

Lupus Pathogenesis May Involve Epstein-Barr Virus

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NEW YORK — Evidence is mounting that implicates the Epstein-Barr virus as the trigger that sets off the autoantibody production central to the pathogenesis of systemic lupus erythematosus, according to Dr. John B. Harley.

It has long been assumed that an etiologic agent from the environment would be required to initiate the production of the

antinuclear antibodies that begin to appear in lupus patients' sera long before clinical disease develops. An association of lupus with Epstein-Barr virus (EBV) was first noted more than 3 decades ago, but the technical means of proving a connection was lacking, and the idea was set aside.

The EBV hypothesis was resurrected during the 1990s, however. Because almost all adults are infected with the virus—a hindrance to finding an epidemiologic connection—Dr. Harley and

his colleagues investigated a group of 117 children and adolescents with lupus. Among patients aged 4-19 years, an infection rate of approximately 70% would be expected, and indeed, that was what was found among 153 controls, he said.

Among the lupus patients, however, 99% had seroconverted against EBV. "This was an odds ratio of 50," Dr. Harley said at a rheumatology meeting sponsored by New York University.

Certain characteristics of the virus itself

also lend credence to its etiologic probability. It infects B cells—B-cell dysregulation is prominent in lupus—and EBV itself can cause B-cell activation and autoantibody production. Among the antibodies that have been identified in patients with EBV-related mononucleosis are those targeting the Sm autoantigen, which otherwise is considered specific for lupus.

Infection is lifelong, providing continuous immune stimulation, and curiously, the virus also generates proteins that inhibit its own immune-mediated destruction, Dr. Harley said.

In lupus, it is the host response to the virus that is the crucial aberrant factor, rather than the virus itself, said Dr. Harley, professor of immunology and medicine,

University of Oklahoma Health Sciences Center, Oklahoma City. An alteration in humoral response to Epstein-Barr nuclear antigen 1 (EBNA-1) appears to be involved, and in describing his findings in the pediatric cohort, Dr. Harley

explained the altered response: "In the present study, lupus patients were shown to make higher concentrations of antibody against the fragments encompassing the amino and carboxyl ends of EBNA-1, while normal EBV-positive controls actually made higher levels of antibody against the middle fragment than did lupus patients" (Arthritis Rheum. 2006;54:360-8).

Further evidence has come from molecular techniques including epitope mapping and peptide sequencing. The first anti-Sm autoantibodies that appear in lupus patients' sera bind to a structure known as PPPGMRPP that cross-reacts with a similar peptide, PPPGRRP, on EBNA-1, Dr. Harley explained. A similar capability has been identified with anti-Ro antibodies, and the generation of cross-reacting antibodies to Sm or Ro may be the "central and critical step that defines the onset of lupus-specific autoimmunity," he said. This critical step involving cross-reactive antibodies is then followed by epitope spreading and, ultimately, clinical disease.

Moreover, proof of the principle that a viral structure could generate autoimmunity was demonstrated by immunization of rabbits with the PPPGMRPP peptide. Following immunization, the animals went on to develop proteinuria, thrombocytopenia, elevated antinuclear antibody titers, and anti-double-stranded DNA antibodies (Nat. Med. 2005;11:85-9).

Dr. Harley's group also is focusing on the genetics of autoimmunity, and the Arthritis and Immunology Research Program, which he heads, at the Oklahoma Medical Research Foundation in Oklahoma City maintains a registry and repository of multiplex lupus families that is available for academic work. The registry can be accessed at <http://lupus.omrf.org>.

ARTHROTEC® (diclofenac sodium /misoprostol) tablets

Before prescribing, please consult complete prescribing information.

CONTRAINDICATIONS AND WARNINGS

ARTHROTEC® CONTAINS DICLOFENAC SODIUM AND MISOPROSTOL. ADMINISTRATION OF MISOPROSTOL TO WOMEN WHO ARE PREGNANT CAN CAUSE ABORTION, PREMATURE BIRTH, OR BIRTH DEFECTS. UTERINE RUPTURE HAS BEEN REPORTED WHEN MISOPROSTOL WAS ADMINISTERED IN PREGNANT WOMEN TO INDUCE LABOR OR TO INDUCE ABORTION BEYOND THE EIGHTH WEEK OF PREGNANCY (See also PRECAUTIONS). ARTHROTEC SHOULD NOT BE TAKEN BY PREGNANT WOMEN (See CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS). PATIENTS MUST BE ADVISED OF THE ABORTIFICANT PROPERTY AND WARNED NOT TO GIVE THE DRUG TO OTHERS.

