PRODUCT INFORMATION

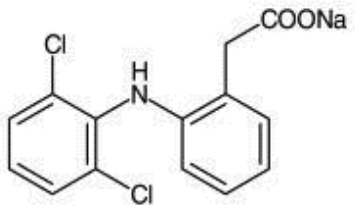
ARTHROTEC® 50 (Diclofenac sodium/Misoprostol)

NAME OF THE MEDICINE

ARTHROTEC 50 Diclofenac sodium 50 mg/Misoprostol 200 µg tablets.

Diclofenac sodium

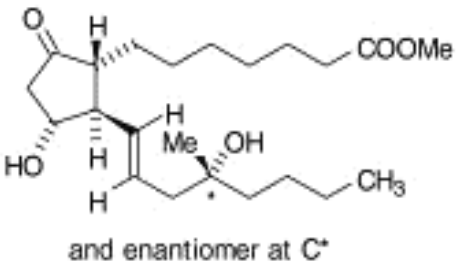
The structural formula of diclofenac sodium is shown below:



Chemical name:	sodium [0-(2,6-dicloroanilino)phenyl] acetate
Molecular formula:	$C_{14}H_{10}CI_2NO_2Na$
Molecular weight:	318.1
CAS registry number:	15307-86-5.

Misoprostol

The structural formulae of the two diastereomers of misoprostol are shown below:



Chemical name:	(±)-methyl(13E)-11,16-dihydroxy-16-methyl-9-oxoprost-13-enoate
Molecular formula:	$C_{22}H_{38}O_5$
Molecular weight:	382.5
CAS registry number:	59122-46-2.

DESCRIPTION

Diclofenac sodium is a white to off-white, virtually odourless, crystalline powder.

Misoprostol is a water-soluble, viscous liquid and is a racemic compound containing approximately equal amounts of the two diastereomers.

ARTHROTEC 50 tablets consist of a diclofenac sodium core and a misoprostol mantle. The tablets also contain castor oil-hydrogenated, starch-maize, cellulose-microcrystalline, crospovidone, talc-purified, hypromellose lactose, magnesium stearate, povidone, silica-colloidal anhydrous, methacrylic acid copolymer, sodium hydroxide and triethyl citrate.

PHARMACOLOGY

Pharmacodynamics

ARTHROTEC 50 is effective in treating the signs and symptoms of rheumatoid arthritis and osteoarthritis. This activity is due to the presence of diclofenac which has been shown to have anti-inflammatory and analgesic properties. As with other non-steroidal anti-inflammatory drugs (NSAIDs), the exact mechanism of action of diclofenac is not known. However, it may be related to the ability of diclofenac to inhibit prostaglandin synthetase.

Antiarthritic Effects

Diclofenac sodium (75-150 mg daily) has equivalent or superior efficacy to aspirin (3-5 g daily), and indomethacin (75-100 mg daily), and a variety of other NSAIDs in treating rheumatoid arthritis. Likewise, diclofenac sodium (75-150 mg daily) has efficacy equal to that of aspirin (1.8-3.6 g daily) and indomethacin (75-150 mg daily) and numerous other NSAIDs in treating osteoarthritis.

Gastrointestinal Effects

Misoprostol is a synthetic prostaglandin E_1 analog that enhances several of the factors that maintain gastroduodenal mucosal integrity. It inhibits both stimulated and unstimulated gastric acid secretion. Misoprostol also maintains gastric mucosal blood flow, and increases duodenal bicarbonate and gastric mucous secretion.

The ability of misoprostol to protect the gastric and duodenal mucosa from NSAID-induced damage has been confirmed in healthy volunteers and in patients with osteoarthritis, or rheumatoid arthritis.

Misoprostol 200 µg BID or TID co-administered with diclofenac sodium 50 mg BID or TID significantly reduces the incidence of gastroduodenal lesions induced by diclofenac. After six months of treatment in a multicentre, double-blind, controlled trial, patients with rheumatoid arthritis and/or osteoarthritis who received misoprostol had significantly fewer gastric and duodenal lesions, including ulcers, due to diclofenac, than those who received placebo.

In two multicentre, double-blind, controlled trials in patients with osteoarthritis, misoprostol 100 µg QID and 200 µg QID co-administered with ibuprofen, piroxicam or naproxen was significantly better than placebo in preventing gastric ulcers induced by these NSAIDs.

