פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר

1. NAME OF THE MEDICINAL PRODUCT

ARTHROTEC 50

ARTHROTEC 75

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients:

Diclofenac sodium 50 mg or 75 mg
Misoprostol 200 mcg

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. ARTHROTEC SHOULD NOT BE TAKEN BY PREGNANT WOMEN (see *CONTRAINDICATIONS, SPECIAL WARNINGS and PRECAUTIONS*).
PATIENTS MUST BE ADVISED OF THE ABORTIFACIENT 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 *SPECIAL WARNINGS AND PRECAUTIONS FOR USE)*. 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 *SPECIAL WARNINGS AND PRECAUTIONS FOR USE*).

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

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 *SPECIAL WARNINGS AND PRECAUTIONS FOR USE*).

3.PHARMACEUTICAL FORM

White, round, biconvex tablets approximately 10-11 mm in diameter. Each tablet consists of an enteric-coated core containing either 50 mg or 75 mg of diclofenac sodium surrounded by an outer mantle containing 200 mcg misoprostol.

Tablets are for oral administration.

4.CLINICAL PARTICULARS

4.1. Therapeutic indications

For patients requiring longterm anti-inflammatory treatment, in such circumstances where there is a high risk of developing hemorrhage or ulcer, i.e. , patients with a peptic ulcer or past gastric bleeding, patients with cardiovascular disease, patients over 65 and smokers.

4.2. Posology and method of administration

Undesirable effects may be minimized by using the minimum effective dose for the shortest duration necessary to control symptoms (see section 4.4 Special warnings and precautions for use).

Diclofenac/misoprostol is recommended at the following doses:

- Osteoarthritis, Rheumatoid arthritis
  - 50 mg/200 mcg—1 tablet two or three times daily
  - 75 mg/200 mcg—1 tablet twice daily
- Ankylosing spondylitis
  - 50 mg/200 mcg—1 tablet two, three, or four times daily
  - 75 mg/200 mcg—1 tablet twice daily
- Musculoskeletal disorders
  - 50 mg/200 mcg—1 tablet two or three times daily
  - 75 mg/200 mcg—1 tablet twice daily

Diclofenac/misoprostol tablets should be taken with a meal, and should not be chewed, crushed, or dissolved.

Elderly: *No dosage adjustment is recommended in elderly patients.*

Renal, Cardiac, and Hepatic Impairment: Caution is required for patients with renal, cardiac, or hepatic impairment, since the use of NSAIDs, including diclofenac/misoprostol, may result in deterioration of renal function (See section 4.4 **Special warnings and precautions for use**, **Renal Effects**).

Pediatric: Safety and effectiveness of diclofenac/misoprostol in children under the age of 18 years have not been established.

4.3. Contraindications

Diclofenac/misoprostol is contraindicated in:

- Patients with active peptic ulcer/haemorrhage or perforation or who have active GI bleeding or other active bleedings e.g. cerebrovascular bleedings.

- Pregnant women or in whom pregnancy has not been excluded (See sections 4.6 **Fertility, pregnancy and lactation** and **4.8 Undesirable effects**), and in women planning a pregnancy.

- Patients with a known hypersensitivity to diclofenac, aspirin, other NSAIDs, misoprostol, other prostaglandins, or any other ingredient of the product.

- Patients in whom attacks of asthma, urticaria or acute rhinitis are precipitated by aspirin or other non-steroidal anti-inflammatory agents.

- Treatment of peri-operative pain in the setting of coronary bypass graft (CABG) surgery.

- Patients with severe renal and hepatic failure.

- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The use of diclofenac/misoprostol with concomitant NSAIDs including COX-2 inhibitors should be avoided.

Warnings

Use in pre-menopausal women (see also section 4.3)

Arthrotec should not be used in pre-menopausal women unless they use effective contraception and have been advised of the risks of taking the product if pregnant (see section 4.6). The label will state: 'Not for use by pre-menopausal women unless using effective contraception'.

Precautions

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

• Renal/Cardiac/Hepatic

In patients with renal, cardiac or hepatic impairment caution is required since the use of NSAIDs may result in deterioration of renal function. In the following conditions Arthrotec should be used only in exceptional circumstances and with close clinical monitoring: advanced liver disease, severe dehydration.

