PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]ARTHROTEC® 50

diclofenac sodium and misoprostol enteric-coated tablets

50 mg diclofenac/200 mcg misoprostol, Oral

[Pr]ARTHROTEC® 75

diclofenac sodium and misoprostol enteric-coated tablets

75 mg diclofenac/200 mcg misoprostol, Oral

NSAID with a Mucosal Protective Agent

Pfizer Canada ULC

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Kirkland, QC H9J 2M5

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RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	02/2022
3 SERIOUS WARNINGS AND PRECAUTIONS BOX	02/2022
7 WARNINGS AND PRECAUTIONS, Skin	02/2022
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7 WARNING AND PRECAUTIONS, 7.1.1 pregnant women	02/2022

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ARTHROTEC (diclofenac sodium and misoprostol) is indicated for:

- Acute and chronic use in the relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

Throughout this document, the term NSAIDs refers to both non-selective NSAIDs and selective COX-2 inhibitor NSAIDs, unless otherwise indicated.

Diclofenac, particularly at higher doses, is associated with an increased risk of serious cardiovascular related adverse events that is comparable to COX-2 inhibitors and high dose ibuprofen. For patients with pre-existing risk factors for cardiovascular disease (including ischemic heart disease, cerebrovascular disease and/or congestive heart failure NYHA II-IV) other management strategies that do not include NSAIDs, particularly COX-2 inhibitors, ibuprofen and diclofenac, should be considered first (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

For patients with increased risk of developing GI adverse events other management strategies that do not include NSAIDs should be considered first (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

Use of ARTHROTEC 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 7 WARNINGS AND PRECAUTIONS).

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

ARTHROTEC, 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): Arthrotec is contraindicated in the pediatric population (see **2 CONTRAINDICATIONS; 7.1.3 Pediatrics**).

1.2 Geriatrics

Geriatrics (> 65 years of age): Evidence from clinical studies and post-market experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see **7.1.4 Geriatrics**).

2 CONTRAINDICATIONS

ARTHROTEC (diclofenac sodium plus misoprostol) is contraindicated in:

- The peri-operative setting of coronary artery bypass graft surgery (CABG). Although ARTHROTEC 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.
- The women who are pregnant, or in whom pregnancy has not been excluded. Women of

childbearing potential should be fully counseled about misoprostol's abortifacient potential and the importance of effective contraception (oral contraceptive or intrauterine device) and prevention of pregnancy while undergoing treatment (see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX** and **7.1.1 Pregnant Women**).

- Prolonged parturition.
- 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 7 WARNINGS AND PRECAUTIONS, Cardiovascular).
- Known or suspected hypersensitivity to diclofenac sodium, misoprostol, other NSAIDs, or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.
- History of asthma, urticaria, or allergic-type reactions after taking 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. 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. The potential for cross-reactivity between different NSAIDs must be kept in mind (see **7 WARNINGS AND PRECAUTIONS – Immune**).
- Patients with active gastric / duodenal / peptic ulcer, active gastrointestinal bleeding, a history of recurrent ulceration or active inflammatory disease of the gastrointestinal system.
- Cerebrovascular bleeding or other bleeding disorders.
- Inflammatory bowel disease.
- Significant hepatic impairment or active liver disease (see **7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).
- Severely impaired or deteriorating renal function (creatinine clearance <30 mL/min or 0.5 mL/sec). 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.
- Diclofenac is contraindicated for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects (see **9 DRUG INTERACTIONS**).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions
• **Risk of Cardiovascular (CV) Adverse Events: Cardiovascular Disease (including Ischemic Heart**

Disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV) (see 7 WARNINGS AND PRECAUTIONS – Cardiovascular)

- **Diclofenac is associated with an increased risk of serious cardiovascular (CV) thrombotic events (such as myocardial infarction and stroke), which can be fatal. The increased risk is comparable to COX-2 inhibitors and high-dose ibuprofen. An increased risk of CV serious thrombotic events may occur early in the treatment and become higher with the duration of treatment. The risk may increase with the dose. Patients with CV disease or CV risk factors may be at greater risk (See 7 WARNINGS AND PRECAUTIONS – Cardiovascular).**
- For patients with a high risk of developing an adverse CV event, other management strategies that do NOT include NSAIDs, particularly COX-2 inhibitors, ibuprofen and diclofenac, 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.**
- **Treatment with ARTHROTEC is not recommended in patients with pre-existing cardiovascular disease (congestive heart failure NYHA -II-IV, ischemic heart disease, peripheral arterial disease) cerebrovascular disease, uncontrolled hypertension or patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidemia, diabetes mellitus and smoking). These patients should be treated with ARTHROTEC only after careful consideration.**
- **Use of NSAIDs, such as ARTHROTEC, 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*).**
- **Risk of Gastrointestinal (GI) Adverse Events (see 7 WARNINGS AND PRECAUTIONS – Gastrointestinal).**
- **Use of NSAIDS, such as ARTHROTEC, is associated with an increased incidence of gastrointestinal adverse events (such as peptic/duodenal ulceration, perforation, obstruction and gastrointestinal bleeding).**
- **Risk in Pregnancy: ARTHROTEC is CONTRAINDICATED for use in women who are pregnant (all trimesters), or in whom pregnancy has not been excluded and in prolonged parturition. Misoprostol administration to pregnant women induces uterine contractions and is associated with abortion, premature birth, birth defects and fetal death (see 2 CONTRAINDICATIONS and 8.5 Post-Market Adverse Drug Reactions).**

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Use of ARTHROTEC 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 **7 WARNINGS AND PRECAUTIONS**).

- **In elderly patients**: the dosage should be reduced to the lowest dose that will provide control of symptoms, adjusted when necessary, and closely supervised (see **7.1.4 Geriatrics**).
- **Cardiovascular disease or cardiovascular risk factors**: Treatment with ARTHROTEC (diclofenac sodium) is not recommended in patients with pre-existing cardiovascular disease (congestive heart

failure NYHA II-IV, ischemic heart disease, peripheral arterial disease), cerebrovascular disease, uncontrolled hypertension, or patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidemia, diabetes mellitus and smoking). These patients should be treated with ARTHROTEC only after careful consideration (see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**).

- ***Renal Insufficiency:*** In patients with mild to moderate renal insufficiency, the lowest dose of ARTHROTEC should be considered, and patients should be monitored closely (see **7 WARNINGS AND PRECAUTIONS – Renal**). ARTHROTEC is contraindicated in patients with severe renal impairment (estimated creatinine clearance < 30 mL/min or 0.5mL/sec) (see **2 CONTRAINDICATIONS**).
- ***Hepatic Insufficiency:*** If ARTHROTEC must be used in patients with mild to moderate hepatic impairment, these patients must be closely monitored (see **7 WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic**). ARTHROTEC is contraindicated in patients with significant hepatic impairment or active liver disease (see **2 CONTRAINDICATIONS**). Diclofenac metabolism is predominantly mediated via cytochrome P450 CYP 2C9 in the liver. Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates should be administered diclofenac with caution (see **9.2 Drug Interactions Overview**). Caution should be exercised when prescribing ARTHROTEC with concomitant drugs that are known to be potentially hepatotoxic (e.g. antibiotics, anti-epileptics).

4.2 Recommended Dose and Dosage Adjustment

- Use of ARTHROTEC should be limited to the lowest effective dose and the shortest possible duration of treatment in every patient (see **7 WARNINGS AND PRECAUTIONS**).
- The recommended daily oral dose of ARTHROTEC (diclofenac sodium plus misoprostol) for treating the signs and symptoms of rheumatoid arthritis and osteoarthritis is 100 mg administered as two divided doses (50 mg twice per day) (see **7 WARNINGS AND PRECAUTIONS – Cardiovascular**).
- The recommended maximum daily dose is 100 mg.

4.4 Administration

ARTHROTEC should be taken **immediately after a meal or with food or milk** and the tablets should be swallowed whole.

4.5 Missed Dose

If a dose of ARTHROTEC is missed, the next dose should be taken at the regular time. The dose should not be doubled.

5 OVERDOSAGE

Diclofenac Sodium

There is no specific antidote for diclofenac. In cases of overdosage, absorption should be prevented as soon as possible by means of induction of vomiting, gastric lavage or treatment with activated charcoal.

Supportive and symptomatic treatment should be given for complications such as drowsiness, confusion, general hypotonia, hypotension, renal failure, convulsions, gastrointestinal irritation and respiratory depression. Measures to accelerate elimination (forced diuresis, hemoperfusion, dialysis)

may be considered, but may be of limited use because of the high protein-binding and extensive metabolism (diclofenac 99% protein bound and misoprostol acid less than 90% protein bound).

Misoprostol

The toxic dose of misoprostol in humans has not been determined. Cumulative total daily doses of 1,600 mcg have been tolerated with only symptoms of gastrointestinal discomfort being reported.

Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnea, abdominal pain, diarrhea, fever, palpitations, hypotension, or bradycardia. Symptoms should be treated with supportive therapy.

It is not known if misoprostol acid is dialyzable. However, because misoprostol is metabolized like a fatty acid, it is unlikely that dialysis would be appropriate treatment for overdosage.

The use of oral activated charcoal may help to reduce the absorption of diclofenac and misoprostol.

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 /50 mg diclofenac sodium and 200 mcg misoprostol tablet /75 mg diclofenac sodium and 200 mcg misoprostol	Colloidal Silicon Dioxide, Corn Starch, Crospovidone, Hydrogenated Castor Oil, Hypromellose, Lactose, Magnesium Stearate, Methacrylic Acid Copolymer, Microcrystalline Cellulose, Povidone K-30, Sodium Hydroxide, Talc, Triethyl Citrate

ARTHROTEC 50 tablets (diclofenac sodium plus misoprostol) are white to off-white, round biconvex tablets, engraved "SEARLE" over "1411" on one side, 4 x "A" around the circumference of the reverse side with a "50" in the middle. Each tablet has an enteric-coated core containing 50 mg diclofenac sodium, surrounded by an outer mantle containing 200 mcg misoprostol. Bottles of 250.