Pharmacokinetics

The pharmacokinetic profiles of diclofenac and misoprostol administered as ARTHROTEC 50 are similar to the profiles when the two drugs are administered as separate tablets. No pharmacokinetic interaction between the two drugs has been observed following multiple doses.

Following administration of a single dose of ARTHROTEC 50 to 36 healthy male subjects, the mean ($\pm$SD) C_{max}, AUC (0-24) and t_{max} for diclofenac were 1.13 (0.53) µg/mL, 1.63 (0.63) µg.h/mL and 3.9 (1.1) h, respectively, while the mean C_{max}, AUC (0-4) and t_{max} for the principal active metabolite

of misoprostol (misoprostol acid) were 136 (48) pg/mL, 238 (55) pg.h/mL and 0.87 (0.76) h, respectively.

Pharmacokinetics of Misoprostol

Orally administered misoprostol is rapidly and extensively absorbed, and undergoes rapid metabolism to its biologically active metabolite, misoprostol acid, which is thereafter quickly eliminated, with an elimination half-life of approximately 30 minutes. There is high variability in plasma levels of misoprostol acid between, and within, studies, but mean values after single doses show a linear relationship with dose over the range of 200 to 400 µg. No accumulation of misoprostol acid has been found in multiple-dose studies. Approximately 70% of the administered dose is excreted in the urine, mainly as biologically inactive metabolites. In patients with mild-to-moderate renal impairment there was no significant difference in the pharmacokinetics compared to the matching normal subjects. However, in anuric patients, an approximate doubling of $C_{max,}$ AUC and $t_{1/2}$ of misoprostol acid was observed compared to normal subjects, and in the elderly the AUC was increased by about 40% (see **CONTRAINDICATIONS** and **DOSAGE AND ADMINISTRATION**).

Pharmacokinetics of Diclofenac sodium

In man, orally administered diclofenac is rapidly and almost completely absorbed and distributed to the blood, liver and kidneys. It is highly but reversibly protein 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. The kinetics and metabolism of diclofenac do not appear to be affected by age or hepatic impairment. Forty (40%) to 60% of the drug and its metabolites (conjugates of the 3'-, 4'- and 5'-hydroxy derivatives of diclofenac) are eliminated in the urine and the balance in the bile and hence in the faeces (see **CONTRAINDICATIONS** and **DOSAGE AND ADMINISTRATION**).

INDICATIONS

ARTHROTEC 50 is indicated for patients who require a non-steroidal anti-inflammatory drug (NSAID) together with misoprostol. The diclofenac component of ARTHROTEC 50 is indicated for the treatment of osteoarthritis, and rheumatoid arthritis. The misoprostol component of ARTHROTEC 50 is indicated for the prophylaxis of NSAID-induced gastric and duodenal ulceration. Known risk factors for NSAID induced gastropathy include age in excess of 60 years, a history of peptic ulcer disease, smoking, previous NSAID gastrointestinal intolerance and the presence of a concomitant disease.

CONTRAINDICATIONS

The contraindications of ARTHROTEC 50 are those of the components of the product.

ARTHROTEC 50 is contraindicated in patients with active peptic ulceration or with its specific complications of recent bleeding and/or perforation or in other cases of gastrointestinal bleeding.

ARTHROTEC 50 is contraindicated in patients who have known hypersensitivity to diclofenac sodium, aspirin, other NSAIDs, misoprostol or other prostaglandins, or any other ingredient of the product. ARTHROTEC 50 should not be given to patients in whom aspirin and other NSAIDs induce symptoms of asthma, nasal polyps, angioedema or urticaria.

ARTHROTEC 50 is contraindicated in pregnant women and in women planning a pregnancy, or in whom pregnancy has not been excluded, because misoprostol induces uterine contractions and is associated with abortion, premature birth and fetal death. Use of misoprostol has been associated with congenital anomalies (see **PRECAUTIONS** and **ADVERSE EFFECTS**, **Post-Marketing Experience**); it may cause premature closure of the ductus arteriosus.

ARTHROTEC 50 is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

ARTHROTEC 50 is contraindicated in patients with severe renal failure and in patients with severe hepatic impairment.

ARTHROTEC 50 is contraindicated in patients with severe heart failure.

PRECAUTIONS

The use of ARTHROTEC 50 with concomitant systemic non-aspirin NSAIDs, including COX-2 inhibitors, should be avoided. Concomitant use with one or more systemic NSAIDs may increase frequency of gastrointestinal ulcers and bleeding.