In a large trial where patients received diclofenac for a mean of 18 months, ALT/AST elevations were observed in 3.1% of patients. ALT/AST elevations usually occur within 1-6 months. 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 diclofenac/misoprostol therapy, liver function should be monitored periodically. If diclofenac/misoprostol is used in the presence of impaired liver function, close monitoring is necessary. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, treatment with diclofenac should be discontinued.

Diclofenac metabolites are eliminated primarily by the kidneys (see section 5.2). 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.

In rare cases, NSAIDs, including diclofenac/misoprostol, may cause interstitial nephritis, glomerulitis, papillary necrosis and the nephrotic syndrome. NSAIDs inhibit the synthesis of renal prostaglandin which plays a supportive role in the maintenance of renal perfusion in patients whose renal blood flow and blood volume are decreased. In these patients, administration of an NSAID may precipitate overt renal decompensation, which is typically followed by recovery to pretreatment state upon discontinuation of NSAID therapy. Patients at greatest risk of such a reaction are those with congestive heart failure, liver cirrhosis, nephrotic syndrome and overt renal disease. Such patients should be carefully monitored while receiving NSAID therapy.

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

As with all NSAIDS, diclofenac/misoprostol can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. NSAIDs, including diclofenac/misoprostol, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with diclofenac/misoprostol and throughout the course of therapy.

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration. As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

Clinical trial and epidemiological data suggest that use of diclofenac, particularly at high dose (150mg daily) and in long term treatment may be associated with a small increased risk of serious arterial thrombotic events (for example myocardial infarction or stroke), which can be fatal.

Physicians and patients should remain alert for the development of such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur (see section 4.3).

• Blood system/Gastrointestinal

NSAIDs, including diclofenac/misoprostol, 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. When GI bleeding or ulceration occurs in patients receiving diclofenac/misoprostol, the treatment should be withdrawn. These events can occur at any time during treatment, with or without warning symptoms or in patients with a previous history of serious GI events.

Patients most at risk of developing these types of GI complications with NSAIDs are those treated at higher doses, the elderly, patients with cardiovascular disease, patients using concomitant aspirin, or patients with a prior history of, or active, gastrointestinal disease, such as ulceration, GI bleeding or inflammatory conditions.

Therefore, diclofenac/misoprostol should be used with caution in these patients and commence on treatment at the lowest dose available (see section 4.3).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. Caution should be advised in patients receiving concomitant medicines which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

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 on long-term treatment with NSAIDs, including ARTHROTEC, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

Arthrotec, in common with other NSAIDs, may decrease platelet aggregation and prolong bleeding time. Extra supervision is recommended in haematopoietic disorders or in conditions with defective coagulation or in patients with a history of cerebrovascular bleeding.

Caution is required in patients suffering from ulcerative colitis or Crohn's Disease as these conditions may be exacerbated (see section 4.8).

Care should be taken in elderly patients and in patients treated with corticosteroids, other NSAIDs, or anti-coagulants (see section 4.5).

• Skin Reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs, including diclofenac/misoprostol (see section 4.8). 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. Diclofenac/misoprostol should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

• Hypersensitivity

NSAIDs may precipitate bronchospasm in patients suffering from, or with a history of, bronchial asthma or allergic disease.

- Allergic reactions, including anaphylaxis, have been reported with NSAIDs, including diclofenac/misoprostol, and have occurred without prior exposure to the NSAID.

• Long-term treatment

All patients who are receiving long-term treatment with NSAIDs should be monitored as a precautionary measure (e.g. renal, hepatic function and blood counts). During long-term, high dose treatment with analgesic/anti-inflammatory drugs, headaches can occur which must not be treated with higher doses of the medicinal product.

Arthrotec may mask fever and thus an underlying infection.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Aseptic meningitis

As with other NSAIDs, aseptic meningitis with fever and coma has been observed on rare occasions in patients on diclofenac therapy. Although it is probably more likely to occur in patients with systemic lupus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease. If signs or symptoms of meningitis develop in a patient on diclofenac, the possibility of its being related to diclofenac should be considered.

Porphyria

The use of ARTHROTEC in patients with hepatic porphyria should be avoided. To date, one patient has been described in whom diclofenac sodium probably triggered a clinical attack of porphyria. The postulated mechanism, demonstrated in rats, for causing such attacks by diclofenac sodium, as well as some other NSAIDs, is through stimulation of the porphyrin precursor delta-aminolevulinic acid (ALA).

