

1. NAME OF THE MEDICINAL PRODUCT

Rhumalgan XL 100 mg modified-release capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is sodium-[o-[(2,6-dichlorophenyl)-amino]-phenyl]-acetate (diclofenac sodium).

Each capsule contains 100 mg diclofenac sodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified release capsule for oral use.

Pink opaque hard capsules marked 'DIC100'.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults and Elderly:

Relief of all grades of pain and inflammation in a wide range of conditions, including:

(i) arthritic conditions: rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout,

(ii) acute musculo-skeletal disorders such as periartthritis (for example frozen shoulder): tendinitis, tenosynovitis, bursitis,

(iii) other painful conditions resulting from trauma: including fracture, low back pain, sprains, strains: dislocations, orthopaedic, dental and other minor surgery.

Children: Rhumalgan XL 100mg Modified Release Capsules are not suitable for children.

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 Rhumalgan XL 100 once daily, swallowed whole, preferably with or after food.

Where the symptoms are most pronounced during the night or in the morning Rhumalgan XL 100 capsules should preferably be taken in the evening.

Special populations

Paediatrics

Children: Rhumalgan XL 100 are not recommended for use in children.

Elderly:

Although the pharmacokinetics of Rhumalgan XL 100 are not impaired to any clinically relevant extent in elderly patients, nonsteroidal anti-inflammatory drugs (NSAIDs) 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 for the shortest possible duration 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.

Renal impairment

No adjustment of the starting dose is required for renally impaired patients (see section 4.4 special warnings and precautions).

Hepatic impairment

No adjustment of the starting dose is required for hepatically impaired patients (see section 4.4 special warnings and precautions).

4.3 Contraindications

- Hypersensitivity to the active substance or any of the excipients.
- Active, gastric or intestinal ulcer, bleeding or perforation.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs or diclofenac therapy.
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- Last trimester of pregnancy (See section 4.6 Pregnancy and lactation).
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral

arterial disease and/or cerebrovascular disease.

- Severe hepatic, renal and cardiac failure (See section 4.4 Special warning and precautions for use).
- Like other NSAIDs, diclofenac is also contraindicated in patients in whom attacks of asthma, angioedema, urticaria or acute rhinitis are precipitated by ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.

4.4 Special warnings and precautions for use

General

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 Rhumalgan SR 75 with systemic NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects (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.

Caution is indicated in the elderly on basic medical grounds. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight (see section 4.2 Posology and Method of administration).

As with other nonsteroidal 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).

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

Rhumalgan SR 75 mg Modified Release Capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Rhumalgan SR 75 mg Modified Release Capsules also contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucosegalactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Gastrointestinal effects:

Gastrointestinal bleeding (haematemesis, melaena), ulceration or perforation which can be fatal has been reported with all NSAIDs including diclofenac and may occur at any time during treatment, with or without warning symptoms or a previous history of serious GI

events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occurs in patients receiving diclofenac, the drug should be withdrawn.

As with all NSAIDs, including diclofenac close medical surveillance is imperative and particular caution should be exercised when prescribing diclofenac in patients with symptoms indicative of gastrointestinal disorders, or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see section 4.8 Undesirable effects). The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses including diclofenac, and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3 Contraindications).

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.

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

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose.

Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low dose acetylsalicylic acid (ASA/aspirin or medicinal products likely to increase gastrointestinal risk. (See section 4.5 Interactions with other medicaments and other forms of interaction).

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

Caution is recommended 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 acetylsalicylic acid (see section 4.5 Interaction with other medicaments and other forms of interaction).

Close medical surveillance and caution should be exercised in patients with ulcerative colitis, or with Crohn's disease as these conditions may be exacerbated (see section 4.8 Undesirable effects).

Hepatic effects:

Close medical surveillance is required when prescribing Rhumalgan SR 75 to patients with impairment of hepatic function as their condition may be exacerbated.

As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with diclofenac, regular monitoring of hepatic function is indicated as a precautionary measure.

If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), Rhumalgan SR 75 should be discontinued.

Hepatitis may occur with diclofenac without prodromal symptoms.

Caution is called for when using diclofenac in patients with hepatic porphyria, since it may trigger an attack.

Renal effects:

As fluid retention and oedema have been reported in association with NSAIDs therapy, including diclofenac, particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery (see section 4.3 Contraindications). Monitoring of renal function is recommended as a precautionary measure when using diclofenac in such cases. Discontinuation therapy is usually followed by recovery to the pre-treatment state.