ARTHROTEC should not be used in women of childbearing potential unless the patient requires nonsteroidal anti-inflammatory drug (NSAID) therapy and is at high risk of developing gastric or duodenal ulceration or for developing complications from gastric or duodenal ulcers associated with the use of the NSAID. (See WARNINGS). In such patients, ARTHROTEC may be prescribed if the patient:

- has had a negative serum pregnancy test within 2 weeks prior to beginning therapy.
- is capable of complying with effective contraceptive measures.
- has received both oral and written warnings of the hazards of misoprostol, the risk of possible contraception failure, and the danger to other women of childbearing potential should the drug be taken by mistake.
- will begin ARTHROTEC only on the second or third day of the next normal menstrual period.

Cardiovascular Risk

• NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See WARNINGS).

• ARTHROTEC is contraindicated for treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (See WARNINGS).

Gastrointestinal Risk: NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (See WARNINGS).

INDICATIONS AND USAGE: Carefully consider the potential benefits and risks of ARTHROTEC and other treatment options before deciding to use ARTHROTEC. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (See WARNINGS).

ARTHROTEC is indicated for treatment of the signs and symptoms of osteoarthritis or rheumatoid arthritis in patients at high risk of developing NSAID-induced gastric and duodenal ulcers and their complications. See WARNINGS—Gastrointestinal effects for a list of factors that may increase the risk of NSAID-induced gastric and duodenal ulcers and their complications.

CONTRAINDICATIONS: See boxed CONTRAINDICATIONS AND WARNINGS related to misoprostol. ARTHROTEC should not be taken by pregnant women.

ARTHROTEC is contraindicated in patients with hypersensitivity to diclofenac or to misoprostol or other prostaglandins. ARTHROTEC should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactoid-like reactions to diclofenac sodium have been reported in such patients (See WARNINGS—Anaphylactoid Reactions, and PRECAUTIONS—Preexisting Asthma). ARTHROTEC is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (See boxed CONTRAINDICATIONS AND WARNINGS).

WARNINGS: Regarding misoprostol: See boxed CONTRAINDICATIONS AND WARNINGS. Regarding diclofenac: See boxed CONTRAINDICATIONS AND WARNINGS.

CARDIOVASCULAR EFFECTS: Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur. There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (See GI WARNINGS). Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (See CONTRAINDICATIONS).

Hypertension: NSAIDs including ARTHROTEC, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including ARTHROTEC, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema: Fluid retention and edema have been observed in some patients taking NSAIDs. ARTHROTEC should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal Effects—Risk of Ulceration, Bleeding and Perforation: NSAIDs, including ARTHROTEC, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk. NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk of developing a GI bleed compared to patients treated with neither of these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulcerations and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects: Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease: No information is available from controlled clinical studies regarding the use of ARTHROTEC in patients with advanced renal disease. Therefore, treatment with ARTHROTEC is not recommended in these patients with advanced renal disease. If ARTHROTEC therapy must be initiated, close monitoring of the patient's renal function is advisable.

Hepatic effects: Elevations of one or more liver tests may occur during therapy with ARTHROTEC. Borderline elevations (ie, less than 3 times the ULN [ULN = the upper limit of the normal range]), or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients. Of the hepatic enzymes, ALT (SGPT) is the one recommended for the monitoring of liver injury. In clinical trials, meaningful elevations (ie, more than 3 times the ULN) of AST (SGOT) [ALT was not measured in all studies] occurred in about 2% of approximately 5,700 patients at some time during

diclofenac treatment. In a large, open, controlled trial, meaningful elevations of ALT and/or AST occurred in about 4% of 3,700 patients treated for 2-6 months, including marked elevations (ie, more than 8 times the ULN) in about 1% of the 3,700 patients. In that open-label study, a higher incidence of borderline elevations (less than 3 times the ULN, moderate (3-8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs.

Postmarketing surveillance has found rare cases of severe hepatic reactions, including liver necrosis, jaundice, and fulminant fatal hepatitis with and without jaundice. Some of these rare reported cases underwent liver transplantation. Severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. Transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac. The misoprostol component of ARTHROTEC does not appear to exacerbate the hepatic effects caused by the diclofenac sodium component. 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 ARTHROTEC. If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (eg, eosinophilia, rash, etc.), ARTHROTEC should be discontinued immediately. Inform patients of the warning signs and symptoms of hepatotoxicity (eg, nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms), and the appropriate action patients should take if these signs and symptoms appear.