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

NSAIDs may attenuate the natriuretic efficacy of diuretics due to inhibition of intrarenal synthesis of prostaglandins. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, hence serum potassium should be monitored.

Because of their effect on renal prostaglandins, cyclo-oxygenase inhibitors such as diclofenac can increase the nephrotoxicity of cyclosporin. There is a possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Steady state plasma lithium and digoxin levels may be increased and ketoconazole levels may be decreased.

Pharmacodynamic studies with diclofenac have shown no potentiation of oral hypoglycaemic and anticoagulant drugs. However as interactions have been reported with other NSAIDs, caution and adequate monitoring are, nevertheless advised (see statement on platelet aggregation in Precautions).

Because of decreased platelet aggregation caution is also advised when using Arthrotec with anti-coagulants. NSAIDs may enhance the effects of anti-coagulants, such as warfarin, antiplatelet agents, such as aspirin, and serotonin re-uptake inhibitors (SSRIs) thereby increasing the risk of gastrointestinal bleeding (see section 4.4).

Cases of hypo and hyperglycaemia have been reported when diclofenac was associated with antidiabetic agents.

Caution is advised when methotrexate is administered concurrently with NSAIDs because of possible enhancement of its toxicity by the NSAID as a result of increase in methotrexate plasma levels.

Concomitant use with other NSAIDs or with corticosteroids may increase the frequency of side effects generally.

Anti-hypertensives including diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II antagonists (AIIA): NSAIDs can reduce the efficacy of diuretics and other antihypertensive drugs.

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 an AIIA with a cyclo-oxygenase inhibitor can increase the deterioration of the renal function, including the possibility of acute renal failure, which is usually reversible. The occurrence of these interactions should be considered in patients taking diclofenac/misoprostol with an ACE inhibitor or an AIIA.

Therefore, the concomitant administration of these drugs should be done with caution, especially in elderly patients. Patients should be adequately hydrated and the need to monitor the renal function should be assessed in the beginning of the concomitant treatment and periodically thereafter.

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

Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Diclofenac is displaced from its binding sites by aspirin, resulting in lower plasma concentrations, peak plasma levels, and AUC values. Therefore, concomitant administration of diclofenac sodium and aspirin is not recommended.

Phenobarbital toxicity has been reported to have occurred in a patient on chronic phenobarbital treatment following the initiation of diclofenac therapy.
In vitro, diclofenac interferes minimally with the protein binding of prednisolone (10% decrease in binding).
Benzylpenicillin, ampicillin, oxacillin, chlortetracycline, doxycycline, cephalothin, erythromycin, and sulfamethoxazole have no influence, *in vitro,* on the protein binding of diclofenac in human serum.

Potent CYP2C9 inhibitors: 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.

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

4.6. FERTILITY, PREGNANCY AND LACTATION

Fertility
Based on the mechanism of action, the use of NSAIDs, including diclofenac/misoprostol 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 NSAIDs, including diclofenac/misoprostal should be considered.

Pregnancy
Diclofenac/misoprostol is contraindicated in women who are pregnant because misoprostol induces uterine contractions and is associated with abortion, premature birth, and fetal death. Use of misoprostol has been associated with birth defects. Diclofenac may cause premature closure of the ductus arteriosus.

Inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from 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.

Women of childbearing potential should not be started on diclofenac/misoprostol until pregnancy is excluded, and should be fully counseled on the importance of adequate contraception while undergoing treatment. If pregnancy is suspected, use of the product should be discontinued.

Lactation
Misoprostol is rapidly metabolised in the mother to misoprostol acid, which is biologically active and is excreted in breast milk. Diclofenac/misoprostol should not be administered to nursing mothers because the excretion of misoprostol acid could cause undesirable effects such as diarrhea in nursing infants.

4.7.EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients who experience dizziness or other central nervous system disturbances while taking NSAIDs should refrain from driving or operating machinery.

4.8. Undesirable effects

In the table below the incidence of adverse drug reactions reported in controlled clinical studies where Arthrotec was administered to more than 2000 patients are listed. Additionally, adverse drug reactions reported during post-marketing surveillance are whose frequency cannot be estimated from the available data, such as spontaneous reports, have been listed at frequency 'unknown'. The most commonly observed adverse events are gastrointestinal in nature.

