Product Summary

1. Trade Name of the Medicinal Product

Rhumalgan CR 75

2. Qualitative and Quantitative Composition

Each tablet contains 75mg diclofenac sodium BP.

3. Pharmaceutical Form

Controlled Release Tablet.

Clinical Particulars

4.1. Therapeutic Indications

Rheumatoid arthritis; osteoarthritis; low back pain; acute gout; relief of pain in fractures; acute musculo-skeletal disorders and trauma including periarthritis (particularly frozen shoulder), bursitis, tendinitis, tenosynovitis, dislocations, sprains and strains; ankylosing spondylitis; and the control of pain and inflammation in orthopaedic, dental and other minor surgery.

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).

For oral administration

Adults: One tablet once or twice daily, taken whole with liquid, preferably at meal times. The recommended maximum daily dose of diclofenac sodium is 150mg.

Children: These tablets are not recommended for children.

Elderly: Although the pharmacokinetics of diclofenac sodium 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 during NSAID therapy

4.3 Contraindications

- Hypersensitivity to the active substance or any of the excipients.
- Patients who have previously shown hypersensitivity reactions (eg asthma angioedema, urticaria, or acute rhinitis) to ibuprofen, aspirin or other non-steroidal anti-inflammatory drugs.
- Patients with a history of, or active, gastro-intestinal ulcers, bleeding or perforation (two or more distinct episodes of proven ulceration or bleeding).
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Severe hepatic, renal and heart failure (see section 4.4 Special warnings and precautions for use).
- During the last trimester of pregnancy.
- History of gastro-intestinal bleeding or perforation, relating to previous NSAID therapy.
- Acute porphyria

4.4 Special warnings and precautions for use

Warnings:
In all patients:
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2 Posology and method of administration and GI and cardiovascular risks below).
The use of diclofenac with concomitant NSAIDs including cyclo-oxygenase-2- selective inhibitors should be avoided (see section 4.5 Interactions with other medicaments and other forms of interaction)

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac 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.

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs especially to gastrointestinal bleeding and perforation which may be fatal (see section 4.2 Posology and method of administration).

Gastro-intestinal: As with other NSAIDs, including diclofenac close medical surveillance is imperative in patients with symptoms indicative of gastro-intestinal disorders, with a history suggestive of gastro-intestinal ulceration, with ulcerative colitis or with Crohn's disease as these conditions may be exacerbated (see section 4.8 Undesirable effects).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding).

Gastro-intestinal bleeding or ulceration/perforation: Haematemesis, melaena, ulceration or perforation which can be fatal has been reported with all NSAIDs including diclofenac. They can occur at any time during treatment with or without warning symptoms or a previous history of serious GI events. In the rare instances where gastro-intestinal bleeding or ulceration occurs in patients receiving diclofenac sodium the drug should be withdrawn.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses including diclofenac, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3 Contraindications), and in the elderly. These patients should commence treatment on the lowest dose available. 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 section 4.5 Interactions with other medicaments and other forms of interaction).
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.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors (SSRIs) or anti-platelet agents such as aspirin (see section 4.5 Interaction with other medicaments and other forms of interaction).

Hepatic: Close medical surveillance is also imperative in patients suffering from impairment of hepatic function.

Hypersensitivity reactions: As with other non-steroidal anti-inflammatory drugs including diclofenac, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug (see section 4.8 Undesirable effects).

In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (ie nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions with NSAIDs such as exacerbation of asthma (so called intolerance to analgesics / analgesics-asthma), Quincke's oedema (angioedema) or urticaria are more frequent than in other patients. Therefore special precautions are recommended in such patients (readiness for emergency). This is also applicable to patients who are allergic to other substances, for example those with skin reactions, pruritis or urticaria.

As with other NSAIDs, diclofenac sodium may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Precautions:
Renal: Patients with renal, cardiac or hepatic impairment, a history of hypertension and the elderly, should be kept under surveillance, since the use of NSAIDs including diclofenac 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 other products that can significantly impact renal function, or those recovering from major surgery. Effects on renal function are usually reversible on withdrawal of diclofenac sodium.

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.

Hepatic: If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), diclofenac sodium should be discontinued. Hepatitis may occur with diclofenac without prodromal symptoms.

Use of diclofenac sodium in patients with hepatic porphyria may trigger an attack. Use in acute porphyria is contraindicated.

