1 NAME OF THE MEDICINAL PRODUCT

Masidemen 50mg/200microgram Modified-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Masidemen 50 mg/200 microgram modified-release tablet contains 50 mg diclofenac sodium and 200 microgram misoprostol.

Excipient with known effect:
Each Masidemen 50 mg/200 microgram modified-release tablet contains 20 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release tablet.

White, circular, biconvex uncoated tablets, 11.5 mm in diameter and 6.2 mm in thickness, plain on one side and embossed “DM2” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The diclofenac component of Masidemen is indicated for the symptomatic treatment of osteoarthritis and rheumatoid arthritis. The misoprostol component of Masidemen 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 or three times daily. Tablets should be swallowed whole, not chewed.

**Elderly and patients with renal, cardiac or 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 diclofenac/misoprostol in children has not been established.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

### 4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Patients with active peptic ulcer/haemorrhage or perforation or who have active gastrointestinal (GI) bleeding or other active bleedings e.g. cerebrovascular bleedings.
- Patients who previously suffered from gastro-intestinal bleeding caused by NSAIDs.
- Pregnant women and in women planning a pregnancy.
- Breastfeeding women
- Patients with a known hypersensitivity to aspirin, other NSAIDs, or other prostaglandins.
- 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.

### 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)**

Diclofenac/misoprostol 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 or hepatic impairment**

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 diclofenac/misoprostol should be used only in exceptional circumstances and with close clinical monitoring: advanced cardiac failure, advanced kidney failure, 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 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 (150 mg 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).

Diclofenac/misoprostol, 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.

**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.

Diclofenac/misoprostol 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 also advised when using diclofenac/misoprostol 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 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
Diclofenac/misoprostol is contraindicated in pregnant women and in women planning a pregnancy because misoprostol induces uterine contractions and is associated with abortion, premature birth, and foetal 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 counselled on the importance of adequate contraception while undergoing treatment. If pregnancy is suspected, use of the product should be discontinued.

Breastfeeding
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. Diclofenac/misoprostol should therefore not be administered to nursing mothers.

Fertility
No fertility data are available

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 diclofenac sodium/misoprostol 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 with frequency unknown. The most commonly observed adverse events are gastrointestinal in nature.

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Very common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000)</th>
<th>Frequency unknown (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Aseptic meningitis¹</td>
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<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
<td>Aplastic anaemia, agranulocytosis, haemolytic anaemia, leucopenia</td>
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<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>Anaphylactic reaction</td>
<td></td>
<td></td>
<td>Hypersensitivity</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
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<td>Anorexia</td>
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<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td>Insomnia</td>
<td></td>
<td></td>
<td>Psychotic reaction, disorientation, depression, anxiety, nightmares, mood change, irritability</td>
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<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td>Headache, dizziness</td>
<td></td>
<td></td>
<td>Convulsions, memory disturbance, drowsiness, tremor, taste disturbance, paraesthesia</td>
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<tr>
<td>Eyes disorders</td>
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<td></td>
<td>Visual disturbances, blurred vision</td>
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<tr>
<td>Ear and labyrinth disorders</td>
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<td></td>
<td>Tinnitus</td>
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<tr>
<td>Cardiac disorders</td>
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<td></td>
<td>Cardiac failure, palpitations</td>
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<tr>
<td>Vascular disorders</td>
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<td></td>
<td></td>
<td>Shock, hypertension, hypotension, vasculitis</td>
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<tr>
<td>Respiratory, thoracic and abdominal disorders</td>
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<td>Asthma,</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain, diarrhoea&lt;sup&gt;2&lt;/sup&gt;, nausea, dyspepsia</td>
<td>Gastritis, vomiting, flatulence, eructation, constipation, peptic ulcer</td>
<td>Stomatitis</td>
<td>GI perforation&lt;sup&gt;3&lt;/sup&gt;, gastrointestinal bleeding&lt;sup&gt;3&lt;/sup&gt;, melena, haematemesis, colitis, Crohn's disease, oesophageal disorder, mouth ulceration, glossitis, tongue oedema, dry mouth</td>
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<tr>
<td>Hepato-biliary disorders</td>
<td>Alanine aminotransferase increased</td>
<td>Hepatitis, jaundice</td>
<td>Hepatic failure</td>
<td>Hepatitis fulminant, aspartate aminotransferase increased, blood bilirubin increased</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Erythema multiforme, rash, pruritus</td>
<td>Purpura, urticaria</td>
<td>Angioedema</td>
<td>Toxic epidermal necrolysis&lt;sup&gt;4&lt;/sup&gt;, Stevens-Johnson syndrome&lt;sup&gt;4&lt;/sup&gt;, dermatitis exfoliative&lt;sup&gt;4&lt;/sup&gt;, dermatitis bullous, Henoch Schonlein purpura, mucocutaneous rash, rash vesicular, photosensitivity reaction, alopecia, urticaria</td>
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<tr>
<td>Renal and urinary disorders</td>
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<td></td>
<td></td>
<td>Renal failure, acute renal failure, renal papillary necrosis, nephritis interstitial, nephrotic syndrome, proteinuria, haematuria</td>
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<tr>
<td>Pregnancy, puerperium and perinatal conditions</td>
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<td>Intra-uterine death, uterine rupture, incomplete abortion, premature baby, anaphylactoid syndrome of pregnancy,</td>
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<tr>
<td><strong>Reproductive system and breast disorders</strong></td>
<td>Menorrhagia, metrorrhagia, vaginal haemorrhage, postmenopausal haemorrhage</td>
<td>Uterine haemorrhage</td>
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<tr>
<td><strong>Congenital, familial and genetic disorders</strong></td>
<td>Birth defects</td>
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<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>Blood alkaline phosphatase increased</td>
<td>Decreased haemoglobin</td>
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<tr>
<td><strong>Investigations</strong></td>
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<tr>
<td><strong>Injury, poisoning and procedural complications</strong></td>
<td></td>
<td>Uterine perforation</td>
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</tbody>
</table>

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 Masidemen 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 ).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

The toxic dose of diclofenac/misoprostol 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

Masidemen 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.

Masidemen 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.
5.2 Pharmacokinetic properties

The pharmacokinetic profiles following oral administration of a single dose or multiple doses of diclofenac sodium and misoprostol administered as diclofenac sodium/misoprostol 50 mg/200 microgram and diclofenac sodium/misoprostol 75 mg/200 microgram are similar to the profiles when the two drugs are administered as separate tablets and there are no pharmacokinetic interactions between the two components, apart from a slight decrease in diclofenac sodium C\text{max} 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 T\text{max} 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 diclofenac sodium/misoprostol 75 mg/200 microgram with food, C\text{max} 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\text{1/2} 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.

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

Core:
- Microcrystalline cellulose (E460)
- Lactose monohydrate
- Maize starch
- Povidone K30
- Magnesium stearate (E470b)
- Purified talc (E553b)

Mantle/Coat:
- Hydroxypropylmethylcellulose type 2910 (E464)
- Methacrylic acid-ethyl acrylate copolymer (1:1)
- Purified talc (E553b)
- Triethyl citrate (E1505)
- Microcrystalline cellulose (E460)
- Sodium starch glycolate
- Hydrogenated castor oil

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister packs- 3Ply Alu-Alu laminated film and a plain blister foil which is hard tempered, heat sealable against PVC with 10, 20, 30, 60, 90 and 100 modified-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.
Reykjavíkurvegi 76-78
220 Hafnarfjörður
Iceland

8 MARKETING AUTHORISATION NUMBER(S)

PL 30306/0389

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

13/02/2014

10 DATE OF REVISION OF THE TEXT

13/02/2014