Arthrotec®

Diclofenac Sodium/Misoprostol

Modified Release Tablets

CDS

AfME Markets using same as LPD: Ghana, Nigeria

1. NAME OF THE MEDICINAL PRODUCT

Arthrotec® 75 modified-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients:

Diclofenac sodium 75 mg
Misoprostol 200 mcg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White, round, biconvex tablets approximately 10 mm to11 mm in diameter. Each tablet consists of an enteric-coated core containing 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

Diclofenac/misoprostol is indicated for acute and chronic treatment of the signs and symptoms of:

- rheumatoid arthritis
- osteoarthritis
- ankylosing spondylitis
- acute musculoskeletal disorders.

The diclofenac component is effective in treating the signs and symptoms of arthritic conditions. The misoprostol component is indicated for prophylaxis of nonsteroidal anti-inflammatory drug (NSAID)-induced gastric and duodenal ulceration.

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.

Diclofenac/misoprostol is recommended at the following doses:

- Osteoarthritis, Rheumatoid arthritis
    - 75 mg/200 mcg—1 tablet twice daily

- Ankylosing spondylitis
    - 75 mg/200 mcg—1 tablet twice daily
- Musculoskeletal disorders
    - 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 sections **4.3 Contraindications** and **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 gastrointestinal bleeding.

Women who are pregnant, or in whom pregnancy has not been excluded (see sections **4.6 Fertility, pregnancy and lactation** and **4.8 Undesirable effects**).

Patients with known hypersensitivity to diclofenac sodium, misoprostol, or to any of the excipients. The potential exists for cross sensitivity to aspirin and other NSAIDs. Diclofenac/misoprostol should not be given to patients in whom aspirin and other NSAIDs induce the symptoms of asthma, nasal polyps, angioedema or urticaria.

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

The use of diclofenac/misoprostol with concomitant systemic non-aspirin NSAIDs including cyclooxygenase-2 (COX-2) inhibitors should be avoided. Concomitant use of a systemic NSAID and another systemic NSAID may increase frequency of gastrointestinal ulcers and bleeding.

Cardiovascular Effects

NSAIDs may cause an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with 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 cardiovascular disease or CV risk factors may be at greater risk in terms of absolute incidence, due to their increased rate at baseline. To minimize the potential risk for an adverse cardiovascular event in patients treated with diclofenac/misoprostol, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous 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 Contraindications**).

Hypertension

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/misprostol, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with diclofenac/misprostol and throughout the course of therapy.

Fluid Retention and Edema

As with other drugs known to inhibit prostaglandin synthesis, fluid retention and edema have been observed in some patients taking NSAIDs, including diclofenac/misoprostol. Therefore, diclofenac/misoprostol should be used with caution in patients with compromised cardiac function and other conditions predisposing to, or worsened by, fluid retention. Patients with pre-existing congestive heart failure or hypertension should be closely monitored.

Gastrointestinal (GI) Effects

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. Patients most at risk of developing these types of GI complications with NSAIDs are the elderly, patients with cardiovascular disease, patients using concomitant corticosteroids, antiplatelet drugs (such as aspirin), selective serotonin reuptake inhibitors, patients who consume alcohol 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 (see section **4.3 Contraindications**).

Renal Effects

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, overt renal disease, and the elderly. Such patients should be carefully monitored while receiving NSAID therapy.

In patients with renal, cardiac, or hepatic impairment, caution is required since the use of NSAIDs,

including diclofenac/misoprostol, may result in deterioration of renal function. Caution should be used when initiating treatment with diclofenac/misoprostol in patients with severe dehydration. Caution is also recommended in patients with kidney disease (see section **4.3 Contraindications**). The dose should be kept as low as possible and renal function should be monitored.

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

Skin Reactions

Serious skin reactions, some of them fatal, including drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and generalized bullous fixed drug eruption (GBFDE) have been reported very rarely in association with the use of NSAIDs, including diclofenac/misoprostol. 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.