Cardiovascular Effects

Cardiovascular Thrombotic Events

Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular (CV) events including myocardial infarction and stroke, which can be fatal. This risk may increase with dose or duration of use. The relative increase of this risk appears to be similar in those with or without known CV disease or CV risk factors. However, patients with known CV disease, history of atherosclerotic CV disease, or CV risk factors may be at greater risk in the terms of absolute incidence, due to their increased rate at baseline.

Treatment with diclofenac is generally not recommended in patients with established CV disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension. If needed, patients with established CV disease, uncontrolled hypertension, or significant risk factors for CV disease (e.g. hypertension, hyperlipidemia, diabetes mellitus and smoking) should be treated with diclofenac only after careful consideration and only at doses ≤100 mg daily when treatment continues for more than 4 weeks.

To minimise the potential risk of an adverse CV event in patients taking a NSAID especially in those with CV risk factors, the lowest effective dose should be used for the shortest possible duration. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially when treatment continues for more than 4 weeks. Physicians and patients should remain alert for such CV events, even in the absence of previous CV symptoms. Patients should be informed about signs and/or symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech) and the steps to take if they occur (see **CONTRAINDICATIONS**).

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use.

Hypertension

NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension and patients taking antihypertensives with NSAIDs may have an impaired antihypertensive response.

Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals throughout the course of therapy.

Heart Failure

Fluid retention and oedema have been observed in some patients taking NSAIDs, including ARTHROTEC 50. Therefore, ARTHROTEC 50 should be used with caution in patients with a history of congestive heart failure or conditions predisposing to or worsened by fluid retention. Patients with pre-existing congestive heart failure or hypertension should be closely monitored.

Gastrointestinal Effects

The presence of misoprostol in ARTHROTEC 50 protects against the mucosal damaging effects of the NSAID component, diclofenac. However, serious, potentially fatal gastrointestinal (GI) toxicity, including inflammation, bleeding, ulceration, and perforation, have been reported in patients receiving NSAID therapy, including ARTHROTEC 50. 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. Therefore, physicians and patients should remain alert for ulceration, even in the absence of GI symptoms. Patients most at risk of developing GI complications with NSAIDs are the elderly; patients with CV disease; patients using concomitant aspirin, corticosteroids or selective serotonin reuptake inhibitors (SSRIs); patients with a prior history of or active GI disease (such as ulceration, bleeding or inflammatory conditions); and patients with a history of smoking or who consume alcohol. When GI bleeding or ulcerations occur in patients receiving NSAIDs, the drug should be withdrawn immediately.

Hepatic Effects

ARTHROTEC 50 contains diclofenac which, like other NSAIDs, has been shown to produce elevations in one or more liver tests in up to 15% of patients. These laboratory abnormalities may progress, remain unchanged, or may be transient with continued therapy and are usually reversible on cessation of therapy.

However, signs and symptoms of liver disease including jaundice have occurred with diclofenac.

In clinical trials, clinically significant elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase or bilirubin were observed in less than 10% of patients who received ARTHROTEC 50 and approximately the same percentage of those who received diclofenac/placebo. In clinical trials, hepatitis has been observed in patients who received diclofenac, and in postmarketing experience, other hepatic reactions have been reported including jaundice and hepatic failure.

During ARTHROTEC 50 therapy, liver function should be monitored periodically. The first assessment should not be later than eight weeks after initiating the drug. Physicians and patients should remain alert for hepatotoxicity. Patients should be informed about the signs and/or symptoms of hepatotoxicity and the steps to take should they occur. If ARTHROTEC 50 is to be used in the presence of impaired liver function, it must be done under close observation. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop (e.g. nausea, fatigue, lethargy, pruritis, jaundice, abdominal tenderness in the right upper quadrant and "flu-like" symptoms), or if systemic manifestations occur, treatment with diclofenac should be discontinued (see **CONTRAINDICATIONS**).

Allergic Reactions

Allergic reactions including anaphylaxis have been reported with diclofenac and have occurred without prior exposure to the drug.

Renal Effects

As a class, NSAIDs have been associated with renal pathology such as papillary necrosis, glomerulitis, interstitial nephritis and nephrotic syndrome. In clinical trials, creatinine test values indicative of mild to moderate renal failure were observed in 1.3% of patients who received ARTHROTEC 50 and 1.0% of those who received diclofenac/placebo. Values suggestive of renal insufficiency were reported in 0.5% of patients who received ARTHROTEC 50 and 0.5% of those who received diclofenac/placebo.

