SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICAL PRODUCT

Remethan 25 mg gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 25 mg diclofenac sodium.

Excipient(s) with known effect
Each gastro-resistant tablet contains 52.8 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablet.

Yellow, round, enteric-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Remethan is indicated for the treatment of rheumatoid arthritis, ankylosing spondylitis, osteoarthrosis, low back pain, frozen shoulder, tendinitis, tenosynovitis, bursitis, strains, sprains and acute gout. Remethan is also indicated for the control of pain and inflammation in orthopaedic, dental and other minor surgery.
In children it is indicated for the treatment of Juvenile chronic arthritis.

4.2 Posology and method of administration

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

Posology
Adults:
The recommended adult dose of Remethan is 75-150 mg daily given in two or three divided doses. The maximum daily dose is 150 mg.

Children:

Children should be given 1-3 mg/kg per day in divided doses.

Elderly:
Although the pharmacokinetics of Remethan are not impaired to any clinically relevant extent in elderly patients, non-steroidal anti-inflammatory drugs should be used with particular caution in such patients who generally are more prone to adverse reactions. In particular it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight (see also Precautions) and the patient should be monitored for GI bleeding for 4 weeks following initiation of NSAID therapy.

Method of administration
Oral administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Remethan is contra-indicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, urticaria or acute rhinitis) to diclofenac sodium, aspirin, any other non-steroidal anti-inflammatory drug and during pregnancy.

Remethan is also contra-indicated in patients with history of gastrointestinal bleeding or perforation related to previous NSAIDs therapy, active or history of recurrent peptic ulcer / haemorrhage (two or more distinct episodes of proven ulceration or bleeding) and severe heart 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

Undesirable effects may be minimized by using the minimum effective dose for the shortest duration necessary to control symptoms (see paragraph 4.2 and gastro-intestinal and cardiovascular hazards mentioned below).

Gastro-intestinal: The use of Remethan with concomitant NSAIDs including cyclooxygenase-2-selective inhibitors should be avoided. Undesirable effects may be minimized by using the minimum effective dose for the shortest duration necessary to control symptoms.
Close medical surveillance is imperative in patients with symptoms indicative of gastro-intestinal disorders, with a history suggestive of gastric or intestinal ulceration, with ulcerative colitis, or with Crohn's disease. GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events. The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3) and in the elderly. These patients should commence treatment on the lowest dose available.
The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding or perforation, which may be fatal. Gastrointestinal bleeding or ulceration / perforation, haematemesis and malaena have in general more serious consequences in the elderly.

NSAIDs should be given with care in patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these condition may be exacerbated.
Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and 4.5). 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 medications 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). When gastro-intestinal bleeding or ulceration occurs in patients receiving Remethan, the drug should be withdrawn.
NSAIDs, including diclofenac, may be associated with increased risk of gastro-intestinal anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac after gastro-intestinal surgery.

Hepatic: Close medical surveillance is also imperative in patients suffering from severe impairment of hepatic function. If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), Remethan should be discontinued. Hepatitis may occur without prodromal symptoms. Use of Remethan in patients with hepatic porphyria may trigger an attack.

Hypersensitivity reactions: As with other non-steroidal anti-inflammatory drugs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to diclofenac**.**
Like other NSAIDs, diclofenac sodium may mask the signs and symptoms of infection due to its pharmacodynamic properties.
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 (see 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Remethan should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

Renal: Patients with renal, cardiac or hepatic impairment and the elderly should be kept under surveillance, since the use of NSAIDS may result in deterioration of renal function. The lowest effective dose should be used and renal function monitored. The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, those being treated with diuretics or recovering from major surgery. Effects on renal function are usually reversible on withdrawal of Remethan.

Haematological: Diclofenac may reversibly inhibit platelet aggregation (see anticoagulants in "Drug Interactions"). Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.

Cardiovascular and cerebrovascular effects: 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. The necessary monitoring and consultation should be given to patients with a history of hypertension or/and mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.
Data from clinical trials and epidemiological researches show that the use of diclofenac, especially in high doses (150mg daily) and for long-term use, may be associated with a small increase of arterial thrombotic episodes (for example myocardial infarction or cerebrovascular episode).
Patients with non controlled hypertension, congestive heart failure, proved ischaemic cardiopathy, peripheral vascular disease or/and cerebrovascular disease, should be treated with diclofenac only after careful examination. The same examination should be conducted before the initiation of long-term treatment in patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidemia, diabetes mellitus, smoking).