ARTHROTEC 75 tablets are white to off-white, round and biconvex, engraved "SEARLE" over "1421" on one side, 4 x "A" around the circumference of the reverse side with a "75" in the middle. Each tablet has an enteric-coated core containing 75 mg diclofenac sodium, surrounded by an outer mantle containing 200 mcg misoprostol. Bottles of 250.

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.

The use of diclofenac/misoprostol 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 including gastrointestinal ulcers and bleeding (see **9.4 Drug-Drug Interactions – *Acetylsalicylic acid (ASA) or other NSAIDs***).

In common with other anti-inflammatory drugs, ARTHROTEC may mask the usual signs of infection, such as fever.

Carcinogenesis and Mutagenesis

(See **16. NON-CLINICAL TOXICOLOGY**)

Cardiovascular

Diclofenac is associated with an increased risk of serious cardiovascular (CV) thrombotic events (such as myocardial infarction and stroke), which can be fatal. The increased risk is comparable to COX-2 inhibitors and high-dose ibuprofen. An increased risk of CV serious thrombotic events may occur early in the treatment and become higher with the duration of treatment. The risk may increase with the dose. Patients with CV disease or CV risk factors may be at greater risk (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).

Meta-analyses of randomized clinical trials comparing several different NSAIDs suggest that diclofenac, particularly at higher doses, is associated with an increased risk of cardiovascular adverse events that is comparable to COX-2 inhibitors and high dose ibuprofen. Large population-based observational studies conducted in the general population also support these findings. Some observational studies showed that the increased risk of the CV thrombotic events began as early as the first weeks of treatment. Such risk increased with duration of NSAID treatment. The relative increase in risk of serious CV thrombotic events during NSAID treatment appears to be similar in patients with or without CV disease or CV risk factors. However, patients with CV disease or CV risk factors during the treatment had a higher absolute risk of serious CV thrombotic events due to their increased baseline rate.

As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the lowest effective daily dose should be used for the shortest duration possible. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

Patients should remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a physician immediately in case of such an event.

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

Use of NSAIDs, such as ARTHROTEC, 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***).

Caution should be exercised in prescribing ARTHROTEC 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 II-IV)**
- **Ischemic heart disease**
- **Peripheral Arterial Disease**
- **Smoking**
- **Creatinine Clearance < 60 mL/min or 1 mL/sec**
- **Acute myocardial infarction, history of myocardial infarction and/or angina**
- **Stroke, cerebrovascular accident, transient ischemic attacks, and/or amaurosis fugax**

If needed, these patients should be treated only after careful consideration (See **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**).

Driving and Operating Machinery

Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking ARTHROTEC should refrain from driving or using machines.

Endocrine and Metabolism

With nonsteroidal anti-inflammatory treatment there is a potential risk of hyperkalemia, particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patients; or in patients receiving concomitant therapy with beta-adrenergic blockers, angiotensin converting enzyme inhibitors or some diuretics. Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients who are at risk.

Corticosteroids: ARTHROTEC (diclofenac sodium plus misoprostol) 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

The presence of misoprostol in the product may protect against the mucosal damaging effects of the other component, diclofenac.

However, serious GI toxicity, such as peptic/duodenal ulceration, inflammation, perforation, obstruction and gastrointestinal bleeding, sometimes severe and occasionally fatal can occur at any time, with or without symptoms in patients treated with NSAIDs including ARTHROTEC (diclofenac sodium plus misoprostol). NSAIDs, including ARTHROTEC, should be used with caution in patients with a history of, or

active, GI disease, such as ulceration, bleeding, or inflammatory conditions. 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***).

Minor upper GI problems, such as dyspepsia, commonly occur at any time. Physicians should remain alert for ulceration and bleeding in patients treated with nonsteroidal anti-inflammatory drugs, even in the absence of previous GI tract symptoms.

Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and instruct them to discontinue using ARTHROTEC and seek emergency medical attention if they experience any such symptoms. 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.

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 3-6 months, and in about 2-4% 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.

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

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

No studies, to date, have identified any group of patients not at risk of developing ulceration and bleeding. Studies to date show that all NSAIDs can cause GI tract adverse events. Although existing data do not clearly identify differences in risk between various NSAIDs, this may be shown in the future.

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 an NSAID. Some cases have become severe on continued treatment. Should urinary symptoms occur, in the absence of an alternate explanation, treatment with ARTHROTEC (diclofenac sodium plus misoprostol) must be stopped to ascertain if symptoms disappear. This should be done before any

urological investigations or treatments are carried out.

Post-menopausal vaginal bleeding may be related to ARTHROTEC administration. If this occurs, diagnostic workup should be undertaken to rule out gynecological pathology (see **8 ADVERSE DRUG REACTIONS**).

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 monitored when ARTHROTEC is administered.

Anti-coagulants: The concomitant use of NSAIDs, including diclofenac/misoprostol, with anticoagulants increases the risk of GI and non-GI bleeding and should be given with caution. Concurrent therapy of ARTHROTEC with anticoagulants requires close monitoring of the international normalized ratio (INR) (see **9 DRUG INTERACTIONS**).

Even with therapeutic INR monitoring, increased bleeding may occur.

Anti-platelet Effects: NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike acetylsalicyclic acid (ASA), their effect on platelet function is quantitatively less, or of shorter duration, and is reversible. Misoprostol does not exacerbate the effects of diclofenac on platelet activity.

ARTHROTEC 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 ARTHROTEC with low dose ASA increases the risk of GI ulceration and associated complications.

Blood dyscrasias: Cases of agranulocytosis and hemolytic anemia, some serious, were identified in patients taking diclofenac sodium or diclofenac/misoprostol.

Other blood dyscrasias (such as neutropenia, leucopenia, thrombocytopenia, aplastic anemia) associated with the use of NSAIDs are rare, but could occur with severe consequences.

Anemia is sometimes seen in patients receiving NSAIDs, including ARTHROTEC. 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 ARTHROTEC, should have their haemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss.

Hepatic/Biliary/Pancreatic

As with other NSAIDs, including ARTHROTEC, borderline elevations of one or more liver function 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. In clinical trials of 4 to 12 weeks duration, clinically significant (>3 times the upper limit of normal) elevations of SGPT (ALT) and/or SGOT (AST), were observed in 2.5% or less of patients who received diclofenac/misoprostol or diclofenac/placebo. In a large trial where patients received diclofenac for a mean of 18 months, ALT/AST elevations >3xULN were observed in 3.1% of patients and elevations >5xULN were observed in 1.3% of patients. ALT/AST elevations usually occur within 1-6 months. However, clinically important liver events,

resulting in hospitalization, occurred at various times during the study, and not necessarily early in the course of therapy. Furthermore, more meaningful elevations in transaminases were detected before patients became symptomatic due to routine testing during the trial (see **7 Warnings and Precautions - Monitoring and Laboratory testing**).

In post-marketing reports of patients receiving diclofenac, cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first 2 months of therapy, but can occur at any time during the treatment. 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 more severe hepatic reaction while on therapy with this drug. Post-marketing surveillance has reported cases of severe hepatic reactions including jaundice, fulminant hepatitis with and without jaundice, liver necrosis and hepatic failure. Some of these cases have resulted in fatalities or liver transplantation.

Physicians should measure transaminases periodically in patients receiving ARTHROTEC because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. Severe hepatic reactions can occur at any time during treatment with diclofenac. Although such reactions are rare, if abnormal liver function 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, rash, etc.), this drug should be discontinued immediately.

To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g. nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and «flu-like» symptoms), and the appropriate action patients should take if these signs and symptoms appear. Use of ARTHROTEC is contraindicated in patients with significant hepatic impairment or active liver disease. If there is a need to prescribe this drug in the presence of all other patients with liver impairment, it must be done under strict observation.

Caution is advised when using ARTHROTEC in patients with hepatic porphyria, since ARTHROTEC may trigger an attack.

Immune

Anaphylactoid Reactions: As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to ARTHROTEC. In post-marketing experience, rare cases of anaphylactic/anaphylactoid reactions and angioedema have been reported in patients receiving ARTHROTEC. ARTHROTEC 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: ARTHROTEC 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.

Infection

ARTHROTEC, in common with other NSAIDs, may mask signs and symptoms of an underlying infections 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. Therefore, in such patients, the health care provider must be vigilant to the development of this complication.

Monitoring and Laboratory Tests

Cardiovascular (Hypertension)**:** Blood pressure should be monitored regularly during therapy with ARTHROTEC.

Hematologic**:** Patients on long-term treatment with NSAIDs, including ARTHROTEC, should have their hemoglobin, hematocrit, red blood cells, white blood cells, and platelets checked if they exhibit any signs or symptoms of anemia or blood loss or blood dyscrasia.

Concurrent therapy of ARTHROTEC with warfarin requires close monitoring of the international normalized ratio (INR). See **9 DRUG INTERACTIONS**.

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

Hepatic: Hepatic functions (e.g. serum transaminases, bilirubin) should be performed within 4 to 8 weeks of starting therapy, and then monitored regularly during therapy with ARTHROTEC. Patient with symptoms and/or signs of liver dysfunction, or in whom an abnormal liver function test has occurred, their hepatic function (e.g. serum transaminases, bilirubin) should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with ARTHROTEC. If abnormal liver tests persist or worsen, ARTHROTEC should be discontinued.

Pregnancy*:* ARTHROTEC is contraindicated in all trimesters of pregnancy.

Ophthalmologic: Patients on long-term treatment with ARTHROTEC should have an ophthalmologic examination performed periodically, and if they experience blurred and/or diminished vision.

Renal: Renal function should be monitored in high-risk populations, such as the elderly, patients with advanced renal disease, patients with cardiovascular disease and diabetes mellitus, as well as in the setting of concomitant use of diuretics and ACE inhibitors (see **2 CONTRAINDICATIONS**). If abnormal renal tests persist or worsen, ARTHROTEC should be discontinued.

Electrolytes, including serum potassium, should be monitored periodically, 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, cyclosporine, or some diuretics.

Laboratory abnormalities included increased alkaline phosphatase, decreased hematocrit and elevated SGPT (ALT).

Persistently abnormal or worsening renal, hepatic or hematological test values should be followed up carefully since they may be related to therapy.