Anaphylactoid reactions: As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to ARTHROTEC. ARTHROTEC should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions: NSAIDs, including ARTHROTEC, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy: In late pregnancy, as with other NSAIDs, ARTHROTEC should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS: General: ARTHROTEC cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids. The pharmacological activity of ARTHROTEC in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions. **Hepatic Effects:** See WARNINGS. **Hematological Effects:** Anemia is sometimes seen in patients receiving NSAIDs, including ARTHROTEC. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia. Patients receiving ARTHROTEC who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Preexisting Asthma: The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. ARTHROTEC should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma. **Renal effects:** Caution should be used when initiating treatment with ARTHROTEC in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with ARTHROTEC. Caution is also recommended in patients with preexisting kidney disease (See WARNINGS—Advanced renal disease). Diclofenac metabolites are eliminated primarily by the kidneys. The extent to which the metabolites may accumulate in patients with renal failure has not been studied. As with other NSAIDs, metabolites of which are excreted by the kidney, patients with significantly impaired renal function should be more closely monitored. **Aseptic meningitis:** As with other NSAIDs, aseptic meningitis with fever and coma has been observed on rare occasions in patients on diclofenac therapy. **Porphyria:** The use of ARTHROTEC in patients with hepatic porphyria should be avoided.

Laboratory tests: Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs of symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (eg, eosinophilia, rash, etc) or if abnormal liver tests persist or worsen, ARTHROTEC should be discontinued.

Drug interactions: ARTHROTEC may increase the serum levels of diploxin, methotrexate, lithium and phenobarbital; patients should be monitored for toxicity. ARTHROTEC may increase cyclosporine nephrotoxicity, exacerbate GI bleeding in patients on warfarin, and inhibit the activity of antihypertensives and diuretics. Use caution in administering ARTHROTEC with any of these agents, particularly if renal function is impaired. Aspirin may diminish the therapeutic effect of diclofenac and coadministration is not recommended. Diclofenac Na may alter a diabetic patient's response to insulin or oral hypoglycemic agents. Antacids containing magnesium may exacerbate diarrhea and should not be coadministered with ARTHROTEC. **Animal toxicology:** A reversible increase in the number of normal surface gastric epithelial cells occurred in the dog, rat, and mouse during long-term toxicology studies with misoprostol. No such increase has been observed in humans administered misoprostol for up to 1 year. An apparent response of the female mouse to misoprostol in long-term studies at 100 to 1000 times the human dose was hyperostosis, mainly of the medulla of sternbrae. Hyperostosis did not occur in long-term studies in the dog and rat and has not been seen in humans treated with misoprostol.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term animal studies to evaluate the potential for carcinogenesis and animal studies to evaluate the effects on fertility have been performed with each component of ARTHROTEC given alone. ARTHROTEC itself (diclofenac sodium and misoprostol combinations in 250:1 ratio) was not genotoxic in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward mutation test, the rat lymphocyte chromosome aberration test or the mouse micronucleus test. In a 24-month rat carcinogenicity study, oral misoprostol at doses up to 24x the recommended maximum human dose of 0.6 mg/m²/day was not tumorigenic. In a 21-month mouse carcinogenicity study, oral misoprostol at doses up to 80x the recommended maximum human dose based on body surface area, was not tumorigenic. Misoprostol, when administered to male and female breeding rats in an oral dose-range of 1 to 100 times the recommended maximum human dose based on body surface area) produced dose-related pre- and post-implantation losses and a significant decrease in the number of live pups born at the highest dose. These findings suggest the possibility of a general adverse effect on fertility in males and females. In a 24-month rat carcinogenicity study, oral diclofenac sodium up to 2 mg/kg/day (12 mg/m²/day) was not tumorigenic. For a 50-kg person of average height (1.46m² body surface area), this dose represents 0.08 times the recommended maximum human dose (148 mg/m²) on a body surface area basis. In a 24-month mouse carcinogenicity study, oral diclofenac sodium at doses up to 0.006x the recommended maximum human dose based on body surface area) in males and 0.02x the recommended maximum human dose in females was not tumorigenic. Diclofenac sodium at oral doses up to 0.16x the recommended maximum human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy, pregnancy category X: See boxed CONTRAINDICATIONS AND WARNINGS regarding misoprostol.