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

Hepatic Effects

In clinical trials of 4 to 12 weeks duration, clinically significant (>3 times the upper limit of normal) elevations of SGPT (ALT) and/or SGOT (AST), were observed in 1.6% or less of patients who received diclofenac/ misoprostol or diclofenac/placebo. 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 to 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. (see section **4.3 Contraindications.**)

Hematological Effects

NSAIDs, including diclofenac, increase platelet aggregation time. Misoprostol does not exacerbate the effects of diclofenac on platelet activity.

Use with oral anticoagulants

The concomitant use of NSAIDs, including diclofenac/misoprostol, with oral anticoagulants increases the risk of GI and non-GI bleeding and should be given with caution. Oral anticoagulants include 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 (see section **4.5 Interactions with other medicinal products and other forms of interactions**).

General

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

4.5. Interaction with other medicinal products and other forms of interaction

Acetylsalicylic Acid: 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/misoprostol and aspirin is not recommended.

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

Anti-coagulants: Some NSAIDs have been shown to interact with oral anticoagulants, although diclofenac has not been shown to interact with anticoagulants of the warfarin type. Therefore, patients receiving concurrent therapy with diclofenac/misoprostol should be monitored to ensure that no change in anticoagulant dosage is required.

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

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 and/or diuretics with a cyclooxygenase 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 and/or diuretics.

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.

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding.

Cyclosporine: Because of their effect on renal prostaglandins, NSAIDs such as diclofenac may increase the risk of nephrotoxicity with cyclosporine.

When co-administered with cyclosporine, there is a two-fold increase in diclofenac systemic exposure. It is prudent to start with the lowest dose of diclofenac/misoprostol and to monitor closely for signs of toxicity.

Digoxin: Elevated digoxin levels have been reported in patients receiving digoxin and diclofenac. Patients receiving digoxin and diclofenac/misoprostol should be monitored for possible digoxin toxicity.

Hypoglycemic agents: Diclofenac does not alter glucose metabolism in normal subjects, and the effects of oral hypoglycemic agents were not altered by the concomitant administration of diclofenac. However, there have been reports of changes in the effects of oral hypoglycemic agents in the presence of NSAIDs. Therefore, diclofenac/misoprostol should be administered with caution in patients receiving insulin or oral hypoglycemic agents.

Lithium: Diclofenac decreases lithium renal clearance and increases lithium plasma levels. Therefore, diclofenac/misoprostol should be administered with caution in patients receiving lithium.

Methotrexate: Caution is advised when methotrexate is administered concurrently with NSAIDs, including diclofenac/misoprostol, because NSAID administration may result in increased plasma levels of methotrexate especially in patients receiving high doses of methotrexate.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

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.

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/misoprostol 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 (see sections **4.3 Contraindications** and **4.8 Undesirable effects**). 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.

If used during second or third trimester of pregnancy, NSAIDs 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 and are usually reversible upon discontinuation. Pregnant women on NSAIDs should be closely monitored for amniotic fluid volume.

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 diarrhoea in nursing infants.

4.7. Effects on ability to drive and use machines

The effect of diclofenac/misoprostol on the ability to drive and use machines has not been systematically evaluated.

4.8. Undesirable effects

Adverse drug reactions reported from clinical trials and post marketing experience include:

Adverse Drug Reactions Table	
System Organ Class	**Adverse Drug Reactions**
Infections and infestations	Vaginal infection
Blood and lymphatic system disorders	Haemolytic anaemia*, agranulocytosis*, thrombocytopenia*, platelet aggregation inhibition*
Immune system disorders	Anaphylactic reaction*
Metabolism and nutritional disorders	Fluid retention*
Psychiatric disorders	Insomnia, nightmare*, mood altered*
Nervous system disorders	Cerebrovascular accident*, meningitis aseptic*, headache, dizziness
Eye disorders	Vision blurred*
Cardiac disorders	Myocardial infarction*, cardiac failure*
Vascular disorders	Hypertension*, vasculitis*
Respiratory, thoracic, and mediastinal disorders	Dyspnoea*
Gastrointestinal disorders	Gastrointestinal perforation*, gastrointestinal haemorrhage*, pancreatitis*, gastrointestinal ulcer*, duodenitis, gastritis, oesophagitis, stomatitis*, gastrointestinal inflammation*, abdominal pain, diarrhoea, nausea, dyspepsia, vomiting, constipation, flatulence, eructation
Hepatobiliary disorders	Hepatic failure*, jaundice*, hepatitis*
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis*, Stevens-Johnson syndrome*, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)*,erythema multiforme*, dermatitis bullous*, dermatitis exfoliative*, angioedema*, urticaria*, purpura, mucocutaneous reactions*, rash*, pruritus, generalized bullous fixed drug eruption (GBFDE)*
Renal and urinary disorders	Renal failure*, renal impairment*, renal papillary necrosis*, nephrotic syndrome*, tubulointerstitial nephritis*, glomerulonephritis membranous*, glomerulonephritis minimal lesion*, glomerulonephritis*
Pregnancy, puerperium, and perinatal conditions	Foetal death*, anaphylactoid syndrome of pregnancy*, abortion incomplete*, premature baby*, abnormal uterine contractions*, retained placenta or membranes*