Neurologic

Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss, insomnia or depression with the use of NSAIDs such as ARTHROTEC. If patients experience these side effects, they should exercise caution in carrying out activities that require alertness.

Ophthalmologic

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

Peri-Operative Considerations

(See **2 CONTRAINDICATIONS**)

Psychiatric

Some patients may experience depression with the use of diclofenac (see **7 WARNINGS AND PRECAUTIONS – Neurologic**).

Renal

Long-term administration of nonsteroidal anti-inflammatory drugs 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 prerenal conditions leading to the 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 formation and may precipitate overt renal decompensation. 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, heart failure, cirrhosis, liver dysfunction, those taking angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, cyclosporin, diuretics, and the 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 demonstrated 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.

Diclofenac and its metabolites are eliminated primarily by the kidneys, therefore ARTHROTEC should be used with great caution in patients with impaired renal function. In these cases, utilization of lower doses of diclofenac should be considered and patients carefully monitored. Caution should be used when initiating treatment with NSAIDs, such as ARTHROTEC, in patients with dehydration. It is advisable to rehydrate patients first and then start therapy. The dose should be kept as low as possible and renal function should be monitored.

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 ARTHROTEC, 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 ARTHROTEC 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 ARTHROTEC, 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**).

Reproductive Health: Female and Male Potential

The use of ARTHROTEC, as with any drug known to inhibit cyclooxygenase/ prostaglandin synthesis, may impair fertility and is contraindicated in women attempting to conceive.

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 ARTHROTEC, have been associated with post-market cases of serious, fatal or otherwise life-threatening skin reactions, including:

- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- Stevens-Johnson syndrome (SJS)
- toxic epidermal necrolysis (TEN)
- generalized bullous fixed drug eruption (GBFDE)
- exfoliative dermatitis
- erythema multiforme.

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

DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection, and eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident.

ARTHROTEC may cause sensitivity to sunlight. Any exposure to sunlight or sunlamps may cause sunburn, skin blisters, skin rash, redness, itching or discolouration. Patients should be advised that if they experience any of these symptoms, they should discontinue their NSAID and contact their physician for assessment and advice, including which additional therapies to discontinue.

7.1 Special Populations

7.1.1 Pregnant Women

ARTHROTEC is CONTRAINDICATED for use in women who are **pregnant**, or in whom **pregnancy has not been excluded**. Misoprostol administration to pregnant women induces uterine contractions and is associated with abortion, premature birth, birth defects and fetal death. Misoprostol can cause uterine tetany and uterine rupture if administered to pregnant women beyond the eighth week of pregnancy

(see **2 CONTRAINDICATIONS** and **8.5 Post-Market Adverse Drug Reactions**).

ARTHROTEC is contraindicated for use during all trimesters of pregnancy due to the misoprostol component.

Published studies and post-marketing 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 post-marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or the embryo-foetal 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-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

7.1.2 Breast-feeding

Misoprostol is rapidly metabolised in the mother to misoprostol acid, which is biologically active and is excreted in breast milk. Diclofenac/misoprostol is contraindicated in nursing mothers because the excretion of misoprostol acid could cause undesirable effects such as diarrhea in nursing infants **(**see **2 CONTRAINDICATIONS**).

7.1.3 Pediatrics

Pediatrics (< 18 years of age): Arthrotec is contraindicated in the pediatric population (see **2 CONTRAINDICATIONS**).

7.1.4 Geriatrics

Patients older than 65 years and frail or debilitated patients are most 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 ulceration and bleeding (see **10 CLINICAL PHARMACOLOGY**). 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. As with any NSAID, the elderly are likely to tolerate adverse events less well than younger patients.

Diclofenac is known to be substantially excreted by the kidney, and the risk of toxic reactions to ARTHROTEC may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see **7 WARNINGS AND PRECAUTIONS – Renal**).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

Most fatal gastrointestinal events occur in the elderly or debilitated patients. Gastrointestinal adverse events can develop at any time in the course of the therapy.

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 may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

In clinical trials, 3549 arthritic patients have been treated with ARTHROTEC (diclofenac sodium plus misoprostol), 506 of whom received ARTHROTEC for more than one year. A total of 285 patients have been treated with ARTHROTEC 75 in clinical trials for a duration of up to 12 weeks.

Table 2 - Adverse reactions occurred with an incidence of 1% or greater with at least one of the ARTHROTEC or Diclofenac dosing regimens

	A50[1] BID N=391	A50[1] TID N=692	A50[1] BID/TID N=750	D50[2] BID/TID N=754	A75[3] BID* N=285	D75[4] BID* N=260
Body as a Whole:						
Influenza-Like Symptoms	1.0	0.6	2.0	1.5	1.1	2.3
Pain	0.5	1.0	0.7	0.8	4.2	1.9
Back Pain	0.8	0.6	1.2	1.1	3.2	3.5
Chest Pain	1.0	0.3	1.1	0.5	0.7	3.1
Fever	0.0	0.6	0.7	1.1	1.4	0.0
Asthenia	0.0	0.1	0.1	0.7	1.1	0.4
Myalgia	0.8	0.7	0.8	0.3	1.1	0.4
Arthralgia	0.0	0.7	0.3	0.3	2.8	3.5
Arthrosis	0.0	0.1	0.3	0.0	1.4	1.2
Cardiovascular:						
Hypertension	0.0	0.5	0.0	0.1	1.1	2.3
Edema	0.8	0.7	0.0	0.3	1.1	1.2

Dependent Edema	0.0	0.3	0.4	0.5	1.1	0.4
Leg Edema	0.0	0.1	0.0	0.1	1.1	0.8

Nervous System disorders:						
Headache	9.2	6.4	7.3	9.2	12.3	15.8
Dizziness	2.6	2.0	3.5	5.3	3.9	4.2
Migraine	1.3	0.6	0.4	0.9	1.4	0.8
Paresthesia	0.3	0.3	0.7	0.7	1.1	0.4
Skin and subcutaneous disorders:						
Rash	0.8	1.4	1.5	1.1	2.1	3.5
Pruritis	1.0	0.4	1.2	0.9	2.1	1.9
Skin ulceration	0.0	0.0	0.1	0.0	1.1	0.4
Gastrointestinal:						
Abdominal Pain	19.4	19.4	23.2	19.5	24.6	24.2
Diarrhea	15.9	17.8	19.9	11.3	20.4	16.2
Dyspepsia	7.2	14.5	11.3	7.8	33.3	34.6
Nausea	10.2	10.0	11.7	6.5	14.0	9.2
Flatulence	6.1	8.7	8.0	3.1	18.2	9.2
Gastritis	2.8	2.3	3.6	6.8	7.4	13.1
Vomiting	2.6	3.3	3.1	1.3	3.9	5.4
Constipation	1.8	2.6	2.1	2.9	4.9	6.9
Eructation	2.6	0.3	2.0	0.8	2.1	0.4
	A50[1] BID N=391	**A50[1] TID N=692**	**A50[1] BID/TID N=750**	**D50[2] BID/TID N=754**	**A75[3] BID* N=285**	**D75[4] BID* N=260**
Esophagitis	0.8	1.7	1.1	0.8	3.9	1.9
Duodenitis	2.3	0.9	0.9	2.3	3.5	5.0
Gastroesophageal Reflux	0.0	1.0	0.4	1.7	1.1	1.2
Duodenal Ulcer	0.0	1.2	0.1	0.4	0.7	2.7
Gastric Ulcer	0.8	0.6	0.7	1.7	3.2	6.9
Tooth Disorder	0.3	0.6	0.0	0.0	1.1	0.8
Hepatobiliary disorders:						
SGPT (ALT) Increased	0.5	0.6	0.1	0.7	2.5	2.3
SGOT (AST) Increased	0.5	0.4	0.0	0.5	1.1	2.3
Psychiatric:						
Insomnia	1.3	0.4	0.9	1.2	2.5	1.9
Somnolence	0.8	0.6	0.7	0.9	1.1	0.8

Respiratory:						
Upper Respiratory Tract Infection	1.0	2.7	1.1	2.1	2.8	3.8
Pharyngitis	0.5	1.9	1.1	1.9	3.5	1.5
Rhinitis	0.8	2.6	0.3	0.9	3.2	4.2
Sinusitis	0.0	0.9	0.1	0.1	6.0	2.7
Coughing	0.3	1.2	0.4	1.2	1.8	3.5
Bronchitis	0.0	0.4	0.7	1.1	2.1	1.5
Dyspnea	0.3	0.4	0.4	0.7	1.4	0.4
Urogenital:						
Menorrhagia	0.9	0.6	1.3	0.0	0.0	0.5
Vaginitis	0.0	0.9	0.0	0.0	1.0	1.1
Perineal Pain, male	0.6	0.0	0.0	0.0	1.1	0.0

[1] A50 = Arthrotec 50

[2] D50 = Diclofenac 50mg

[3] A75 = Arthrotec 75

[4] D75 = Diclofenac 75 mg

*Patients must have experienced ulceration in order to enter study. This represents an extremely high-risk cohort

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

At the time of authorization, no clinical trials in the pediatric population have been conducted.

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse events were reported by 1% or less of the subjects receiving ARTHROTEC. Causal relationships between ARTHROTEC and these events have not been established but cannot be excluded.

Body as a Whole: hot flushes, malaise, rigors

Blood and lymphatic system disorders: leukopenia and thrombocytopenia

Cardiovascular: palpitation and syncope

Female reproductive disorders: menstrual disorder, intermenstrual bleeding, dysmenorrhea, leukorrhea, vaginal bleeding, breast pain and uterine cramping. (Post-menopausal vaginal bleeding may be related to ARTHROTEC administration. If this occurs, diagnostic workup should be undertaken to rule out gynecological pathology.)