Since diclofenac metabolites are excreted predominantly by the kidneys, patients with renal impairment should be monitored during ARTHROTEC 50 therapy. Control of renal function and dosage can be reduced according to medical judgement.

In patients with renal, cardiac, or hepatic impairment, caution is required since the use of NSAIDs, including ARTHROTEC 50, may result in deterioration of renal function. Caution should be used when initiating treatment in patients with dehydration. The dose should be kept as low as possible and renal function should be monitored.

Platelet Effects

Diclofenac increases platelet aggregation time, prothrombin time and partial thromboplastin time. It has been shown that misoprostol does not exacerbate the effects of diclofenac on platelet activity. In clinical trials there has been no evidence that ARTHROTEC 50 affects haemostasis.

Use with Oral Anticoagulants and Anti-Platelet Agents

The concomitant use of NSAIDs, including ARTHROTEC 50, with oral anticoagulants increases the risk of GI and non-GI bleeding and should be given with caution. Oral anticoagulants and anti-platelet agents include clopidogrel, warfarin/coumarin-type and novel oral anticoagulants (e.g. apixaban, dabigatran, rivaroxaban). Anticoagulation/INR should be monitored in patients taking a warfarin/coumarin-type anticoagulant to ensure that no change in anticoagulant dosage is required.

Masking the Effects of Infection

By reducing inflammation, diclofenac may diminish the utility of diagnostic signs, such as fever, in detecting infections.

Concomitant Use of ACE Inhibitors or Angiotensin Receptor Antagonists and Anti-inflammatory Drugs and Thiazide Diuretics

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), and an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time, increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Concomitant use of all three classes of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the treatment. The concomitant use of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Skin Reactions

NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients appear to be at highest risk for these events early in the course of therapy, the onset of the event occurring in the majority of cases within the first month of treatment. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash, mucosal lesion or any other sign of hypersensitivity. If this occurs, the drug should be promptly discontinued.

Effects on Fertility

Based on the mechanism of action, the use of NSAIDs, such as diclofenac sodium, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of ARTHROTEC 50 should be considered.

Use in Pregnancy

CATEGORY X.

Misoprostol must not be used by pregnant women as it may cause miscarriage. Miscarriages caused by misoprostol may be incomplete which could lead to potentially dangerous bleeding, hospitalisation, surgery, infertility or death.

Misoprostol's effects on a developing fetus are not known. Women should be advised not to become pregnant while taking misoprostol. If a woman becomes pregnant while taking misoprostol, use of the product should be discontinued.

The inhibition of prostaglandin synthesis by NSAIDs, such as diclofenac sodium, may adversely affect pregnancy. Epidemiological studies suggest an increased risk of spontaneous abortion after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss.

NSAIDs given during the latter part of pregnancy, may cause premature closure of the fetal ductus arteriosus, prolong labour and delay birth. Continuous treatment with NSAIDs during the last month of pregnancy should only be given on sound indications. During the last few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided.

NSAIDs given during the second or third trimester of pregnancy may cause fetal renal dysfunction, which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases. Such effects may occur shortly after treatment initiation.. Pregnant women on NSAIDs should be closely monitored for amniotic fluid volume.

Due to the effects discussed above, of NSAIDs on the fetal CV and renal systems and because misoprostol induces uterine contractions and is associated with abortion, premature birth and fetal death, and also because the use of misoprostol has been associated with congenital anomalies, ARTHROTEC 50 is contraindicated in pregnancy (see **CONTRAINDICATIONS** and **ADVERSE EFFECTS, Post-Marketing Experience**).

Women of childbearing potential should not be started on ARTHROTEC 50 until pregnancy is excluded, and should be fully counselled on the importance of adequate contraception (i.e. oral contraceptives or intrauterine devices) while undergoing treatment.

Reproductive studies of misoprostol showed no evidence of embryotoxicity or teratogenicity in rats at oral doses up to 10 mg/kg/day, but in one rabbit study, oral doses greater than 0.3 mg/kg/day caused increases in resorption rate and in the incidence of skeletal variants; these effects were associated with maternal toxicity.