Organ System	Very Common (≥ 1/10)	Common (≥1/100 and <1/10)	Uncommon (≥1/1,000 and <1/100)	Rare (≥1/10,000, and <1/1,000)	Very Rare (<1/10,000)	Frequency: Unknown (Post-marketing experience)
Infections and infestations						Aseptic meningitis[1]
Blood and lymphatic system disorders			Thrombo-cytopenia			Aplastic anaemia, agranulocytosis, haemolytic anaemia, leucopenia
Immune system disorders				Anaphylactic reaction		Hypersensitivity
Metabolism and nutrition disorders						Anorexia
Psychiatric disorders		Insomnia				Psychotic reaction, disorientation, depression, anxiety, nightmares, mood change, irritability
Nervous system disorders		Headache, dizziness				Convulsions, memory disturbance, drowsiness, tremor, taste disturbance, paraesthesia
Eyes disorders						Visual disturbances, blurred vision
Ear and labyrinth disorders						Tinnitus
Cardiac disorders						Cardiac failure, palpitations
Vascular disorders						Shock, hypertension, hypotension, vasculitis
Respiratory, thoracic and mediastinal disorders						Asthma, pneumonitis, dyspnoea
Gastrointestinal disorders	Abdominal pain, diarrhoea[2], nausea, dyspepsia	Gastritis, vomiting, flatulence, eructation, constipation, peptic ulcer	Stomatitis			GI perforation [3], gastrointestinal bleeding [3], melaena, haematemesis, colitis, Crohn's disease, oesophageal disorder, mouth ulceration, glossitis, tongue odema, dry mouth
Hepato-biliary disorders		Alanine amino-transferase increased, aspartate aminotransferase increased		Hepatitis, jaundice	Hepatic failure	Hepatitis fulminant, blood bilirubin increased

Skin and subcutaneous tissue disorders		Erythema multiforme, rash, pruritus	Purpura, urticaria	Angio-edema		Toxic epidermal necrolysis[4], Stevens-Johnson syndrome[4], dermatitis exfoliative[4], dermatitis bullous, Henoch Schonlein purpura, mucocutaneous rash, rash vesicular, photosensitivity reaction, alopecia, urticaria
Renal and urinary disorders						Renal failure, acute renal failure, renal papillary necrosis, nephritis interstitial, nephrotic syndrome, proteinuria, haematuria
Pregnancy, puerperium and perinatal conditions						Intra-uterine death, uterine rupture, incomplete abortion, premature baby, anaphylactoid syndrome of pregnancy, retained placenta or membranes, uterine contractions abnormal
Reproductive system and breast disorders			Menorr-hagia, metrorr-hagia, vaginal haemo-rrhage, postmeno-pausal haemorr-hage			Uterine haemorrhage
Congenital, familial and genetic disorders						Birth defects
General disorders and administration site conditions						Oedema[5], chest pain, face oedema, fatigue, pyrexia, chills, inflammation
Investigations		Blood alkaline phosphatase increased				Decreased haemoglobin
Injury, poisoning and procedural complications						Uterine perforation

[1] Symptoms of aseptic meningitis (stiff neck, headache, nausea, vomiting, fever or impaired consciousness) have been reported during treatment with NSAIDs. Patients suffering from autoimmune disease (e.g. lupus erythematosus, mixed connective tissue disorders) seem to be more susceptible.

[2] Diarrhoea is usually mild to moderate and transient and can be minimised by taking Arthrotec 50 with food and by avoiding the use of predominantly magnesium-containing antacids.

[3] GI perforation or bleeding can sometimes be fatal, particularly in the elderly (see section 4.4).

[4] Serious skin reactions, some of them fatal, have been reported very rarely (see section 4.4).

[5] Especially in patients with hypertension or impaired renal function (see section 4.4).

Given the lack of precise and/or reliable denominator and numerator figures, the spontaneous adverse event reporting system through which post marketing safety data are collected does not allow for a medically meaningful frequency of occurrence of any undesirable effects.

With regard to the relative frequency of reporting of adverse reactions during post marketing surveillance, the undesirable effects at the gastrointestinal level were those received most frequently by the MAH (approximately 45% of all case reports in the company safety database) followed by cutaneous/hypersensitivity-type reactions, which is in agreement with the known side effects profile of the NSAIDs drug class.

Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150mg daily) and in long term treatment (see section 4.3 and 4.4 for Contraindications and Special warnings and special precautions for use).

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 CPK, increased LDH, myocardial infarction, palpitations, phlebitis, 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, gastritis, 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, rectal bleeding, thrombocythemia, thrombocytopenia.

Hypersensitivity: Angioedema, laryngeal/pharyngeal edema, urticaria.

Liver and biliary system: Abnormal hepatic function, bilirubinemia, hepatitis, jaundice, liver failure, pancreatitis.

Male reproductive disorders: Impotence, perineal pain.

Metabolic and nutritional: Alkaline phosphatase increased, BUN increased, dehydration, glycosuria, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypoglycemia, hyponatremia, periorbital edema, porphyria, weight changes.

Musculoskeletal system: Arthralgia, myalgia.

Psychiatric: Anxiety, concentration impaired, confusion, depression, disorientation, dream abnormalities, hallucinations, irritability, nervousness, paranoia, psychotic reaction.insomia

Respiratory system: Asthma, coughing, dyspnea, hyperventilation, pneumonia, respiratory depression.

Skin and appendages: Acne, alopecia, bruising, eczema, erythema multiforme, exfoliative dermatitis, pemphigoid reaction, photosensitivity, pruritus, pruritus ani, rash, skin ulceration, Stevens-Johnson syndrome, sweating increased, toxic epidermal necrolysis, purpura.

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.

4.9.OVERDOSE

The toxic dose of diclofenac/misoprostol has not been determined. However, signs of overdosage from the components of the product have been described.

Diclofenac sodium

Clinical signs that may suggest diclofenac sodium overdose include GI complaints, confusion, drowsiness or general hypotonia. Reports of overdosage with diclofenac cover 66 cases. In approximately one-half of these reports of overdosage, concomitant medications were also taken. The highest dose of diclofenac was 5.0 g in a 17-year-old man who suffered loss of consciousness, increased intracranial pressure, and aspiration pneumonitis, and died 2 days after overdose. A 24-year-old woman who took 4.0 g and the 28- and 42-year-old women, each of whom took 3.75 g, did not develop any clinically significant signs or symptoms. However, there was a report of a 17-year-old female who experienced vomiting and drowsiness after an overdose of 2.37 g of diclofenac.

Animal studies show a wide range of susceptibilities to acute overdosage, with primates being more resistant to acute toxicity than rodents (LD_{50} in mg/kg: rats, 55; dogs, 500; monkeys, 3200).

Misoprostol

The toxic dose of misoprostol in humans has not been determined. Cumulative total daily doses of 1600 mcg have been tolerated, with only symptoms of GI discomfort being reported. In animals, the acute toxic effects are diarrhea, GI lesions, focal cardiac necrosis, hepatic necrosis, renal tubular necrosis, testicular atrophy, respiratory difficulties, and depression of the central nervous system. Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnea, abdominal pain, diarrhea, fever, palpitations, hypotension, or bradycardia.

Arthrotec

Symptoms of overdosage with ARTHROTEC should be treated with supportive therapy. In case of acute overdosage, gastric lavage is recommended. Induced diuresis may be beneficial because diclofenac sodium and misoprostol metabolites are excreted in the urine. The effect of dialysis or hemoperfusion on the elimination of diclofenac sodium (99% protein bound) and misoprostol acid remains unproven. The use of oral activated charcoal may help to reduce the absorption of diclofenac sodium and misoprostol.

5.PHARMACOLOGICAL PROPERTIES

5.1.Pharmacodynamic properties

Pharmacotherapeutic group (ATC code): M01BX

Diclofenac/misoprostol is a fixed combination of a nonsteroidal, anti-inflammatory drug with analgesic properties, and a gastroduodenal mucosal protective prostaglandin E_1 analog.

Diclofenac has been shown to have anti-inflammatory and analgesic properties. The mechanism of action is thought to be related to inhibition of prostaglandin synthetase.

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 mucus secretion.

Misoprostol decreases pepsin output, gastric acid output, and gastric fluid volume under basal and under some stimulated conditions.

5.2.Pharmacokinetic properties

Diclofenac/ misoprostol

The pharmacokinetic profiles of diclofenac and misoprostol administered as the fixed combination 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 dosing , apart from a slight decrease in diclofenac sodium Cmax when administered concomitantly with misoprostol.