Gastrointestinal: mouth dry, abdomen enlarged, esophageal ulceration, glossitis, hematemesis, hiccup and melena

Hepatobiliary disorders:	gall bladder disorder, bilirubinemia, abnormal hepatic function, LDH increased, and alkaline phosphatase increased, hepatitis.
Metabolism and nutrition disorders:	BUN increased, glycosuria and anorexia
Nervous System disorders:	concentration impaired, hypoesthesia, speech disorder and vertigo
Psychiatric disorders:	anxiety and depression
Renal and Urinary disorders:	dysuria and urine abnormal
Respiratory, thoracic and mediastinal disorders:	hyperventilation and sputum increased
Skin and subcutaneous tissue disorders:	angioedema, erythematous rash, sweating increased, urticaria and purpura
Special Senses	earache, eye pain, taste loss, taste abnormalities, tinnitus and vision abnormal

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

At the time of authorization, no clinical trials in the pediatric population have been conducted.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

See **9.7 Drug-Laboratory Test Interactions.**

8.5 Post-Market Adverse Reactions

Additional reports of serious adverse events temporally associated with ARTHROTEC during worldwide post-marketing experience are included below. Because these events are reported voluntary from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to ARTHROTEC exposure.

Body as a whole:	Death, fatigue, infection, sepsis
Immune System Disorders:	Allergic reactions including anaphylaxis and angioedema, Laryngeal/pharyngeal edema,
Cardiovascular Disorders:	Myocardial infarction, stroke, transient ischemic attack, cerebral hemorrhage, hypertension, cardiac failure, vasculitis arrhythmia, atrial fibrillation, congestive heart failure, hypotension, increased CPK, phlebitis, premature ventricular contractions, tachycardia
Nervous System disorders:	Meningitis aseptic, tremor, coma, convulsions, drowsiness, hyperesthesia, hypertonia, neuralgia

Psychiatric disorders:	Changes in mood, nightmares, confusion, disorientation, dream abnormalities, hallucinations, irritability, nervousness, paranoia, psychotic reaction
Skin and subcutaneous tissue disorders:	Cutaneous reactions (including rash, pruritus and bullous eruption), rare cases of mucocutaneous reactions, Edema, urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, dermatitis exfoliative acne, alopecia, bruising, pemphigoid reaction, photosensitivity, pruritus ani, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) and generalized bullous fixed drug eruption (GBFDE)
Gastrointestinal:	Pancreatitis, stomatitis and ulcerative stomatitis, gastrointestinal inflammation, gastrointestinal bleeding, gastrointestinal ulceration, gastrointestinal perforation, gastrointestinal neoplasm benign, heartburn, hemorrhoids, tenesmus, appetite changes, dry mouth, dysphagia, enteritis
Female reproductive diorsders:	Abnormal uterine contractions, uterine hemorrhage, uterine rupture/perforation, retained placenta, amniotic fluid embolism, incomplete abortion, premature birth, fetal death, and birth defects, female fertility decreased, reduction of amniotic fluid volume, reduction of fetal urine production
Blood and lymphatic system disorders:	Thrombocytopenia, platelet aggregation inhibition, hemolytic anemia, agranulocytosis, anemia, aplastic anemia, coagulation time increased, ecchymosis, eosinophilia, epistaxis, leukocytosis, lymphadenopathy, pancytopenia, pulmonary embolism, rectal bleeding, thrombocythemia, decreased hematocrit
Hepatobiliary disorders:	Hepatitis, hepatotoxicity, severe hepatic reactions including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure, with a fatal outcome or requiring liver transplantation (see **7 WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic**).
Special Senses:	Blurred vision, hearing impairment, amblyopia, conjunctivitis, diplopia, glaucoma, iritis, lacrimation abnormal, night blindness
Renal and urinary disorders:	Renal failure, interstitial nephritis, glomerulonephritis, glomerulonephritis membranous, glomerulonephritis minimal lesion, renal papillary necrosis, nephrotic syndrome, renal impairment, impotence, cystitis, hematuria, micturition frequency, nocturia, oliguria/polyuria, proteinuria, urinary tract infection,
Metabolism and nutrition disorders:	Fluid retention, alkaline phosphatase increased, dehydration, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypoglycemia, hyponatremia, periorbital edema, porphyria, weight changes
Respiratory, thoracic and mediastinal disorders:	Asthma, pneumonia, respiratory depression

Meta-analysis and pharmacoepidemiological data point towards an increased risk of arteriothrombotic events associated with the use of diclofenac, particularly at a high dose (see **3 SERIOUS WARNINGS AND**

PRECAUTIONS BOX).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Factors such as excess alcohol intake, smoking, and concomitant NSAID and oral steroid or anticoagulant use have been associated with increased risk of GI adverse events such as ulceration and bleeding. In laboratory studies, misoprostol has shown no significant effect on the cytochrome P450-linked hepatic mixed function oxidase system, and therefore should not affect the metabolism of theophylline, warfarin, benzodiazepines or other drugs normally metabolized by this system

Diclofenac metabolism is predominantly mediated via cytochrome P450 CYP 2C9 in the liver. Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates should be administered diclofenac with caution as they may have abnormally high plasma levels due to reduced metabolic clearance. Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as sulfinpyrazone and voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism. Caution should be exercised when prescribing ARTHROTEC with concomitant drugs that are known to be potentially hepatotoxic (e.g. antibiotics, anti-epileptics).

9.3 Drug-Behavioural Interactions

Smoking and alcohol intake should be discouraged while taking ARTHROTEC as they constitute risk factors for increased cardiovascular and gastrointestinal problems respectively.

9.4 Drug-Drug Interactions

Misoprostol has been used concomitantly with at least 44 different classes of drugs, including more than 150 drugs. There were no reports of any clinically significant drug interactions.

Acetylsalicylic Acid (ASA) or other NSAIDs: When diclofenac and ASA are taken simultaneously, the bioavailability of each is reduced. Concomitant administration of ARTHROTEC and ASA is not recommended because diclofenac is displaced from its binding sites by ASA, resulting in lower plasma concentrations, peak plasma levels and AUC values. Misoprostol does not affect the kinetics of other NSAIDs (e.g., ibuprofen, indomethacin and piroxicam). The use of ARTHROTEC in addition to any other NSAID, including those over the counter ones (such as ASA and ibuprofen) for analgesic and/or anti-inflammatory effects is NOT recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions.

The exception is the use of low dose ASA for cardiovascular protection, when another NSAID is being used for its analgesic/anti-inflammatory effect, keeping in mind that combination NSAID therapy is associated with additive adverse reactions. Some NSAIDs (e.g. ibuprofen) may interfere with the anti-platelet effects of low dose ASA, possibly by competing with ASA for access to the active site of cyclooxygenase-I.

Antacids: Only aluminum-based antacids should be used with ARTHROTEC as magnesium-based antacids may increase the potential for diarrhea (see **8 ADVERSE REACTIONS**). The concomitant administration of aluminum hydroxide or magnesium hydroxide antacids may delay the absorption of

diclofenac but does not affect the total amount of the drug absorbed. The total availability of misoprostol acid is reduced by antacids in large doses.

Anticoagulants: Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of GI adverse events such as ulceration and bleeding. Pharmacodynamic studies have shown no potentiation of anticoagulant drugs due to concurrent administration with diclofenac. However, other NSAIDs have been shown to interact with anticoagulant agents. Although clinical investigations would appear to indicate that diclofenac has no influence on the effect of anticoagulants, there are isolated reports of an increased risk of hemorrhage with the combined use of diclofenac and nicoumalone anticoagulant therapy. Special caution is therefore recommended and frequent laboratory tests should be performed to check that the desired response to the anticoagulant is being maintained. Because prostaglandins play an important role in hemostasis and NSAIDs affect platelet function as well, concurrent therapy of ARTHROTEC with warfarin requires close monitoring to be certain no change in anticoagulant dosage is necessary (**see 7 WARNINGS AND PRECAUTIONS – Hematologic – *Anti-coagulants*)**.

Anti-hypertensives: NSAIDs may diminish the anti-hypertensive effect of diuretics and other antihypertensive drugs including Angiotensin Converting Enzyme (ACE) inhibitors, angiotensin II antagonists (AIIA) and beta-blockers.

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

Dehydrated patients or elderly patients with compromised renal function may be at greater risk.

Anti-platelet Agents (including ASA): There is an increased risk of bleeding, via inhibition of platelet function, when anti-platelet agents are combined with NSAIDs, such as ARTHROTEC (see **7 WARNINGS AND PRECAUTIONS – Hematologic – *Anti-platelet Effects***).

Cyclosporin or Tacrolimus: When co-administered with cyclosporine, there is a two-fold increase in diclofenac systemic exposure. It is prudent to start with the lowest dose of diclofenac/misoprostol and to monitor closely for signs of toxicity.

Co-administration of cyclosporin or tacrolimus may also increase the nephrotoxic effect of cyclosporin or tacrolimus due to the NSAID's effect on renal prostaglandins. Renal function should be monitored when ARTHROTEC and either of these drugs is used in combination.

Digoxin: Diclofenac may increase the plasma concentration of digoxin. Dosage adjustment of the digoxin may be required with ARTHROTEC. Serum digoxin levels should be monitored for possible digoxin toxicity.

Diuretics/Antihypertensives: Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce the effect of diuretics. Concomitant treatment of ARTHROTEC with potassium-sparing diuretics may be associated with increased serum potassium levels, thus making it necessary to monitor the latter. The antihypertensive effect of hydrochlorothiazide and ACE inhibitors may be

decreased by diclofenac in patients with essential hypertension. Coadministration of ARTHROTEC with ACE inhibitors may result in an impairment of renal function.

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

Lithium: Diclofenac, when administered concomitantly with lithium, increases the lithium plasma concentration through an effect on lithium renal clearance. Lithium toxicity may develop in these patients. Dosage adjustment of lithium may be required with ARTHROTEC.

Methotrexate: Concurrent administration of methotrexate and diclofenac may result in increased plasma levels of methotrexate and rare cases of fatal renal toxicity have been reported. Thus, caution should be taken when administering ARTHROTEC and methotrexate.

Oral Contraceptives: No drug interaction data are available for ARTHTROTEC and the co-administration of oral contraceptives.