Long-term treatment: All patients who are receiving non-steroidal anti-inflammatory agents should be monitored as a precautionary measure e.g. renal function, hepatic function (elevation of liver enzymes may occur) and blood counts. This is particularly important in the elderly. Like other drugs that inhibit prostaglandin synthetase activity, diclofenac sodium and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of, bronchial asthma. Caution is required in patients with a history of heart failure or hypertension since oedema has been reported in association with NSAID administration.

This product contains lactose.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Lithium and digoxin: Diclofenac sodium may increase plasma concentrations of lithium and digoxin.

Anticoagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4).

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).
Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding. Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Antidiabetic agents: Clinical studies have shown that diclofenac sodium can be given together with oral antidiabetic agents without influencing their clinical effect. However there have been isolated reports of hypoglycaemic and hyperglycaemic effects which have required adjustment to the dosage of hypoglycaemic agents.

Cyclosporin: Cases of nephrotoxicity have been reported in patients receiving concomitant cyclosporin and NSAIDS, including diclofenac sodium. This might be mediated through combined renal antiprostaglandin effects of both the NSAID and cyclosporin.

Methotrexate: Cases of serious toxicity have been reported when methotrexate and NSAIDS are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.

Quinolone antimicrobials: Convulsions may occur due to an interaction between quinolones and NSAIDS. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.

Other NSAIDS and corticosteroids: Co-administration of diclofenac sodium with aspirin or corticosteroids may increase the risk of gastro-intestinal bleeding. Avoid concomitant use of two or more NSAIDs.

Diuretics: Like other NSAIDS, diclofenac sodium may inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, which should therefore be monitored frequently.
The natriuretic effects of furosemide-type diuretics have been reported to be inhibited by some NSAIDs.

Cardiac glycosides: Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

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

Anti-hypertensives: Concomitant use of NSAIDs with antihypertensive drugs (i.e. beta-blockers, angiotensin converting enzyme (ACE) inhibitors, diuretics) may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis.

4.6 Fertility, pregnancy and lactation

Pregnancy
Although animal studies have not demonstrated teratogenic effects, diclofenac sodium should not be prescribed during pregnancy, unless there are compelling reasons for doing so. The lowest effective dosage should be used.
Congenital abnormalities have been reported in association with the administration of NSAIDs in man; however, these are low in frequency and do not appear to follow any discernible pattern.
In view of the known effects of NSAIDs on the foetal cardiovascular system (e.g. a premature closure of the ductus arteriosus) and in causing uterine inertia, use in late pregnancy should be avoided.

From the 20th week of pregnancy onward, Remethan use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, Remethan should not be given unless clearly necessary. If Remethan is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Remethan for several days from gestational week 20 onward. Remethan should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension).
- renal dysfunction (see above).

The mother and the neonate, at the end of the pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Remethan is contraindicated during the third trimester of pregnancy (see section 4.3).

Breast-feeding
Following doses of 50mg enteric coated tablets every 8 hours, traces of active substance have been detected in breast milk, but in quantities so small that no adverse effects on the breast-fed infant are to be expected.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

If serious side-effects occur, Remethan should be withdrawn.

Frequency estimate: frequent: >10 %, occasional: >1 - 10 %, rare: >0.001 - 1 %, isolated cases: <0.001 %.

Gastro-intestinal tract:
The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4).
Occasional: Epigastric pain, other gastro-intestinal disorders (e.g. nausea, vomiting, diarrhoea, abdominal cramps, dyspepsia, flatulence, anorexia), gastritis.

Rare: Gastro-intestinal bleeding (haematemesis, melaena, bloody diarrhoea), gastro-intestinal ulcers with or without bleeding or perforation.
In isolated cases: Aphthous stomatitis, glossitis, oesophageal lesions, lower gut disorders (e.g. non-specific haemorrhagic colitis and exacerbations of ulcerative colitis or Crohn's proctocolitis, colonic damage and stricture formation), pancreatitis, constipation.
Frequency not know: Ischaemic colitis.

Central Nervous System:
Occasional: Headache, dizziness, or vertigo.
Rare: Drowsiness, tiredness.
In isolated cases: Disturbances of sensation, paraesthesia, memory disturbance, disorientation, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions, aseptic meningitis.

Special senses:
Isolated cases: Disturbances of vision (blurred vision, diplopia), impaired hearing, tinnitus, taste disturbances.

Skin:
Occasional: Rashes or skin eruptions.
Rare: Urticaria.
In isolated cases: Bullous eruptions, eczema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome, (acute toxic epidermolysis), erythroderma (exfoliative dermatitis), loss of hair, photosensitivity reactions, purpura including allergic purpura, toxic epidermal necrolysis.

