Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Arthrotec 75 modified-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet consists of a gastro-resistant core containing 75 mg diclofenac sodium surrounded by an outer mantle containing 200 micrograms misoprostol.

Excipients: Contains lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release tablet.

Product imported from Italy:
White, round, biconvex tablets marked 'SEARLE' over '1421' on one side, and four times 'A' around the circumference with '75' in the centre on the reverse side
Or
White, round biconvex tablets with no markings.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Arthrotec 75 is indicated for patients who require the non-steroidal anti-inflammatory drug diclofenac together with misoprostol.

The diclofenac component of Arthrotec 75 is indicated for the symptomatic treatment of osteoarthritis and rheumatoid arthritis. The misoprostol component of Arthrotec 75 is indicated for patients with a special need for the prophylaxis of NSAID-induced gastric and duodenal ulceration.

4.2 Posology and method of administration

Adults

One tablet to be taken with food, two times daily. Tablets should be swallowed whole, not chewed.

Elderly/Renal, Cardiac and Hepatic Impairment

No adjustment of dosage is necessary in the elderly or in patients with hepatic impairment or mild to moderate renal impairment as pharmacokinetics are not altered to any clinically relevant extent. Nevertheless, elderly patients and patients with renal, cardiac or hepatic impairment should be closely monitored *(see section 4.4 and section 4.8).*

Children (under 18 years)

The safety and efficacy of Arthrotec 75 in children has not been established.

4.3 Contraindications

Arthrotec 75 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 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 artery bypass graft (CABG) surgery.
- Patients with severe renal and hepatic failure.
- Patients with severe heart failure.

4.4 Special warnings and precautions for use

Warnings

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

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

Arthrotec 75 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 in 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 and in the elderly, caution is required since the use of NSAIDs may result in deterioration of renal function. In the following conditions Arthrotec 75 should be used only in exceptional circumstances and with close clinical monitoring: advanced cardiac failure, advanced kidney failure, advanced liver disease, severe dehydration.

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 uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with diclofenac after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

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).

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).*

Arthrotec 75 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

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

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.

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 ciclosporin. 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 advised when using Arthrotec 75 with anti-coagulants. NSAIDs may enhance the effects of anti-coagulants, such as warfarin, aniplatelet 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 gastrointestinal ulceration or bleeding and 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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Arthrotec 75 is contraindicated in pregnant women and in women planning a pregnancy because misoprostol induces uterine contractions and is associated with abortion, premature birth, and fetal death. Use of misoprostol has been associated with birth defects. Also diclofenac may cause premature closure of the ductus arteriosus.

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 is excreted in breast milk in very small quantities. In general, the potential effects on the infant from any exposure to misoprostol and its metabolites via breast feeding are unknown. However, diarrhoea is a recognised side effect of misoprostol and could occur in infants of nursing mothers. Arthrotec 75 should therefore not be administered to nursing mothers.

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 surviellance are whose frequency cannot be estimated from the availalbe 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)	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		Hepatitis, jaundice	Hepatitis fulminant, aspartate aminotransferase increased, blood bilirubin increased

Skin and subcutaneous tissue disorders		Erythema multiforme, rash, pruritus	Purpura, urticaria	Angioedema	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			Menorrhagia, metrorrhagia, vaginal haemorrhage, postmenopausal haemorrhage		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 75 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 suggest that use of diclofenac, particularly at high doses (150 mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) *(see section 4.4).*

4.9 Overdose

The toxic dose of Arthrotec 75 has not been determined and there is no experience of overdosage. Intensification of the pharmacological effects may occur with overdosage.

Management of acute poisoning with NSAIDs essentially consists of supportive and symptomatic measures. It is reasonable to take measures to reduce absorption of any recently consumed drug by forced emesis, gastric lavage or activated charcoal.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group (ATC code): M01BX

Arthrotec 75 is a non-steroidal, anti-inflammatory drug, which is effective in treating the signs and symptoms of arthritic conditions.

This activity is due to the presence of diclofenac, which has been shown to have anti-inflammatory and analgesic properties.

Arthrotec 75 also contains the gastroduodenal mucosal protective component misoprostol, which is a synthetic prostaglandin E1 analogue that enhances several of the factors that maintain gastroduodenal mucosal integrity.