Oral hypoglycemic agents: Diclofenac does not alter glucose metabolism in normal subjects, and pharmacodynamic studies have shown no potentiation of oral hypoglycemic drugs due to concurrent administration with diclofenac. However, other NSAIDs have been shown to interact with oral hypoglycemic agents. Therefore, ARTHROTEC should be administered with caution in patients receiving insulin or oral hypoglycemic agents.

Phenytoin: When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

Selective Serotonin Reuptake Inhibitors (SSRIs): Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal ulceration and bleeding (see **7 WARNINGS AND PRECAUTIONS – Gastrointestinal**).

Sulfinpyrazone: Concomitant administration of diclofenac and sulfinpyrazone could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

Voriconazole: Voriconazole increased Cmax and AUC of diclofenac (50 mg single dose) by 114% and 78%, respectively.

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

Diclofenac increases platelet aggregation time but does not affect bleeding time, plasma prothrombin

clotting time, plasma fibrinogens, or factors V and VII to XII. Statistically significant changes in prothrombin and partial thromboplastin times have been reported in normal volunteers. The mean changes were observed to be less than 1 second in both instances and are unlikely to be clinically important.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

ARTHROTEC (diclofenac sodium plus misoprostol) is a combination of a nonsteroidal anti-inflammatory drug (NSAID) with a mucosal protective synthetic analog of prostaglandin E1. Diclofenac inhibits prostaglandin synthesis by interfering with the action of prostaglandin synthetase. This inhibitory effect may partially explain its actions, both therapeutic and adverse.

10.2 Pharmacodynamics

Misoprostol has been shown to inhibit both basal and stimulated gastric acid secretion. In addition, increases in gastric mucosal blood flow, duodenal bicarbonate secretion and gastric mucus secretion have all been observed following treatment with misoprostol. It is not known whether the ability of misoprostol to prevent gastric and duodenal ulcers is the result of its antisecretory effect, its mucosal protective effect, or both.

10.3 Pharmacokinetics

The pharmacokinetic profiles of diclofenac and misoprostol administered alone are similar to the profiles when they are coadministered as separate tablets, or given as ARTHROTEC (diclofenac sodium plus misoprostol). No pharmacokinetic interaction between the two drugs has been observed following either single or multiple doses.

Table 3 - Summary of ARTHROTEC Pharmacokinetic Parameters in healthy male and female subjects

	C_{max}		T_{max}		$t_{½}$ (h)	$AUC_{0-\infty}$		CL	Vd
	D* (mcg/mL)	M* (pg/mL)	D (h)	M (h)		D (mcg.h/mL)	M (pg.h/mL)		
Single dose mean ARTHROTEC 50	1.13	136	3.9	0.87	N/A*	1.63 ($AUC_{(0-24)}$)	238 ($AUC_{(0-4)}$)	N/A*	N/A*
Single dose mean ARTHROTEC 75	2.03	304	1.96	0.26	N/A*	2.77 ($AUC_{(0-12)}$)	177 ($AUC_{(0-4)}$)	N/A*	N/A*

*N/A: Not Available

Absorption

Orally administered diclofenac is rapidly and almost completely absorbed.

Orally administered misoprostol is also rapidly and extensively absorbed.

With ARTHROTEC the effect of food on the bioavailability of the diclofenac and misoprostol components is similar to that reported for the individual drugs. The times of peak concentration (Tmax) for diclofenac and misoprostol are prolonged by approximately 50% and 100% respectively, while the peak concentrations (Cmax) are decreased by about 25% for diclofenac and 50% for misoprostol: the AUC for diclofenac is decreased by approximately 60%, while that of misoprostol is increased by about 25%.

Distribution: Diclofenac is highly but reversibly bound in the plasma. Following administration of enteric-coated tablets there is high between- and within-subject variability in the plasma concentrations of diclofenac, particularly if the tablets are taken with food. However, the plasma concentrations show a linear relationship to the amount of drug administered and no accumulation occurs provided that the recommended dosage intervals are observed.

There is high variability in plasma levels of misoprostol acid, but mean values after single doses show a linear relationship with dose over the range of 200 to 400 mcg. No accumulation has been found in multiple dose studies and plasma steady state was achieved within two days.

Metabolism: Diclofenac metabolism is predominantly mediated via cytochrome P450 CYP 2C9 in the liver. Diclofenac undergoes single and multiple hydroxylation and methoxylation, producing 3'-, 4'-, 5-hydroxy, 4'-5-hydroxy and 3'-hydroxy-4'-methoxy derivatives of diclofenac. These phenolic metabolites are largely inactive, and (along with the parent compound) are mostly converted to glucuronide conjugates.

Misoprostol undergoes rapid metabolism to misoprostol acid.

Elimination

The half-life of diclofenac is 1 to 2 hours. Forty to 60% of the drug and its metabolites are eliminated in the urine and the balance in the bile.

Misoprostol acid is quickly eliminated (elimination half-life of approximately 30 minutes). Approximately 70% of the dose of misoprostol is excreted in the urine, mainly as biologically inactive metabolites.

Special Populations and Conditions

- **Poor CYP2C9 Metabolizers:** Diclofenac metabolism is predominantly mediated via cytochrome P450 CYP 2C9 in the liver. Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates should be administered diclofenac with caution (see **9.2 Drug Interactions Overview**).
- **Geriatrics** The kinetics and metabolism of diclofenac do not appear to be affected by age. In the elderly, the AUC of misoprostol acid is increased by roughly 40%.
- **Hepatic Insufficiency** The kinetics and metabolism of diclofenac do not appear to be affected by hepatic impairment. Misoprostol does not affect the hepatic mixed function oxidase (cytochrome P-450) enzyme system in animals. In a study of people with mild to moderate hepatic impairment, mean misoprostol acid AUC and Cmax showed approximately double the mean values obtained in healthy people. Three people who had the lowest antipyrine and lowest indocyanine green clearance values had the highest misoprostol acid AUC and Cmax values.
- **Renal Insufficiency** Differences in the pharmacokinetics of diclofenac (50 mg intravenously) have not been detected in studies of patients with renal impairment (N=5, creatinine clearance 3 to 42 mL/min). In these patients, AUC values and elimination rates were comparable to those in healthy people. Following oral administration of misoprostol in patients with mild-to-moderate renal impairment, there was no significant effect on the pharmacokinetic profile compared to normal subjects. However, in anuric patients, an approximate doubling of Cmax, AUC and t1/2 of misoprostol acid has been observed compared to normal subjects.

11 STORAGE, STABILITY AND DISPOSAL

Store at 15 to 25°C and protect from heat and humidity.

Any unused medicinal product should be disposed of in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

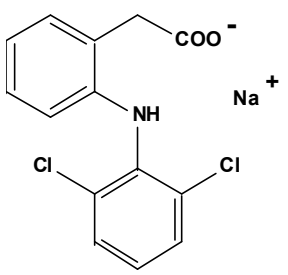
Drug Substance

Proper name: Diclofenac Sodium

Chemical name: Sodium [o-(2,6-dichloroanilino) phenyl acetate]

Molecular formula and molecular mass: $C_{14}H_{10}Cl_2NO_2Na$ and 318.1

Structural formula:



Physicochemical properties: Diclofenac sodium is a white to off-white powder with a salty, bitter taste. At 25°C, diclofenac sodium is 2% soluble in water (pH 7.7). It is practically insoluble in aqueous acidic solutions.

pH: 7.2

Melting Point: 280°-290°C with decomposition

pKa: 3.8 (potentiometry)
4.7 (spectrophotometry)

Pharmaceutical standard: Ph.Eur.

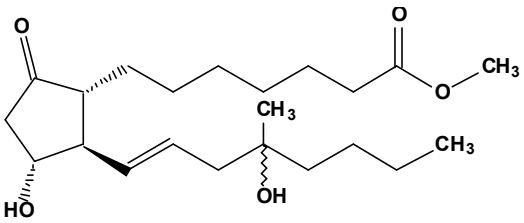
Drug Substance

Proper name: Misoprostol

Chemical name: (±)-(11α, 13E)-11,16-dihydroxy-16-methyl-9-oxoprost-13-en-1-oic acid methyl ester

Molecular formula and molecular mass: $C_{22}H_{38}O_5$ and 382.5

Structural formula:



Physicochemical properties: Misoprostol is a synthetic prostaglandin E_1 analog. It is a colorless to yellow, viscous liquid with a musty odor.

pH: 6.2

Melting Point: None Observed

Aqueous Solubility at 25°C:

Solvent	pH	g/mL
Water	6.2	0.3
HCl, 0.01M	2.0	0.3
Acetate, 0.01M	4.5	0.3
Phosphate, 0.01M	7.0	0.3

Organic Solubility at Ambient Temperature:

Solvent	g/mL
Ethanol	>10
Corn Oil*	>1
Soy Bean Oil*	>1
Cottonseed Oil*	>1

*Containing 10% v/v absolute ethanol

Pharmaceutical standard: Professed

14 CLINICAL TRIALS

14.1 Clinical Trials by Indications

The clinical trial data on which the original indication was authorized is not available.

Large meta-analyses of randomized clinical trials show that diclofenac is associated with an increased incidence of stroke, cardiovascular death, and death from any cause when compared with placebo. Data also suggest that diclofenac, particularly when used at a high dose (150 mg daily), may have a higher risk of thrombotic CV events than other NSAIDs.

Large population-based observational studies, meta-analyses and systematic reviews suggest that diclofenac use is associated with an increased incidence of cardiovascular thrombotic events, including myocardial infarction and ischemic stroke. Results of some studies suggest that the CV risk is related to the dose and duration of diclofenac exposure and is greater in patients with risk factors for CV disease.

In two multicentre, double-blind, controlled clinical trials of 12 weeks duration involving a total of 346 and 339 patients with rheumatoid arthritis respectively, patient global assessments of the arthritic condition revealed no statistically significant differences between ARTHROTEC 50 and a fixed-combination of diclofenac/placebo.

In two multicentre, double-blind, controlled trials of four weeks duration in 455 and 361 patients with osteoarthritis, patient global assessments of the arthritic condition revealed no overall differences between ARTHROTEC 50 and diclofenac/placebo.