Teratology studies of diclofenac sodium have been performed in mice given diclofenac sodium (up to 20 mg/kg/day PO) and in rats and rabbits given diclofenac sodium (up to 10 mg/kg/day PO) and have revealed no evidence of teratogenicity despite the induction of maternal toxicity and embryotoxicity. In rats, maternally toxic doses of diclofenac were associated with dystocia, prolonged gestation, reduced fetal weights and growth and reduced fetal survival. Diclofenac has been shown to cross the placental barrier in mice and rats.

An oral teratology study in rabbits dosed with diclofenac and misoprostol, at oral doses up to 10 and 0.04 mg/kg/day respectively, showed no evidence of teratogenicity, although there was an increase in resorption rate associated with maternal toxicity at the highest dose level.

Use in Lactation

Misoprostol is rapidly metabolised in the mother to misoprostol acid, which is biologically active and is excreted in breast milk. Misoprostol should not be administered to nursing mothers because the excretion of misoprostol acid could cause undesirable effects such as diarrhoea in nursing infants. Diclofenac has been found in the milk of nursing mothers. Thus, ARTHROTEC 50 should not be used by nursing mothers.

Paediatric Use

Safety and effectiveness of ARTHROTEC 50 in children below the age of 18 years have not been established.

Carcinogenicity and Genotoxicity

Dietary administration of diclofenac to mice and rats at doses up to 0.5 mg/kg/day revealed no carcinogenic activity. However, the plasma concentration of diclofenac at this dose level was 20 to 100 times lower than that in humans. Administration of higher doses to rats and mice resulted in increased mortality due to gastrointestinal ulceration. Diclofenac did not show mutagenic potential in various *in vitro* and *in vivo* mutagenicity studies. Diclofenac sodium administered orally to male and female rats at 4 mg/kg/day did not affect fertility.

There was no evidence of an effect of misoprostol on tumour occurrence or incidence in rats receiving oral doses up to 2.4 mg/kg/day for 24 months. Similarly, there was no effect of misoprostol on tumour occurrence or incidence in mice receiving oral doses up to 16 mg/kg/day for 21 months. The mutagenic potential of misoprostol was tested in a battery of assays for gene mutations and chromosomal damage, all of which were negative. In fertility studies, increased pre-implantation losses were observed in dams mated to male rats treated with misoprostol at oral doses greater than 1 mg/kg/day. Post-implantation losses were also increased at 10 mg/kg/day, but it is not known whether this effect is referable to exposure of the males or females.

Misoprostol and diclofenac co-administered at the ratio used in the clinical formulation were not mutagenic in a battery of assays for gene mutation and chromosomal damage. No carcinogenesis or fertility studies have been performed with the combination.

INTERACTIONS WITH OTHER MEDICINES

Aspirin

Concomitant administration of ARTHROTEC 50 and aspirin is not recommended because diclofenac is displaced from its binding sites by aspirin, resulting in lower plasma concentrations, peak plasma levels and AUC values.

Digoxin

Elevated digoxin levels have been reported in patients receiving digoxin and diclofenac. Patients receiving digoxin and ARTHROTEC 50 should be monitored for possible digoxin toxicity.

Antihypertensives

NSAIDs can reduce the efficacy of antihypertensives, including diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists (AIIAs; also known as angiotensin receptor blockers or ARBs) and beta-blockers (see **PRECAUTIONS, Hypertension**).

In patients with impaired renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of an ACE inhibitor or AIIA and/or diuretics with a cyclo-oxygenase inhibitor may increase the deterioration of renal function. The occurrence of these interactions should be considered in patients taking ARTHROTEC 50 with an ACE inhibitor or AIIA and/or diuretics. Thus, caution should be taken when administering ARTHROTEC 50 with such agents, especially in elderly patients (see **PRECAUTIONS, Concomitant Use of ACE Inhibitors or Angiotensin Receptor Antagonists and Anti-inflammatory Drugs and Thiazide Diuretics**).

Patients should be adequately hydrated and the need to monitor renal function should be assessed before, and periodically during, concomitant treatment.

Potassium-Sparing Diuretics

Since concomitant treatment with potassium-sparing diuretics may be associated with increased potassium levels, serum potassium should be monitored.

Anticoagulants

NSAIDs have been shown to interact with oral anticoagulants. Oral anticoagulants include warfarin/coumarin-type and novel oral anticoagulants (e.g. apixaban, dabigatran, rivaroxaban). Concurrent therapy with ARTHROTEC 50 and oral anticoagulants should be monitored to ensure that no change in anticoagulant dosage is required (see **PRECAUTIONS, Use with Oral Anticoagulants and Anti-Platelet Agents**).