Arthrotec 75 administered bd provides 200 micrograms less misoprostol than Arthrotec tds, whilst providing the same daily dose (150 mg) of diclofenac and may offer a better therapeutic ratio for certain patients.

5.2 Pharmacokinetic properties

The pharmacokinetic profiles following oral administration of a single dose or multiple doses of diclofenac sodium and misoprostol administered as Arthrotec 75 are similar to the profiles when the two drugs are administered as separate tablets. There are no pharmacokinetic interactions between the two components, apart from a slight decrease in diclofenac sodium Cmax when administered concomitantly with misoprostol.

Diclofenac sodium is completely absorbed from the gastrointestinal (GI) tract after fasting oral administration. Only 50 % of the absorbed dose is systemically available due to first pass metabolism. Peak plasma levels are achieved in 2 hours (range 1-4 hours) when given as a single dose under fasting conditions. Under fed conditions diclofenac Tmax is increased to 4 hours. The area-under-the plasma-concentration curve (AUC) is dose proportional within the range of 25 mg to 150 mg. The steady state absorption of diclofenac is reduced following the administration of Arthrotec 75 tablets with food, Cmax and AUC are reduced by approximately 40% and 20%, respectively.

The terminal half-life is approximately 2 hours. Clearance and volume of distribution are about 350 ml/min and 550 ml/kg, respectively. More than 99 % of diclofenac sodium is reversibly bound to human plasma albumin, and this has been shown not to be age dependent.

Diclofenac sodium is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Approximately 65 % of the dose is excreted in the urine and 35 % in the bile. Less than 1 % of the parent drug is excreted unchanged.

Misoprostol is rapidly and extensively absorbed, and it undergoes rapid metabolism to its active metabolite, misoprostol acid, which is eliminated with an elimination $t_{½}$ of about 30 minutes. No accumulation of misoprostol acid was found in multiple-dose studies, and plasma steady state was achieved within 2 days. The serum protein binding of misoprostol acid is less than 90 %. Approximately 70 % of the administered dose is excreted in the urine, mainly as biologically inactive metabolites.

Single and multiple dose studies have been conducted comparing the pharmacokinetics of Arthrotec 75 with the diclofenac 75 mg and misoprostol 200 micrograms components administered separately. Bioequivalence between the two methods of providing diclofenac were demonstrable for AUC and absorption rate (Cmax/AUC). In the steady state comparisons under fasted conditions bioequivalence was demonstrable in terms of AUC.

Food reduced the rate and extent of absorption of diclofenac for both Arthrotec 75 and co-administered diclofenac. Despite the virtually identical mean AUCs in the fed, steady state, statistical bioequivalence was not established. This however is due to the broad co-efficients of variation in these studies due to the wide inter-individual variability in time to absorption and the extensive first-pass metabolism that occurs with diclofenac.

Bioequivalence in terms of AUC (0-24 h) was demonstrable when comparing steady state pharmacokinetics of Arthrotec 75 given bd with diclofenac 50 mg/misoprostol 200 micrograms given tds, both regimens providing a total daily dose of 150 mg diclofenac.

With respect to administration of misoprostol, bioequivalence was demonstrated after a single dose of Arthrotec 75 or misoprostol administered alone. Under steady state conditions food decreases the misoprostol Cmax after Arthrotec 75 administration and slightly delays absorption, but the AUC is equivalent.

5.3 Preclinical safety data

In co-administration studies in animals, the addition of misoprostol did not enhance the toxic effects of diclofenac. The combination was also shown not to be teratogenic or mutagenic. The individual components show no evidence of carcinogenic potential.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Arthrotec 75 tablets contain:

Lactose Monohydrate
Microcrystalline Cellulose
Maize Starch
Povidone K-30
Magnesium Stearate
Methylacrylic Acid
Sodium Hydroxide
Talc
Triethylcitrate
Hypromellose
Crospovidone
Hydrogenated Castor Oil
Colloidal Silicon Dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf life expiry date of this product is the date shown on the blister strips and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 25 °C. Store in the original package.

6.5 Nature and contents of container

Cardboard carton containing three blisters (10 tablets per blister).

Pack size: 30 tablets

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Profind Wholesale Ltd.
Unit 625, Kilshane Avenue
Northwest Business Park
Dublin 15

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1500/074/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th February 2011

10 DATE OF REVISION OF THE TEXT