A multicentre, double-blind, controlled trial of 6 weeks duration involving a total of 572 patients (154 in the diclofenac group, 152 in the ARTHROTEC 50 group, 175 in the ARTHROTEC 75 group and 91 in the placebo group) showed that ARTHROTEC 50 three times daily and ARTHROTEC 75 twice daily were equivalent to diclofenac/placebo in relieving the signs and symptoms of osteoarthritis.

A multicentre, double-blind, controlled trial of 12 weeks duration involving a total of 380 patients (107 in the diclofenac group, 107 in the ARTHROTEC 50 group, 111 in the ARTHROTEC 75 group and 55 in the placebo group) showed that ARTHROTEC 50 three times daily and ARTHROTEC 75 twice daily were equivalent to diclofenac/placebo in relieving the signs and symptoms of rheumatoid arthritis.

Misoprostol has been compared to placebo in the prevention of clinically significant and serious gastrointestinal events associated with NSAID use. In a six-month, double-blind study of 8,843 patients (4,404 in the misoprostol group, 4,439 in the placebo group, mean age 68 years) with rheumatoid arthritis, misoprostol significantly reduced the incidence of serious complications, such as gastrointestinal bleeding and ulcer perforation, by 40-50%.

ARTHROTEC is associated with a low incidence of gastroduodenal lesions relative to diclofenac/placebo.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

Diclofenac Sodium

Species	Route	LD_{50} Range (mg/kg)
Mouse	p.o.	185-541
	i.v.	92-147
Rat	p.o.	55-240
	i.v.	97-161
Rabbit	p.o.	125-300
Dog	p.o.	>800
Monkey	p.o.	3200

The main clinical signs included convulsions, saltatory spasms, reduced activity, diarrhea and signs of acute systemic illness. The oral LD_{50} for the dog was >800 mg/kg and for the monkey 3200 mg/kg.

Dogs had transient anorexia, diarrhea and duodenal erosions. Monkeys had diarrhea, anorexia, emesis, salivation and rectal ulcers.

Misoprostol

Species	Route	LD_{50} Range (mg/kg)
Mouse	p.o.	27-138
	i.p.	70-160
Rat	p.o.	81-100
	i.p.	40-62
Dog	p.o.	9.0*

*single value

The main clinical signs were reduced activity and diarrhea in the mouse and rat. The main clinical signs in the dog were emesis, diarrhea, tremors and mydriasis.

Diclofenac Sodium/Misoprostol

(250:1; diclofenac sodium/misoprostol)

Species	Sex	Route	*LD_{50} Range (mg/kg)
Mouse	M	p.o.	110-190
	F	i.p.	140-240
Rat	M	p.o.	220-490
	F	i.p.	110-180

* Expressed as dosage of diclofenac sodium

Chronic Toxicity

Diclofenac Sodium

Studies in Rats with Diclofenac Sodium:
Studies of 4, 13, 15 and 26 weeks were done either in Wistar or Sprague-Dawley strains.

All rats in an oral 4-week study at doses of 0.5 to 16 mg/kg died within seven days. The main findings were necrosis (ulceration of the gastrointestinal mucosa, peritoneal adhesions, hypertrophy of mesenteric nodes and spleen, hemorrhages and hypoplasia of bone marrow). No deaths occurred in a diet admix study at doses up to 2 mg/kg, and there were no gastrointestinal ulcers. There were no adverse effects in one subcutaneous study at doses up to 6 mg/kg but in another subcutaneous study, one female at 10 mg/kg died and three had intestinal ulcers. Two females at the 6 mg/kg dose also had ulcers.

In the 15-week and 90-day studies with 4 and 6 mg/kg, respectively, there were significant decreases in hemoglobin, packed cell volume, total protein and alpha globulin. Significant increases occurred in reticulocytes and neutrophils. No gastrointestinal lesions were found in the 13-week study, but one 6 mg/kg rat in the 15-week study had fibrinopurulent peritonitis.

In a 6-month rat study at doses from 0.25 to 4 mg/kg, no effects occurred up to 1 mg/kg. At 2 mg/kg, females had an increase in neutrophils and hypertrophied mesenteric nodes. At 4 mg/kg, females had lowered hemoglobin, hematocrit and erythrocyte counts and an increase in leucocytes and neutrophils. Some also had intestinal ulcers with peritonitis and enlarged mesenteric nodes.

In a 98-week diet admix study in rats at doses of 0.25, 1.0 and 2.0 mg/kg, the high dose was terminated at 59 weeks because of deaths; 54% in males and 92% in females. Rats in the medium and high-dose groups had lowered hemoglobin, hematocrit and erythrocyte counts, and neutrophilic leucocytosis. Females at 1 and 2 mg/kg had lowered serum glucose and raised serum alkaline phosphatase activity. Livers of the four surviving high-dose females at week 59 weighed about 1.5 times more than control livers. Adrenal weight for medium and high-dose females was significantly increased.

Drug-related morphologic changes included splenomegaly, enlarged mesenteric nodes, ulceration of the small intestine, peritonitis (mainly in 1.0 and 2.0 mg/kg dose females), adrenocortical atrophy, prostatitis and plasma cell hyperplasia of mesenteric nodes.

Studies in Dogs with Diclofenac Sodium:

Studies of 16, 30 and 90 days were done by oral doses ranging from 0.5 to 10 mg/kg. Drug-related deaths or severe illness characterized by weakness and weight loss occurred at doses as low as 1.0

mg/kg. Findings were as follows: lowering of hemoglobin, hematocrit, erythrocyte count, total protein and albumin, elevation of leucocyte and reticulocyte counts and alpha and beta globulins, and marked hematopoiesis in the spleen with splenomegaly.

Changes were associated with erosions and perforated ulcers of the gastric and duodenal mucosa. No changes were reported at the low dose of 0.5 mg/kg in the 90-day study.

Studies in Primates with Diclofenac Sodium:

In a 3-month study in Rhesus monkeys at 5, 15 and 50 mg/kg and in a 6-month study at 5, 15 and 75 mg/kg, deaths occurred only at 75 mg/kg. Diarrhea/loose stools occurred at all doses. Hemoglobin, hematocrit and erythrocyte counts were decreased at all doses, while platelets, leucocytes and reticulocytes were increased. There were no gross or microscopic changes at doses up to 50 mg/kg. At 75 mg/kg the following were noted: alkaline phosphatase and blood urea nitrogen levels were elevated, total protein was decreased, liver weight was increased with signs of cellular vacuolation and hypertrophy, cellular vacuolation of kidneys with hyaline casts and debris in tubules and erosions/ulcers and hemorrhage in the gastrointestinal tract.

A one-year oral toxicity study was done in baboons at doses of 5, 15 and 50 mg/kg/day. Administration of the high dose was discontinued on day 19 and reinitiated on day 38 at a lower dose of 30 mg/kg. The medium dose was reduced from 15 mg/kg to 10 mg/kg on day 254. Five of 16 medium and 15 of 16 high-dose animals died or were killed in extremis. The main signs were emesis, shivering, lethargy, skin ulcers, bloody feces, facial edema and greatly reduced weight gain. At the medium and high doses, there was a dose-related decrease in hemoglobin, hematocrit value and erythrocyte count, and an increase in reticulocytes, neutrophilic leucocytes and platelets, with a left shift in the differential count. Serum globulins were increased. Shallow colonic ulcers were seen at the low dose. At the high dose, there were gastrointestinal ulcers, some of which had perforated with resultant peritonitis. Gastrointestinal changes at the low and medium doses were less severe. Animals allowed to recover had no drug-related lesions of the stomach or intestines.

Misoprostol

Studies in Rats with Misoprostol:

Two 4, 5, 13 and 52 weeks toxicity studies were done in rats at daily oral dosages up to 9,000 mcg/kg. There were no drug related deaths.

The clinical signs were diarrhea, salivation, vaginal dilation and discharge, decreased body weight gain and increased food consumption.

In the 52-week study, there were no abnormal clinical signs at 160 mcg/kg and all signs at the higher doses were absent at the end of a 13-week reversal period.

Clinical laboratory changes included decreases in serum total protein and increases in serum iron. Study serum total protein decreased approximately 7 to 11% at 9,000mcg/kg.

Hyperkeratosis of the aglandular part of the stomach and mucosal epithelial hyperplasia of the glandular part were the prominent gross and microscopic changes at all dosages. Hyperplasia of the superficial epithelial cells of the colon was observed at 9,000 mcg/kg, but were absent at the end of the reversal period. The morphologic changes in the stomach were reflected in increased stomach weights and stomach to body weight ratios.

Electron microscopy of the stomach mucosa of some control and high dose (9,000mcg/kg) animals showed the aglandular part of the stomach of treated animals had hyperkeratosis on the mucosal

surface but the mucosal cells and keratin had normal structure. The corpus and antrum of the high dose rats had increased depth of gastric pits.

Studies in Dogs with Misoprostol:

Two 5, 13, and 52-week toxicity studies were conducted in beagle dogs at daily oral dosages ranging from 30 to 1,000mcg/kg/day. The most prominent clinical signs were emesis, diarrhea, soft and/or mucoid stools and increased rectal temperatures.

The clinical observations were absent or decreased in severity at the end of the reversal periods (13 and 52 week studies).

One animal was killed *in extremis* at 300mcg/kg during the first week of the study because it had stopped eating.

In the 52-week study, mean chloride concentrations were significantly increased, approximately 2, 4 and 5% in females at 30, 100 and 300mcg/kg dosages, respectively. There were no abnormal clinical laboratory findings at the end of the reversal periods.

Radiographic examination of long bones was performed after 10 months in the 52-week toxicity and showed no significant differences between misoprostol-treated and control animals. There was no evidence of hyperostosis.

Reversible gastric mucosal epithelial hyperplasia was a consistent gross and microscopic change.

After a four-week recovery period in the 13-week study, a slight villous epithelial hyperplasia remained in the 480 mcg/kg group. After a three-month recovery period in the 52-week study, there were no gross changes in the stomach and only one 300 mcg/kg group male dog had hyperplasia of the pyloric epithelium.