There was no accumulation of diclofenac or misoprostol acid in plasma following repeated doses of diclofenac/misoprostol.

Diclofenac

In man, orally administered diclofenac is rapidly and almost completely absorbed and distributed to the blood, liver and kidneys and is highly protein bound in the plasma. 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 elimination half-life ($t_{1/2}$) is 1 to 2 hours. 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. Forty percent (40%) to 60% of the drug and its metabolites (conjugates of the 3N-, 4N- and 5N –hydroxy derivatives of diclofenac) are eliminated in the urine and the balance through biliary excretion.

Misoprostol

Orally administered misoprostol is rapidly and extensively metabolized to the free acid, which is the principal pharmacologically active metabolite in the blood. The elimination half-life ($t_{1/2}$) is about 20-30 minutes. Single doses show a linear relationship with dose over the range of 200 to 400 mcg. Plasma steady state was achieved within two days. Approximately 73% of the administered dose is excreted in the urine, mainly as biologically inactive metabolites. In patients with mild-to-moderate renal impairment, $t_{1/2}$, C_{max}, and AUC were increased compared to controls, but there was no clear correlation between the degree of renal impairment and AUC. In patients with total renal failure, AUC was approximately doubled in four of six patients, suggesting that in these patients diclofenac/ misoprostol therapy should be started at the lower end of the dosing range (See section 4.2 **Posology and method of administration**).

The serum protein binding of misoprostol acid is less than 90 % and is concentration-independent in the therapeutic range.

5.3.Preclinical safety data

Diclofenac did not significantly increase tumor incidence in rats, and was negative for mutagenic potential in *in vivo* and *in vitro* tests. Diclofenac also did not affect fertility in rats, although maternotoxicity was induced at 4 mg/kg. No teratogenic effects were evident in teratology studies performed in mice, rats, or rabbits, but maternotoxicity and embryotoxicity occurred in some studies. Diclofenac has been shown to cross the placental barrier in mice and rats.

Misoprostol did not affect tumor occurrence or incidence in mice or rats, and did not show mutagenic potential in *in vitro* and *in vivo* assays. There was no evidence of teratogenicity evidence in rabbits at misoprostol dosages up to 1000 mcg/kg nor in rats at dosages up to 10,000 mcg/kg, which were the highest dosages feasible to test because of maternal toxicity. Rabbits given 1000 mcg/kg had an increased incidence of embryonic deaths. Rats given 1,600 mcg/kg had decreased implantations compared to a control group, but the values remained within the historical control range for the strain. Post-implantation fetal loss was observed in rats given 1,000 mcg/kg.

Misoprostol in multiples of the recommended therapeutic dose in animals has produced gastric mucosal hyperplasia. This characteristic response to E-series prostaglandins reverts to normal on discontinuation of the compound.

An oral teratology study was conducted with rabbits coadministered diclofenac and misoprostol at the ratio of 250:1. Dosages ranged up to 10 mg/kg of diclofenac with 40 mcg/kg of misoprostol. Embryotoxicity was observed at the high dose only; however, there was no evidence of fetotoxicity or teratogenicity at any dose.

No carcinogenicity studies of diclofenac/misoprostol have been done.

6.PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients in ARTHROTEC 50 include: Microcrystalline cellulose, methylhydroxypropylcellulose, lactose monohydrate, crospovidone, corn starch, cellulose acetate phthalate, povidone K30, diethyl phthalate, hydrogenated castor oil, magnesium stearate, colloidal silicone dioxide , talc.
Inactive ingredients in ARTHROTEC 75 include: Microcrystalline cellulose, lactose, maize starch, polyvidone K30, magnesium stearate, methacrylic acid copolymer, sodium hydroxide, talc, triethyl citrate, methylhydoxypropylcellulose, crospovidone, colloidal silicone dioxide, hydrogenated castor oil.

6.2 Special precautions for storage: store below 25°C, in a dry place.

6.3 Nature and contents of container: Arthrotec is presented in Aluminium laminated blisters in pack sizes of 20, 30 and 60 tablets .
Not all pack sizes may be marketed.

MANUFACTURER: Piramal healthcare UK LTD.
LICENSE HOLDER: Pfizer Pharmaceuticals Israel Ltd, 9 Shenkar st., Herzeliya.