Oral Hypoglycaemic Agents

Diclofenac does not alter glucose metabolism in normal subjects, and the effects of oral hypoglycaemic agents were not altered by the concomitant administration of diclofenac. However, there have been reports of changes in the effects of oral hypoglycaemic agents (hypo- and hyperglycaemia) in the presence of NSAIDs. Therefore, ARTHROTEC 50 should be administered with caution in patients receiving insulin or oral hypoglycaemic agents.

Methotrexate

Rare cases of fatal renal toxicity have been reported in patients receiving methotrexate and diclofenac. NSAID administration may result in increased plasma levels of methotrexate, especially in patients receiving high doses of methotrexate. Thus, caution should be taken when administering

ARTHROTEC 50 and methotrexate.

Lithium

Diclofenac decreases lithium renal clearance and increases lithium plasma levels. Therefore, ARTHROTEC 50 should be administered with caution in patients receiving lithium.

Antacids

High doses of antacids have been shown to reduce the bioavailability of misoprostol acid. Antacids may delay absorption of diclofenac. Magnesium-containing antacids have been shown to exacerbate misoprostol associated diarrhoea.

Cyclosporin

Because of their effect on renal prostaglandins, NSAIDs such as diclofenac may increase the nephrotoxicity of cyclosporin.

When co-administered with cyclosporin, there is a two-fold increase in diclofenac systemic exposure. It is prudent to start with the lowest dose of ARTHROTEC 50, and titrate the dose of both medicines depending on the patient's laboratory results and clinical response. The patient should be monitored closely for signs of toxicity, including renal toxicity.

Corticosteroids

Concomitant administration of NSAIDs, such as diclofenac, with corticosteroids increases the risk of gastrointestinal ulceration or bleeding.

Tacrolimus

Concomitant administration of NSAIDs, such as diclofenac, with tacrolimus can increase the risk of nephrotoxicity.

CYP2C9 Inhibitors (such as Sulfinpyrazone and Voriconazole)

Concomitant administration of potent CYP2C9 inhibitors (such as sulfinpyrazone and voriconazole) with diclofenac may result in significant increases in peak plasma levels and exposure to diclofenac due to inhibition of diclofenac metabolism. Caution is recommended when co-prescribing diclofenac with CYP2C9 inhibitors.

ADVERSE EFFECTS

The following have been reported as adverse events in subjects receiving ARTHROTEC 50 tablets.

Gastrointestinal

In subjects receiving ARTHROTEC 50 in clinical trials, the most frequent gastrointestinal adverse events were abdominal pain (19.9%) and diarrhoea (17.2%). The incidence of abdominal pain is comparable with that reported in subjects receiving diclofenac/placebo (18.2%). Conversely, the incidence of diarrhoea in subjects taking ARTHROTEC 50 was approximately 7% greater than in subjects taking diclofenac/placebo.

Both abdominal pain and diarrhoea were generally transient and mild to moderate in severity. Each of these events usually occurred as a single episode, beginning about two to three days after starting ARTHROTEC 50, and lasting for about two to three days. Both events usually resolved spontaneously despite continuing ARTHROTEC 50. Diarrhoea can be minimised by taking

ARTHROTEC 50 with food and by avoiding the use of predominantly magnesium-containing antacids.

Hepatic

The following hepatic disorders were reported among subjects receiving ARTHROTEC 50 in clinical trials: bilirubinaemia (0.1%), hepatic function abnormal (0.1%), LDH increased (0.1%), phosphatase alkaline increased (0.1%) and ALT increased (0.1%).

Renal

As a class, NSAIDs have been associated with renal pathology such as papillary necrosis and interstitial nephritis.

Gynaecological

Women who received ARTHROTEC 50 during clinical trials reported the following gynaecological disorders: menorrhagia (1.3%), menstrual disorder (0.7%), metrorrhagia (0.6%), dysmenorrhoea (0.4%), leucorrhoea (0.4%) and vaginal bleeding (0.4%). Postmenopausal vaginal bleeding may be related to ARTHROTEC 50 administration. If it occurs, diagnostic workup should be undertaken to rule out gynaecological pathology. Breast pain, uterine spasm, and vaginal infection have also been reported.

Elderly

There was no significant difference in the safety profile of ARTHROTEC 50 in patients who were 65 years of age or older compared with younger patients.