Diclofenac Sodium/Misoprostol

Species	Period	No Significant Toxic Effect (mg/kg)*	Minimum Lethal Dose(mg/kg)*
Rat	4 weeks	>6	>6
	6 months	1	6
Dog	4 weeks	0.5	2
Monkeys	6 months	>6	50

*Expressed as dosage of diclofenac sodium (p.o. daily dose)

Studies in Rats with Diclofenac Sodium/Misoprostol:

In a 4-week oral study in rats, the dosages of misoprostol and diclofenac sodium, respectively, were 2, 8 and 24 mcg/kg and 0.5, 2 and 6 mg/kg. Two other groups were given diclofenac sodium alone at 0.5 and 6 mg/kg. There were no deaths, clinical signs and gross and microscopic changes. Serum albumin concentrations were decreased in all treated females at all doses.

In a 6-month oral study in rats, the dosages of misoprostol and diclofenac sodium, respectively, were 4, 10, and 24 mcg/kg and 1, 2.5, and 6 mg/kg. Three other groups were given diclofenac sodium alone at 1, 2.5 and 6 mg/kg. Gross and microscopic findings, seen primarily in the females of the high dosage groups, included jejunal ulceration, frequently associated with a granulation tissue reaction, jejunal dilatation and/or thickening, and diffuse peritonitis.

The splenic enlargement and extramedullary hematopoiesis of the spleen were considered secondary to ulceration. Jejunal ulcers were present in two females of the high combination group after the 4-week reversal period.

Hematological and serum chemical changes included anemia, thrombocytosis, neutrophilic leucocytosis, decreased serum protein and albumin, and increased alkaline phosphatase. Most of the changes were still present at the end of the reversal period. These changes were considered consistent with direct or indirect ulcerogenic effects of diclofenac on the gastrointestinal tract.

Studies in Dogs with Diclofenac Sodium/Misoprostol:

In a 4-week oral study in dogs, the dosages of misoprostol and diclofenac sodium, respectively, were 2, 4 and 8 mcg/kg and 0.5, 1 and 2 mg/kg. Two other groups were given diclofenac sodium alone at 0.5 and 2 mg/kg. One dog died at the high diclofenac dose and three at the high combined dose. These deaths were attributed to the effects of diclofenac.

Clinical signs in the two high dose groups included dark or bloody feces, loose stools, emesis, reduced activity and pale mucous membranes. Gross and microscopic findings included gastrointestinal ulcers, peritonitis, necrosis/edema of the renal crest, increased splenic hematopoiesis, and thymic and prostatic atrophy. Dogs in the two high dose groups were anemic and had neutrophilic leucocytosis, lowered plasma protein, albumin and calcium. In the two high dose groups mean splenic weight was increased and mean thymic weight decreased.

Diclofenac induced injury to the renal crest (hyperemia, edema and necrosis) in equal incidence whether given alone or in combination with misoprostol. There was a significant difference in severity of the lesions with necrosis occurring in 1/8 animals given the combination compared to 3/8 animals given diclofenac alone.

Studies in Monkeys with Diclofenac Sodium/Misoprostol:

In a 26-week oral study in Cynomolgus monkeys, the dosages of misoprostol and diclofenac sodium, respectively, were 24, 68, and 200 mcg/kg and 6, 17, and 50 mg/kg. Two other groups were given diclofenac sodium alone at 6 and 50 mg/kg. Clinical signs of loose stools and salivation were mainly observed in combination groups and were considered to be related to the effect of misoprostol.

Significantly decreased body weight gains were observed in high-diclofenac males starting at week 3 and were not present at the end of the reversal period. Gross and microscopic changes including hyperemia, hemorrhages, and ulcerations of the gastrointestinal tract with various inflammatory reactions in other organs including peritonitis were seen in animals dying during the study and in animals from both high dose groups at the scheduled 26-week sacrifice. In a high-diclofenac female, acute myocarditis and pericarditis were associated with suppurative pyelonephritis. After 4 weeks reversal, cecal mucosal hemorrhage was still observed in two high combination males and one male each from the low and high-diclofenac groups.

Clinical laboratory changes were observed in animals of both high dose groups, but were generally more marked in animals treated with diclofenac alone. These changes included: anemia with increased reticulocytes and neutrophil count and decreased lymphocytes; thrombocytosis; decreased serum albumin and calcium; and increased serum globulin. With the exception of the reticulocyte counts in the high dose diclofenac group, the clinical laboratory changes were no longer observed or were subsiding at the end of the reversal period.

Genotoxicity:

Diclofenac Sodium

No evidence of mutagenic potential was found in the following test systems: Ames Salmonella/microsome assay and yeast (*S. cereviseae*) mutation, mouse lymphoma $TK^{+/-}$ assay, nucleus anomaly in Chinese hamster bone marrow cells, chromosomal aberration and dominant lethal.

Misoprostol

The mutagenic/carcinogenic potential of misoprostol was evaluated in five *in vitro* assays: Ames Salmonella/microsome assay; mouse lymphoma $TK^{+/-}$ assay; sister chromatid exchange assay; yeast gene conversion assay; and the C_3H 10T1/2 cell transformation assay. Misoprostol was negative in all tests. Ames tests were also negative for misoprostol degradation products (SC-29636, SC-32759, SC-33188).

Diclofenac Sodium/Misoprostol

No evidence of mutagenicity was found in the following test systems: Ames Salmonella/microsome assay, CHO/HGPRT mutation assay, *in vitro* chromosome aberration assay in rat lymphocytes and in the mouse bone marrow micronucleus test.

Carcinogenicity:

Carcinogenicity studies were conducted with misoprostol in rats and mice and with diclofenac sodium in rats. Neither diclofenac nor misoprostol is carcinogenic. Carcinogenicity studies have not been conducted with the combination of diclofenac sodium and misoprostol.

Reproductive and Developmental Toxicity:

Diclofenac Sodium

Fertility (Segment I) and perinatal/postnatal (Segment III) studies were performed in the rat and teratology (Segment II) studies were performed in the mouse, rat and rabbit. There was no effect on fertility but maternal toxicity (intestinal ulcers and peritonitis) was produced at the high dose of 4 mg/kg. Postnatal growth and survival of pups in the Segment I study were equal between treated and control groups.

No teratogenic effects were evident in any of the Segment II studies but maternotoxicity and embryotoxicity occurred in some. Diclofenac has been shown to cross the placental barrier in mice and rats. Maternal deaths occurred at both doses of 2 and 4 mg/kg in the Segment III study. All dams that died or were killed *in extremis* had peritonitis, presumably associated with intestinal ulcers. Stillbirths and resorptions were higher in the two treated groups. Pups from dams receiving 4 mg/kg grew at a slower rate after the first week. Viability of offspring from surviving dams was not reduced.

Misoprostol

Fertility (Segment I) and perinatal/postnatal (Segment III) studies in rat and teratology (Segment II) studies in rat and rabbit were performed. There were drug-related clinical signs of salivation, soft feces, lethargy, and unkempt appearance at the higher doses of misoprostol. At a dosage of 100 mcg/kg, no drug-related clinical signs occurred.

Although no drug-related deaths occurred, at doses of 1,600 mcg/kg and above in rats and 300 mcg/kg and above in rabbits decreases in body weights of male or female animals given misoprostol were observed.

In two rat fertility studies the number of implantations was decreased at 1,600 mcg/kg and above. An increased number of resorptions occurred at 1,000 and 10,000 mcg/kg in one study but were not reproduced in other studies. The increased number of resorptions and decreased number of

implantations accounted for a decreased number of live fetuses or pups at 10,000 mcg/kg, whereas the decreased number of implantations accounted for a decreased number of fetuses at 1,600 mcg/kg. Fetal and pup survival or growth were unaffected. Behavioral, sensory, and reproductive assessment of the F1 offspring revealed no adverse effects.

There was no evidence of embryotoxicity, fetotoxicity, or teratogenicity in two teratology rat studies at the maximum dosage of 10,000 mcg/kg.

No evidence of fetotoxicity or teratogenicity was observed in two teratology rabbit studies at the maximum dosage of 1,000 mcg/kg. However, there was an increased number of resorptions, evidence of possible embryotoxicity, in one of the two studies at 1,000 mcg/kg.

In the perinatal/postnatal study, pup growth at 10,000 mcg/kg was retarded as evidenced by the decreased weight gain during lactation. However, pup survival was unaffected.

Diclofenac Sodium/Misoprostol

One oral teratology (Segment II) study was done in rabbits. The dosages of misoprostol and diclofenac sodium, respectively, were 4, 12 and 40 mcg/kg and 1, 3 and 10 mg/kg. At the high dose, there was lowered food intake, decreased weight gain, embryotoxicity and one possibly drug-related death.

At the lower doses, neither embryotoxicity nor maternotoxicity was noted. There was no evidence at any dose of fetotoxicity or teratogenicity.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrARTHROTEC® 50 / PrARTHROTEC® 75

diclofenac sodium and misoprostol enteric-coated tablets

Read this carefully before you start taking **ARTHROTEC** 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 **ARTHROTEC**.

Serious Warnings and Precautions

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

- **Heart attack or angina (chest pain)**
- **Stroke or mini-stroke**
- **Congestive heart failure**
- **High risk for heart disease (e.g. High blood pressure, Diabetes, High levels of fats in your blood, Smoking)**

It is important to take the lowest dose of ARTHROTEC that relieves your pain and/or swelling and for the shortest time possible in order to keep your risk of side effects on the heart and blood vessels as small as possible.

ARTHROTEC can result in increased blood pressure and / or worsening of congestive heart failure.

NSAIDS, like ARTHROTEC, may cause stomach and bowel problems (such as ulceration, perforation, obstruction, and bleeding).

Do not take ARTHROTEC if you are pregnant or think that you may be pregnant. ARTHROTEC may cause uterine contractions that are associated with abortion, premature birth, birth defects and fetal death.

What is ARTHROTEC used for?

- ARTHROTEC is used for short-term and long-term relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

How does ARTHROTEC work?

ARTHROTEC contains two different medicines: diclofenac, a nonsteroidal anti-inflammatory drug (NSAID) and misoprostol, a drug that helps to protect the lining of your stomach (because NSAIDs can cause damage to your stomach).

