, Ontario
L4K 4N7

Last Revised: MAR 24, 2023