Non-teratogenic effects: See boxed CONTRAINDICATIONS AND WARNINGS. Misoprostol may endanger pregnancy (may cause abortion) and thereby cause harm to the fetus when administered to a pregnant woman. Misoprostol may produce uterine contractions, uterine bleeding, and expulsion of the products of conception. Misoprostol has been used to ripen the cervix, to induce labor, and to treat postpartum hemorrhage of the uterus. Uterine rupture, amniotic fluid embolism, severe genital bleeding, shock, fetal bradycardia, and fetal and maternal death have been reported. Higher doses of misoprostol, including the 100mg tablet, may increase the risk of complications from uterine hyperstimulation. ARTHROTEC, which contains 200mg of misoprostol, is likely to have a greater risk of uterine hyperstimulation than the 100mg tablet of misoprostol. Abortions caused by misoprostol may be incomplete. If a woman is or becomes pregnant while taking this drug, the drug should be discontinued and the patient apprised of the potential hazard to the fetus. Cases of amniotic fluid embolism, which resulted in maternal and fetal death, have been reported with use of misoprostol during pregnancy. Severe vaginal bleeding, retained placenta, shock, fetal bradycardia, and pelvic pain have also been reported. These women were administered misoprostol vaginally and/or orally over a range of doses.

Because of the known effects of nonsteroidal anti-inflammatory drugs, including the diclofenac sodium component of ARTHROTEC, on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Teratogenic effects: See boxed WARNINGS. Congenital anomalies sometimes associated with fetal death have been reported subsequent to the unsuccessful use of misoprostol as an

abortifacient, but the drug's teratogenic mechanism has not been demonstrated. Several reports in the literature associate the use of misoprostol during the first trimester of pregnancy with skull defects, cranial nerve palsies, facial malformations, and limb defects.

An oral teratology study has been performed at dose combinations 0.8 times the recommended maximum human dose and has revealed no evidence of teratogenic potential for ARTHROTEC.

However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.

Nursing mothers: Because of the potential for serious adverse reactions in nursing infants, ARTHROTEC is not recommended for use by nursing mothers.

Labor and Delivery: In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred.

Pediatric use: Safety and effectiveness of ARTHROTEC in pediatric patients have not been established.

Geriatric use: As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older). Of the more than 2,100 subjects in clinical studies with ARTHROTEC, 25% were 65 and over, while 6% were 75 and over. In studies with diclofenac, 31% of subjects were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. 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. Based on studies in the elderly, no adjustment of the dose of ARTHROTEC is necessary in the elderly for pharmacokinetic reasons although many elderly may need to receive a reduced dose because of low body weight or disorders associated with aging.

ADVERSE REACTIONS: Adverse reactions associated with ARTHROTEC: Adverse reaction information for ARTHROTEC is derived from Phase III multinational controlled clinical trials in over 2,000 patients, receiving ARTHROTEC 50 or ARTHROTEC 75, as well as from blinded, controlled trials of Voltaren® Delayed-Release Tablets (diclofenac) and Cytotec® Tablets (misoprostol).

Adverse reactions associated with ARTHROTEC: **Gastrointestinal:** In clinical trials, the most frequently reported adverse events were GI disorders: abdominal pain (21%), diarrhea (19%), dyspepsia (14%), nausea (11%), and flatulence (9%). ARTHROTEC can cause more abdominal pain, diarrhea and other GI symptoms than diclofenac alone.

Diarrhea and abdominal pain developed early in the course of therapy, and were usually self-limited (resolved after 2 to 7 days). Rare instances of profound diarrhea leading to severe dehydration have been reported in patients receiving misoprostol. Patients with an underlying condition such as inflammatory bowel disease, or those in whom dehydration, were it to occur, would be dangerous, should be monitored carefully if ARTHROTEC is prescribed. The incidence of diarrhea can be minimized by administering ARTHROTEC with food and by avoiding coadministration with magnesium-containing antacids.