ARTHROTEC helps to relieve joint pain, swelling, and stiffness by reducing the production of certain substances (prostaglandins) and by helping to control inflammation. ARTHROTEC does NOT cure your illness or prevent it from getting worse. ARTHROTEC can only relieve pain and reduce swelling as long as you continue to take it.

What are the ingredients in ARTHROTEC?

Medicinal ingredients: diclofenac sodium and misoprostol

Non-medicinal ingredients: Colloidal Silicon Dioxide, Corn Starch, Crospovidone, Hydrogenated Castor Oil, Hypromellose, Lactose, Magnesium Stearate, Methacrylic Acid Copolymer, Microcrystalline Cellulose, Povidone K-30, Sodium Hydroxide, Talc, Triethyl Citrate

ARTHROTEC comes in the following dosage forms:

- Tablets, 50 mg diclofenac/200 mcg misoprostol
- Tablets, 75 mg diclofenac/200 mcg misoprostol

Do not use ARTHROTEC if:

- You will be having or recently had Heart bypass surgery
- You are pregnant, planning to become pregnant or are in prolonged labor during childbirth
- You are breastfeeding or planning to breastfeed
- You have severe, uncontrolled heart failure
- You are allergic to diclofenac sodium, misoprostol, other NSAIDs or any ingredient found in ARTHROTEC
- You have gastrointestinal issues such as Ulcers, Bleeding from the stomach or gut, Inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis)
- You have bleeding in the brain or other bleeding disorders
- You have active or severe liver disease
- You have severe or worsening kidney disease
- You have high potassium in the blood
- You are taking other NSAIDs

Children and adolescents under the age of 18 should not use ARTHROTEC.

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

- Have liver disease or liver problems
- Have kidney disease or kidney problems
- Have disease of the heart or blood vessels such as uncontrolled high blood pressure, congestive heart failure, established ischemic heart disease, or peripheral arterial disease
- Have high risk factors for cardiovascular disease such as high blood pressure, abnormally high levels of fat (cholesterol, triglycerides) in your blood, diabetes, or if you smoke.
- Have poor circulation to your extremities
- Previously had an ulcer or bleeding from the stomach or gut
- Previously had bleeding in the brain
- Have bleeding problems
- Have a family history of allergy to NSAIDs, such as acetylsalicylic acid (ASA), celecoxib, diclofenac, diflunisal, etodolac, fenoprofen, fluribiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, rofecoxib, sulindac, tenoxicam, tiaprofenic acid, tolmetin, or valdecoxib (NOT a complete list)
- Have a family history of asthma, nasal polyps, long-term swelling of the sinus (chronic sinusitis) or hives

- Have a history of a severe drug hypersensitivity reaction (drug allergy) including skin problems
- Are on any special diet, such as a low-sodium diet
- Drink alcohol;

Other Warnings that you should know about:

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

Driving and Operating Heavy Machinery:
ARTHROTEC may cause visual disturbances, dizziness, vertigo or drowsiness. Do not operate heavy machinery if you experience these effects while taking ARTHROTEC.

Light Sensitivity:

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

SPECIAL NOTE FOR WOMEN OF CHILDBEARING AGE:
Do not take ARTHROTEC if you are pregnant or think you are pregnant or during prolonged labour. Do not start ARTHROTEC until you have been tested to confirm that you are not pregnant. Do not get pregnant or try to get pregnant while you are taking ARTHROTEC and for at least one month (or through one menstrual cycle) after you stop taking it. This means using an effective form of birth control which you should discuss with your doctor. Stop taking ARTHROTEC, and contact your doctor immediately if you do become pregnant during ARTHROTEC therapy.

Misoprostol may cause uterine contractions (contractions of the uterus), premature birth, birth defects and abortion or may otherwise harm the unborn developing baby. Misoprostol has been reported to cause the uterus to tear when given after the eighth week of pregnancy. Tearing of the uterus can result in severe bleeding, hysterectomy, and/or maternal or fetal death. Therefore, if you are pregnant, you must not take this drug.

Diclofenac can potentially prolong labor.

Abortions caused by misoprostol are likely to be incomplete. An incomplete abortion may result in very serious medical complications, resulting in hospitalization, surgery and possibly infertility, and may result in maternal death.

Do not use ARTHROTEC if you are breastfeeding or planning to breastfeed. The body changes misoprostol to the active form of the drug, misoprostol acid, which could get into the breast milk and cause significant diarrhea in the infant.

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 ARTHROTEC:

- Acetylsalicylic Acid (ASA) or other NSAIDs (e.g. ASA, celecoxib, diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen). Your healthcare provider may prescribe low dose ASA while you take ARTHROTEC. Only take ASA as directed by your healthcare provider.
- Antacids. Do not take antacids that contain magnesium (because they can cause diarrhea) while you are taking ARTHROTEC. Ask your pharmacist to help you select a suitable brand.
- Antidepressants
- Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. citalopram, fluoxetine, paroxetine, sertraline)
- Blood pressure medications. Using ARTHROTEC with blood pressure drugs may increase your risk of kidney failure. This is more likely if you are elderly or dehydrated.
- Diuretics (e.g. furosemide, hydrochlorothiazide)
- ACE (Angiotensin converting enzyme) inhibitors (e.g. enalapril, lisinopril, perindopril, ramipril)
- ARBs (angiotensin II receptor blockers) (e.g. candesartan, irbesartan, losartan, valsartan)
- Beta-blockers
- Blood thinners (e.g. warfarin, ASA, clopidogrel). Using ARTHROTEC with a blood-thinner increases the risk of bleeding. This can occur in the stomach or anywhere.
- Corticosteroids (including glucocorticoids) (e.g. prednisone)
- Cyclosporin
- Digoxin
- Lithium
- Methotrexate
- Oral hypoglycemics (diabetes medications)
- Phenytoin (a medicine used to treat seizures)
- Tacrolimus
- Sulfinpyrazone (a medicine used to treat gout)
- Voriconazole (a medicine used to treat fungal infections)
- Drinking alcohol while taking ARTHROTEC may increase your risk of gastrointestinal problems. Do not drink alcoholic beverages while taking this medication.

How to take ARTHROTEC:

- ARTHROTEC should be swallowed whole.
- Take ARTHROTEC immediately after a meal or with food or milk.
- Remain standing or sitting for 15-30 minutes after taking the medicine. This helps prevent irritation that may lead to trouble swallowing.
- **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.**
- Your healthcare provider will prescribe the lowest effective dose of ARTHROTEC to help avoid side effects. Take ARTHROTEC exactly as directed by your healthcare provider.

Usual dose:

Adults: Take 50 mg of diclofenac twice daily. The maximum daily dose is 100 mg of diclofenac.

Overdose:

Symptoms of overdose may include stomach pain, confusion, drowsiness, low muscle tone, shaking hands that you cannot control, seizures, shortness of breath, diarrhea, fever, rapid or pounding heartbeat, slow heartbeat, dizziness or fainting.

If you think you, or a person you are caring for, have taken too much ARTHROTEC, 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 ARTHROTEC, take the next dose at the regular time. Do not take a double dose to catch up for the missed dose. It is important that ARTHROTEC be taken as prescribed. Try to remember to take ARTHROTEC at the appropriate time. Having a regular routine associated with taking your medicine will help.

What are possible side effects from using ARTHROTEC?

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

- ARTHROTEC may cause some undesirable reactions especially when used for a long time or in large doses. When these side effects occur, you may require medical attention. Report all symptoms or side effects to your health care provider.
- Elderly, frail, or debilitated patients often seem to experience more frequent or more severe side effects.
- Check with your healthcare provider IMMEDIATELY if you develop chills, fever, muscle aches or pains, or other flu-like symptoms, especially if they occur before or together with a skin rash. These symptoms may be the first signs of a SERIOUS ALLERGIC REACTION to this medication.
- Stomach upset is one of the common problems with NSAIDs. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your doctor.
- Because misoprostol increases mucus production some patients experience diarrhea. Keep taking your ARTHROTEC. It is just a sign that the drug is working. Usually the diarrhea goes away in two to three days. If it is not gone after a week, check with your doctor.
- While your body gets used to misoprostol you may feel a crampy pain in your stomach. Like the diarrhea it usually goes away in a few days. If it doesn't, check with your doctor.

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			
Indigestion, nausea, abdominal pain or diarrhea	✓		
COMMON			
Dizziness, light headedness	✓		
Headaches	✓		
Insomnia	✓		
Skin rash, itching			✓

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**	
Vomiting, constipation, gas, burping	✓		
UNCOMMON			
Bleeding			✓
Bloody or black tarry stools			✓
Blurred vision or any visual disturbance			✓
Change in heart rate or rhythm, change in blood pressure, heart failure, blood clot, stroke			✓
Malaise, fever, swelling, chills		✓	
Menses pain, abnormal vaginal bleeding, vaginal infection		✓	
Shortness of breath, wheezing, any trouble in breathing or tightness in the chest			✓
Skin bruising, hives or swelling			✓
Sore throat or mouth sores		✓	
Vomiting blood			✓
RARE			
Breast pain		✓	
Nightmare	✓		
Pancreatitis: abdominal pain, nausea, vomiting, loss of appetite			✓
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, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine or dark urine, hives, red or dry itchy skin, purple or red spots on skin, bruising			✓
Swelling of the feet or lower legs		✓	
Yellow skin or eyes, dark urine (red or brown)			✓
UNKNOWN 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	
Agranulocytosis: fever, chills. Flu-like symptoms. Weakness		✓	
Benign mass in the intestine, trouble with swallowing			✓
Hearing problems		✓	
Hemolytic Anemia: Fatigue and short of breath		✓	
Infections: Sepsis (infection of the whole body)			✓
Nausea, fatigue, lethargy, diarrhea, pruritus, yellow discoloration of the skin or eyes with or without itchy skin, right upper quadrant tenderness, and «flu-like» symptoms			✓
Seizure, stiff neck, shaking, loss of consciousness, change in mood or thoughts			✓

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/drug.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 15-25°C and protect from heat and humidity.

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

Keep out of reach and sight of children.

If you want more information about ARTHROTEC:

- 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 www.pfizer.ca, or by calling 1-800-463-6001.

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