Dosage Regimen

There was no significant difference in the safety profile of ARTHROTEC 50 in patients who received the drug BID versus TID.

Long-Term Administration

In patients treated with ARTHROTEC 50 for up to 10 months, the adverse events were primarily gastrointestinal in nature. The incidence of these events decreased over time, and there were no apparent cumulative effects of ARTHROTEC 50.

Additional adverse events which were reported are categorised as follows:

Incidence Greater Than 1%

In clinical trials, the following adverse events were reported by more than 1% of the subjects receiving ARTHROTEC 50 and may be causally related to the fixed-combination product: nausea (9.7%), dyspepsia (9.6%), flatulence (6.6%), headache (6.1%), gastritis (3.0%), dizziness (2.8%), vomiting (2.5%), constipation (1.8%), eructation (1.6%) and rash (1.2%).

Causal Relationship Unknown

The following adverse events were reported by 1% or less of the subjects receiving ARTHROTEC 50. Causal relationships between ARTHROTEC 50 and these events have not been established but cannot be excluded:

Blood and Lymphatic System Disorders: leucopenia, thrombocytopenia.

Cardiac Disorders: chest pain, palpitation.

Ear and Labyrinth Disorders: ear pain, tinnitus, vertigo.

Eye Disorders: eye pain, vision abnormal.

Gastrointestinal Disorders: abdomen enlarged, gastrointestinal ulceration (including duodenal, oesophageal, and gastric ulceration), duodenitis, oesophagitis, gastroesophageal reflux, gastrointestinal haemorrhage, glossitis, haematemesis, melena, dry mouth.

General Disorders and Administration Site Conditions: fatigue, fever, malaise, pain, rigours, oedema.

Hepatobiliary Disorders: gall bladder disorder.

Infections and Infestations: pharyngitis, hepatitis.

Investigations: ALT increase, AST increased, BUN increased, glycosuria, increased alkaline phosphatase, haematocrit decreased.

Metabolism and Nutritional Disorders: anorexia.

Musculoskeletal and Connective Tissue Disorders: myalgia, leg cramps.

Nervous System Disorders: dysgeusia, syncope, appetite increased, concentration impaired, hypoaesthesia, migraine, paraesthesia, somnolence, speech disorder.

Psychiatric Disorders: anxiety, depression, insomnia.

Respiratory, Thoracic and Mediastinal Disorders: dyspnoea, hyperventilation, sputum increased, hiccup.

Renal and Urinary Disorders: dysuria, urine abnormal.

Skin and Subcutaneous Tissue Disorders: angioedema, pruritus, purpura, rash erythematous, sweating increased, urticaria.

Vascular Disorders: hot flushes, hypertension.

Post-Marketing Experience

Additional adverse events reported from post-marketing experience include:

Blood and Lymphatic System Disorders: thrombocytopenia, agranulocytosis, platelet aggregation inhibition, haemolytic anaemia.

Cardiac Disorders: myocardial infarction, cardiac failure.

Congenital, Familial, and Genetic Disorders: congenital anomaly.

Eye Disorders: vision blurred[#].

Gastrointestinal Disorders: gastrointestinal perforation, pancreatitis, stomatitis, gastrointestinal inflammation.

General Disorders and Administration Site Conditions: chills, pyrexia.

Hepatobiliary Disorders: hepatic failure, hepatitis, jaundice.

Immune System Disorders: anaphylactic reaction.

Injury, Poisoning and Procedural Complications: uterine rupture, uterine perforation

Metabolism and Nutritional Disorders: fluid retention.

Nervous System Disorders: meningitis aseptic, cerebrovascular accident.

Pregnancy, Puerperium, and Perinatal Conditions: abnormal uterine contractions, retained placenta or membranes, anaphylactoid syndrome of pregnancy, abortion incomplete, premature baby/birth, fetal death, and congenital anomaly have been reported when misoprostol was administered in pregnant women. ARTHROTEC 50 is contraindicated in pregnant women and in women planning a pregnancy, or in whom pregnancy has not been excluded (see **CONTRAINDICATIONS** and **PRECAUTIONS, Use in Pregnancy**).

Psychiatric Disorders: mood altered, nightmares[#].

Renal and Urinary Disorders: tubulointerstitial nephritis, glomerulonephritis, glomerulonephritis membranous, glomerulonephritis minimal lesion, renal papillary necrosis, nephrotic syndrome, renal impairment, renal failure.