Gynecological: Gynecological disorders previously reported with misoprostol use have also been reported for women receiving ARTHROTEC (see below). Postmenopausal vaginal bleeding may be related to administration of ARTHROTEC. If it occurs, diagnostic workup should be undertaken to rule out gynecological pathology. (See boxed CONTRAINDICATIONS AND WARNINGS) **Elderly:** Overall, there were no significant differences in the safety profile of ARTHROTEC in over 500 patients 65 years of age or older compared with younger patients. Other adverse experiences reported occasionally or rarely with ARTHROTEC, diclofenac or other NSAIDs, or misoprostol are: **Body as a whole:** Asthenia, death, fatigue, fever, infection, malaise, sepsis. **Cardiovascular system:** Arrhythmia, atrial fibrillation, congestive heart failure, hypertension, hypotension, increased C/CK, increased LDH, myocardial infarction, palpitations, plebitis, premature ventricular contractions, syncope, tachycardia, vasculitis. **Central and peripheral nervous system:** Coma, convulsions, dizziness, drowsiness, headache, hyperesthesia, hypertonia, hypoesthesia, insomnia, meningitis, migraine, neuralgia, paresthesia, somnolence, tremor, vertigo. **Digestive:** Anorexia, appetite changes, constipation, dry mouth, dysphagia, enteritis, esophageal ulceration, esophagitis, eructation, gastric, gastroesophageal reflux, GI bleeding, GI neoplasm benign, glossitis, heartburn, hematemesis, hemorrhoids, intestinal perforation, peptic ulcer, stomatitis and ulcerative stomatitis, tenesmus, vomiting. **Female reproductive disorders:** Breast pain, dysmenorrhea, intermenstrual bleeding, leukorrhea, menstrual disorder, menorrhagia, vaginal hemorrhage. **Hemic and lymphatic system:** Agranulocytosis, anemia, aplastic anemia, coagulation time increased, ecchymosis, eosinophilia, epistaxis, hemolytic anemia, leukocytosis, leukopenia, lymphadenopathy, melena, pancytopenia, pulmonary embolism, purpura, retinal bleeding, thrombocytopenia, thrombocytopenia. **Hypersensitivity:** Angioedema, laryngeal/pharyngeal edema, urticaria. **Liver and biliary system:** Abnormal hepatic function, bilirubinemia, hepatitis, jaundice, liver failure, pancreatitis. **Male reproductive disorders:** Impotence, penile pain. **Metabolic and nutritional:** Alkaline phosphatase increased, BUN increased, dehydration, glycosuria, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypoglycemia, hypoproteinemia, periorbital edema, porphyria, weight changes. **Musculoskeletal system:** Anthrax, myalgia. **Psychiatric:** Anxiety, concentration impaired, confusion, depression, disorientation, dream abnormalities, hallucinations, irritability, nervousness, paranoia, psychotic reaction. **Respiratory system:** Asthma, coughing, dyspnea, hyperventilation, pneumonia, respiratory depression. **Skin and appendages:** Acne, alopecia, bruising, eczema, erythema multiforme, exfoliative dermatitis, pemphigoid reaction, photosensitivity, pruritus, pruritic ani, rash, skin ulceration, Stevens-Johnson syndrome, sweating increased, toxic epidermal necrolysis. **Special senses:** Hearing impairment, taste loss, taste perversion, tinnitus. **Urinary system:** Cystitis, dysuria, hematuria, interstitial nephritis, micturition frequency, nocturia, nephrotic syndrome, oliguria/polyuria, papillary necrosis, proteinuria, renal failure, urinary tract infection. **Vision:** Amblyopia, blurred vision, conjunctivitis, diplopia, glaucoma, iritis, lacrimation abnormal, night blindness, vision abnormal.

OVERDOSAGE: The toxic dose of ARTHROTEC has not been determined. However, signs of overdose from the components of the product may include: diclofenac—GI complaints, confusion, drowsiness or general hypotonia; misoprostol—sedation, tremor, convulsions, dyspnea, abdominal pain, diarrhea, fever, palpitations, hypotension, or bradycardia. Symptoms of overdose with ARTHROTEC should be treated with supportive therapy. In case of acute overdose, gastric lavage is recommended. Induced diuresis may be beneficial. The use of oral activated charcoal may help to reduce the absorption of diclofenac sodium and misoprostol.

HOW SUPPLIED: ARTHROTEC (diclofenac sodium/misoprostol) is supplied as a film-coated tablet in dosage strengths of either 50 mg diclofenac sodium/200 mg misoprostol or 75 mg diclofenac sodium/200 mg misoprostol. The 50 mg/200 mg dosage strength is a round, bicover, white to off-white tablet imprinted with four "AS" encircling a "50" in the middle on one side and "SEARLE" and "1411" on the other. The 75 mg/200 mg dosage strength is a round, bicover, white to off-white tablet imprinted with four "AS" encircling a "75" in the middle on one side and "SEARLE" and "1421" on the other. The dosage strengths are supplied in:

Strength	NDC Number	Size
50/200	0025-1411-60	bottle of 60
	0025-1411-90	bottle of 90
	0025-1411-34	carton of 100 unit dose
75/200	0025-1421-60	bottle of 60
	0025-1421-34	carton of 100 unit dose

Store at or below 25°C (77°F), in a dry area.

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