Haematological: Diclofenac sodium may reversibly inhibit platelet aggregation (see anticoagulants in Section 4.5 Interaction with other medicaments and other forms of interactions). Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.

Respiratory disorders: 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.

Cardiovascular and cerebrovascular effects: 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 including diclofenac.

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

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. 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.

SLE *and mixed connective tissue disease:* In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8 Undesirable effects).

Dermatological: 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 (see section 4.8 Undesirable effects). Patients appear to be at the highest risk of 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. Diclofenac should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

Female fertility: The use of diclofenac sodium may impair female fertility and is not recommended in women attempting to conceive. In women who may have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of diclofenac sodium should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Lithium: Diclofenac sodium may increase plasma concentrations of lithium.

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. As with other non-steroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

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.

Ciclosporin and tacrolimus: Cases of nephrotoxicity have been reported in patients receiving concomitant ciclosporin and NSAIDs, including diclofenac sodium. Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through combined renal anti-prostaglandin effects of both the NSAID and calcineurin inhibitor.

Methotrexate: Cases of serious toxicity have been reported when methotrexate and NSAIDs including diclofenac 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 already receiving an NSAID.

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.

Phenytoin

When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

Other NSAIDs including cyclo-oxygenase-2 selective inhibitors and corticosteroids: Co-administration of diclofenac sodium with these agents may increase the risk of gastro-intestinal bleeding or ulceration. Avoid

concomitant use of two or more NSAIDs (see section 4.4 Special warnings and precautions for use).

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of systemic NSAIDs, including diclofenac may cause increased risk of gastrointestinal bleeding (see section 4.4 Special warnings and precautions for use).

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.

Antihypertensives: 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.

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 effects of mifepristone.

Baclofen: NSAIDs possibly reduce excretion of baclofen (increased risk of toxicity).

Drospirenone: Risk of hyperkalaemia when given with drospirenone (monitor serum potassium during first cycle).

Ketorolac: Increased side effects and haemorrhage if used with NSAIDs.

Penicillamine: Possible increased risk of nephrotoxicity.

Erlotinib, iloprost, pentoxifylline, sibutramine, venlafaxine: Possible increased risk of bleeding.

Phenytoin: NSAIDS possibly enhance effects of phenytoin.

Ritonavir: Plasma concentration of NSAIDs possibly increased by ritonavir.

Zidovudine: Increased risk of haematological toxicity when NSAIDs given with zidovudine.

4.6 Fertility, pregnancy and lactation

Pregnancy

From the 20th week of pregnancy onward, Rhumalgan CR 75 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, Rhumalgan CR 75 should not be given unless clearly necessary. If Rhumalgan CR 75 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 Rhumalgan CR 75 for several days from gestational week 20 onward. Rhumalgan CR 75 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 (with premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

the mother and the neonate, at the end of 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, Rhumalgan CR 75 is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Lactation

Like other NSAIDs, diclofenac passes into breast milk in small amounts. Therefore, NSAIDs should if possible be avoided when breast-feeding.

See section 4.4 Special warnings and precautions for use, regarding female fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), including isolated reports.

The following undesirable effects include those reported with diclofenac gastro-resistant tablets and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

Blood and lymphatic system disorders
Very rare: Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.

Immune system disorders
Rare: Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).
Very rare: Angioneurotic oedema (including face oedema).

Psychiatric disorders
Very rare: Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder/reactions, confusion, hallucinations.

Nervous system disorders
Common: Headache, dizziness.
Rare: Somnolence, drowsiness, tiredness, hypotension.
Very rare: Paraesthesia, memory impairment/disturbance, convulsion, anxiety, tremor, taste disturbances, cerebrovascular accident, disturbances of sensation, taste disturbances, malaise, aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus and mixed tissue disease) with symptoms such as fever, stiff neck, headache, nausea and vomiting.

Eye disorders
Very rare: Visual disturbance, vision blurred, diplopia, optic neuritis.

Ear and labyrinth disorders
Common: Vertigo.
Very rare: Tinnitus, hearing impaired.

Cardiac disorders

Very rare: Palpitations, chest pain, cardiac failure/congestive heart failure, myocardial infarction.
Unknown: Kounis syndrome

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).

Vascular disorders
Very rare: Hypertension, vasculitis.

Respiratory, thoracic and mediastinal disorders
Rare: Asthma (including dyspnoea), alveolitis, pulmonary eosinophilia.
Very rare: Pneumonitis.
Aggravated asthma or bronchospasm have also been reported.