Reproductive system and breast disorders	Metrorrhagia, menorrhagia, uterine haemorrhage*, vaginal haemorrhage (including postmenopausal bleeding), menstrual disorder, breast pain, dysmenorrhoea, uterine spasm, infertility female (female fertility decreased)*
Congenital, familial, and genetic disorders	Congenital anomaly*
General disorders and administration site conditions	Pyrexia*, oedema*, chills*
Investigations	Alanine aminotransferase increased, haematocrit decreased, aspartate aminotransferase increased, blood alkaline phosphatase increased
Injury, poisoning, and procedural complications	Uterine rupture*, uterine perforation*

* Adverse reactions identified from post-marketing experience.

Clinical Trials:

Adverse reactions reported from controlled clinical trials up to 24 months duration involved primarily the gastrointestinal system. Abdominal pain and diarrhoea were generally transient and mild to moderate in severity, occurring early in the course of therapy, and lasting several days. The abdominal pain and diarrhoea usually resolved spontaneously while continuing diclofenac/misoprostol.

In general, the adverse event profile of diclofenac/misoprostol in patients 65 years of age and older was similar to that of younger patients. The only clinically relevant differences were that patients 65 years of age and older appeared to be less tolerant to the gastrointestinal effects of diclofenac/misoprostol given three times a day.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after marketing 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 according to their local requirements.

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. Clinical signs that may indicate diclofenac overdose include gastrointestinal complaints, confusion, drowsiness, or general hypotonia. Clinical signs that may indicate misoprostol overdose are sedation, tremor, convulsions, dyspnea, abdominal pain, diarrhoea, fever, palpitations, hypotension, or bradycardia.

Patients should be managed by symptomatic and supportive care following an overdose with diclofenac/misoprostol. There are no specific antidotes. In case of acute overdosage, emesis and/or gastric lavage may be considered dependent upon amount ingested and time since ingestion. The use of oral activated charcoal may help to reduce the absorption of diclofenac/misoprostol. 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 (less

than 90% protein bound) remains unproven.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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. 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. (see sections **4.2 Posology and method of administration** and **4.3 Contraindications**).

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 to 30 minutes. Single doses show a linear relationship with dose over the range of 200 mcg 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 (see sections **4.2 Posology and method of administration** and **4.3 Contraindications**).

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.

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

Arthrotec 75 tablets contain:

Core:
lactose monohydrate
microcrystalline cellulose
maize starch
povidone K-30
magnesium stearate

Mantle/Coat:
methylacrylic acid copolymer type C
sodium hydroxide
talc
triethylcitrate
hypromellose
crospovidone

hydrogenated castor oil
colloidal silicon dioxide
microcrystalline cellulose

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Do not use Arthrotec after the expiry date which is stated on the Carton/Blister after EXP:. The expiry date refers to the last day of that month.

6.4. Special precautions for storage

Keep out of the sight and reach of children.

Store below 30ºC.

6.5. Nature and contents of container

Arthrotec 75 is presented in cold-formed aluminium blisters in pack sizes of 20, 100 tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

Keep out of the sight and reach of children.

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

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. FURTHER INFORMATION

MANUFACTURED BY

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8. PRESCRIPTION STATUS

Prescription only medicine

9. DATE OF REVISION OF THE TEXT

June 2023