Reproductive System and Breast Disorders: infertility female (female fertility decreased), uterine haemorrhage.

Respiratory, Thoracic, and Mediastinal Disorders: dyspnoea.

Skin and Subcutaneous Tissue Disorders: cutaneous reactions (including rash and bullous eruption), mucocutaneous reactions[#], dermatitis exfoliative, erythema multiforme, uticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Vascular Disorders: vasculitis.

Description of selected adverse drug reactions

Arteriothrombotic events

Meta-analysis and pharmacoepidemiological data point towards an increased risk of arteriothrombotic events (for example myocardial infarction) associated with the use of diclofenac, particularly at a high dose (150 mg daily) and during long-term treatment (see **PRECAUTIONS**). A recent meta-analysis (CNT) estimated that, in comparison with placebo, allocation to diclofenac caused around 3 additional major vascular events per 1000 participants per year. This estimate reflects data from long term treatment with high dose diclofenac (150 mg/day).

These adverse reactions have been reported in very rare cases during treatment with ARTHROTEC 50.

DOSAGE AND ADMINISTRATION

After assessing the risk versus benefit for each patient, use the minimum effective dose for the shortest duration possible. Patients on long term treatment should be reviewed regularly with regards to

efficacy, risk factors and ongoing need for treatment.

Adults

Osteoarthritis and Rheumatoid Arthritis

The recommended adult oral dosage is one tablet to be taken with food, two or three times daily.

Tablets should be swallowed whole, not chewed.

Elderly/Renal Impairment/Hepatic Impairment

No adjustment of dosage is necessary in the elderly or in patients with hepatic impairment or mild[1] to moderate[1] renal impairment as pharmacokinetics are not altered to any clinically relevant extent. However, patients with severe[1] renal or hepatic impairment should be closely monitored.

Caution is also required for patients with renal, cardiac, or hepatic impairment, since the use of NSAIDs, including ARTHROTEC 50, may result in deterioration of renal function (see **CONTRAINDICATIONS** and **PRECAUTIONS**).

Children

The safety and efficacy of ARTHROTEC 50 in children has not been established.

OVERDOSAGE

The toxic dose of ARTHROTEC 50 tablets has not been determined. However, signs of overdosage from the components of the product have been described.

Signs and Symptoms

Diclofenac: Clinical signs that may indicate diclofenac overdose include gastrointestinal complaints, confusion, drowsiness, general hypotonia, and hallucinations. The highest reported overdose (5.0 g) in a 17 year old male resulted in loss of consciousness, increased intracranial pressure, aspiration pneumonitis and death 2 days after the overdose.

Low grade fever, hypotension and sinus tachycardia have been reported following NSAID overdose. Rarely, severe overdose may cause coma, respiratory depression, gastrointestinal bleeding and acute renal insufficiency.

Misoprostol: Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnoea, abdominal pain, diarrhoea, fever, palpitations, hypotension, bradycardia, hyperthermia and increased respiratory rate. Overdose in pregnancy has resulted in uterine contractions and fetal death.

Treatment of Overdosage

Treatment of ARTHROTEC 50 overdose should be symptomatic and supportive. Induced diuresis may be beneficial because diclofenac and misoprostol metabolites are excreted in the urine. The effect of dialysis on the elimination of diclofenac (99% protein bound) and misoprostol acid remains unproven. The use of oral activated charcoal may help to reduce the absorption of diclofenac and misoprostol. Activated charcoal is most effective when administered within 1 hour of ingestion. In

[1] Mild, moderate or severe renal impairment can be defined as **Mild**: creatinine clearance of 50-79 mL/min/1.73 m^2; **Moderate**: creatinine clearance of 20-49 mL/min/1.73 m^2 and **Severe**: less than 20 mL/min/1.73 m^2

patients who are not fully conscious or who have an impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube once the airway is protected.

Contact the Poisons Information Centre on 13 11 26 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

ARTHROTEC 50 (diclofenac sodium 50 mg/misoprostol 200 µg) tablets are available in cartons containing 10, 20, 60 or 90 tablets.

Not all pack sizes may be available.

ARTHROTEC 50 tablets are white, round, biconvex marked  on one side and SEARLE 1411 on the other side.

Storage

ARTHROTEC 50 tablets should be stored below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
West Ryde NSW 2114.

POISON SCHEDULE OF THE MEDICINE

S4 - Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

19 February 1998.

DATE OF MOST RECENT AMENDMENT

16 June 2017

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