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain or cramps, flatulence, anorexia, local irritation.
Rare: Gastritis, gastrointestinal haemorrhage or bleeding, haematemesis, diarrhoea haemorrhagic/bloody, melaena, gastrointestinal ulcer, with or without bleeding or perforation (sometimes fatal, particularly in the elderly).
Very rare: Lower gut disorders such as colitis (including colonic damage, non specific haemorrhagic colitis/ haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease/Crohn’s proctocolitis), constipation, stomatitis/aphthous stomatitis, glossitis, oesophageal disorder/lesions, diaphragm-like intestinal strictures/stricture formation, pancreatitis, exacerbation of haemorrhoids.
Not known: Ischaemic colitis

Hepatobiliary disorders
Common: Transaminases (serum aminotransferase enzymes) increased (eg AST, ALT).
Rare: Hepatitis, jaundice, liver disorder.
Very rare: Fulminant hepatitis, hepatic necrosis, hepatic failure

Skin and subcutaneous tissue disorders.
Common: Rash, skin eruptions.
Rare: Urticaria.
Very rare: Bullous eruptions/dermatoses, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis/acute toxic epidermolysis (Lyell's syndrome), dermatitis exfoliative (erythroderma), loss of hair, photosensitivity reactions, purpura, allergic purpura, pruritus.

Renal and urinary disorders
Rare: Interstitial fibrosis has been reported with NSAIDs and may lead to renal failure.

Very rare: Acute renal failure or insufficiency, urinary abnormalities (eg haematuria, proteinuria), nephrotic syndrome, interstitial nephritis, renal papillary necrosis.

General disorders and administration site conditions
Rare: Oedema.
Very rare: Impotence.

4.9 Overdose

Symptoms:
There is no typical clinical picture resulting from diclofenac over dosage. Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, tinnitus, fainting, occasionally, convulsions. In rare cases of significant poisoning acute renal failure and liver damage are possible.

Therapeutic measures:
Management of acute poisoning with NSAIDs, including diclofenac, essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications, such as hypotension, renal failure, convulsions, gastrointestinal disorder and respiratory depression.

Special measures, such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism.

Activated charcoal may be considered after ingestion of a potentially toxic overdose and gastric decontamination (e.g. vomiting, gastric lavage) after ingestion of a potentially life-threatening overdose.

Pharmacological Properties

5.1. Pharmacodynamic Properties

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. It is an inhibitor of prostaglandin synthetase.

5.2. Pharmacokinetic Properties

Rhumalgan CR tablets are extended release preparations designed to release diclofenac over a period of time. Following a pharmacokinetic study with the 100mg tablets in volunteers it was found that the average time to reach maximum plasma concentration was 6.05 hours. The average elimination half life was found to be 6.75 hours. The average maximum plasma concentration was found to be 262ng/ml.

a)

General characteristics of the active substance

Diclofenac sodium is almost totally absorbed after oral administration, and it is subject to significant first-pass metabolism with only approximately 60% of an oral dose reaching the systemic circulation.

Diclofenac sodium is highly protein bound (>99%). It is mainly excreted in the form of metabolites via the urine but also in the bile.

The main metabolite has minimal anti-inflammatory activity compared to the parent drug.

b) Characteristics in patients

Plasma concentrations of unchanged diclofenac are not reported to be significantly affected by age, renal or hepatic impairment. The metabolite concentrations may be increased by severe renal impairment.

5.3. Preclinical Safety Data

None stated.

Pharmaceutical Particulars

6.1. List of Excipients

Talc Ph.Eur, ethylcellulose Ph.Eur, magnesium stearate Ph.Eur, povidone Ph.Eur, stearic acid Ph.Eur , hydroxypropyl methylcellulose Ph.Eur, diethyl phthalate USP, titanium dioxide Ph.Eur and polyethylene glycol BP.

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

36 months.

6.4. Special Precautions for Storage

Store in a dry place below 25^{o}C. Protect from light.

6.5. Nature and Contents of Container

PVdC/PVC/aluminium/PVdC blister strip

Number of tablets per carton: 28, 30, 50, 56, 60, 84, 100, 250, 500 and 1,000.

6.6. Instructions for Use/Handling

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
Frimley Business Park,
Frimley,
Camberley,
Surrey,
GU16 7SR,
United Kingdom.

8. MARKETING AUTHORISATION NUMBER(S)

PL 4416/0242

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13/02/2008

10 DATE OF REVISION OF THE TEXT

18/04/2023