Kidney:
Rare: Oedema
In isolated cases: Acute renal insufficiency, urinary abnormalities (e.g. haematuria, proteinuria), interstitial nephritis, nephrotic syndrome, papillary necrosis.

Liver:
Occasional: Elevation of serum aminotransferase enzymes (ALT, AST).
Rare: Liver function disorders including hepatitis (in isolated cases fulminant) with or without jaundice.

Blood:
In isolated cases: Thrombocytopenia, leucopenia, agranulocytosis, haemolytic anaemia, aplastic anaemia.

Hypersensitivity:
Rare: Hypersensitivity reactions (e.g. bronchospasm, anaphylactic/anaphylactoid systemic reactions including hypotension).
Isolated cases: Vasculitis, pneumonitis.

Cardiovascular system:
Isolated cases: Palpitations, chest pain, hypertension, congestive heart failure, oedema.
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).
Not known: Kounis syndrome.

Other organ systems:
Isolated cases: Impotence.

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 national reporting system.

Malta
ADR Reporting Website:
www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

Management of a non-steroidal anti-inflammatory drug intoxication is primarily supportive and symptomatic for complications such as hypotension, renal failure, convulsions, gastro-intestinal irritation and respiratory depression. Fluid therapy is commonly effective in managing the hypotension that may occur following acute NSAID overdosage, except when this is due to an acute blood loss. The therapeutic measures to be taken are: absorption should be prevented as soon as possible after overdosage by means of gastric lavage and treatment with activated charcoal.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinflammatory and Antirheumatic products, Antiinflammatory and Antirheumatic products, Non-Steroids, ATC Code; M01AB05

Remethan is a non-steroidal phenylacetic acid derivative, which has marked analgesic, antipyretic and anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase.

5.2 Pharmacokinetic properties

Absorption
Absorption is complete but onset is delayed until passage through the stomach, which may be affected by food which delays stomach emptying. The mean peak plasma diclofenac concentration reached at about 2 hours (50mg dose produces 1,48 ± 0,65µg/ml).

Bioavailability
About half of the administered diclofenac is metabolized during its first passage through the liver ("first-pass effect"), the area under the concentrations curve (AUC) following oral administration is about half that following an equivalent parenteral dose.

Pharmacokinetic behaviour does not change on repeated administration. Accumulation does not occur, provided the recommended dosage intervals are observed. The plasma concentrations attained in children given equivalent doses (mg/kg, b.w.) are similar to those obtained in adults.

Distribution
The active substance is 99.7% protein bound, mainly to albumin (99.4%).
Diclofenac enters the synovial fluid, where maximum concentrations are measured 2-4 hours after the peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3-6 hours. Two hours after reaching the peak plasma values, concentrations of the active substance are already higher in the synovial fluid than they are in the plasma and remain higher for up to 12 hours.

Metabolism
Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites, most of which are converted to glucuronide conjugates. Two phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

Elimination
The total systemic clearance of diclofenac in plasma is 263 ± 56 mL/min (mean value ± SD). The terminal half-life in plasma is 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3 hours.

About 60% of the administered dose is excreted in the urine in the form of the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

Characteristics in patients
Elderly: No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed, other than the finding that in five elderly patients, a 15 minute iv infusion resulted in 50% higher plasma concentrations than expected with young healthy subjects.
Patients with renal impairment: In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of less than 10 mL/min, the calculated steady-state plasma levels of the hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.
Patients with hepatic disease: In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

5.3 Preclinical safety data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Microcrystalline Cellulose
Lactose
Maize Starch
Povidone
Pregelatinized Starch
Colloidal Silicon Dioxide
Magnesium Stearate
Talc

Coating
Methacrylic Acid Copolymer 30%
Macrogol 6000
Talc
Titanium Dioxide
Polysorbate 80
Yellow Ferric Oxide E172
Silicon Antifoam

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 25 °C. Protect from light and moisture.

6.5 Nature and contents of container

PVC/Aluminium blisters. Pack sizes of 30 and 1000 gastro-resistant tablets.
PP containers with PE closure. Pack size 1000 gastro-resistant tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Remedica Ltd,
Aharnon Str., Limassol Industrial Estate,
3056 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER

MA084/03001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 02 November 2006
Date of latest renewal: 26 January 2012

10. DATE OF REVISION OF THE TEXT

29th October 2022

For internal use only: mt-spc-remethan-25-mg-ec-tabs-v07-r00-a0