Skin effects:

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 Rhumalgan SR 75 (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. Rhumalgan SR 75 should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

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).

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 dose (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.

Haematological effects:

During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.

Rhumalgan SR 75 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.

Pre-existing asthma:

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

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.

Female fertility:

The use of Rhumalgan SR 75 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 Rhumalgan SR 75 should be considered (see section 4.6 Pregnancy and Lactation).

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions have been observed with diclofenac. Care should be taken in patients treated with any of the following drugs.

Lithium: If used concomitantly, Rhumalgan SR 75 may increase plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

Digoxin: If used concomitantly, Rhumalgan SR 75 may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

Diuretics and antihypertensive agents: Like other NSAIDs, concomitant use of Rhumalgan SR 75 with diuretics and antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis.

Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity.

Drugs known to cause hyperkalemia: Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently (see section 4.4 Special warnings and precautions for use).

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 nonsteroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

Other NSAIDs including cyclooxygenase-2 selective inhibitors and corticosteroids: Co-administration of diclofenac with other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of two or more NSAIDs (see section 4.4 Special warnings and precautions for use).

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of SSRI's may increase the risk of gastrointestinal bleeding (see section 4.4 Special warnings and precautions for use).

Antidiabetics: Clinical studies have shown that diclofenac can be given together with oral anti-diabetic agents without influencing their clinical effect. However there have been isolated reports of hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Methotrexate: Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increase. 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.

Ciclosporin: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostaglandin effects of both NSAID and calcineurin inhibitor.

Quinolone antibacterials: 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.

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

Colestipol and cholestyramine: These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/cholestyramine.

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.

Potent CYP2C9 inhibitors: Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

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.

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

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and or cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1% up to approximately 1.5%.

The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has shown to result in increased pre- and post-implantation loss and embryo-foetal lethality.

In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during organogenetic period. From the 20th week of pregnancy onward, Rhumalgan XL 100 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 XL 100 should not be given unless clearly necessary. If Rhumalgan XL 100 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 XL 100 for several days from gestational week 20 onward. Rhumalgan XL 100 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 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, Rhumalgan XL 100 is contra-indicated 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 diclofenac should not be administered during breast feeding in order to avoid undesirable effects in the infant (see section 5.2 Pharmacokinetic properties).

Female fertility

As with other NSAIDs, the use of diclofenac 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 should be considered (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, vertigo, somnolence, central nervous system disturbances, drowsiness or fatigue while taking NSAIDs should refrain from driving or operating machinery.

4.8 Undesirable effects

Adverse reactions are ranked under the heading of frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$, $<1/10$); uncommon ($\geq 1/1,000$, $<1/100$); rare ($\geq 1/10,000$, $<1/1000$); very rare ($<1/10,000$); not known: cannot be estimated from available data.

The following undesirable effects include those reported with other short-term or long-term use.

Table 1

Blood and lymphatic system disorders	
Very rare	Thrombocytopenia, leucopenia, 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.
Nervous system disorders	
Common	Headache, dizziness.
Rare	Somnolence, tiredness.
Very rare	Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.
Unknown	Confusion, hallucinations, disturbances of sensation, malaise.
Eye disorders	
Very rare	Visual disturbance, vision blurred, diplopia.
Unknown	Optic neuritis.
Ear and labyrinth disorders	
Common	Vertigo.
Very rare	Tinnitus, hearing impaired.
Cardiac disorders	
Very rare	Palpitations, chest pain, cardiac failure, myocardial infarction.
Unknown	Kounis syndrome
Vascular disorders	
Very rare	Hypertension, hypotension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare	Asthma (including dyspnoea).
Very rare	Pneumonitis.
Gastrointestinal disorders	

Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.
Rare	Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer with or without bleeding or perforation (sometimes fatal, particularly in the elderly).
Very rare	Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis.
Not known	Ischaemic colitis
Hepatobiliary disorders	
Common	Transaminases increased.
Rare	Hepatitis, jaundice, liver disorder.
Very rare	Fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	
Common	Rash.
Rare	Urticaria.
Very rare	Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus.
Renal and urinary disorders	
Very rare	Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.
General disorders and administration site conditions	
Rare	Oedema
Reproductive system and breast disorders	
Very rare	Impotence

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).

4.9 Overdose

Symptoms

There is no typical clinical picture resulting from diclofenac over dosage. Over dosage can cause symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting, occasionally convulsions. In 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 complication 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC: M01AB05

Pharmacotherapeutic group

Non-steroidal anti-inflammatory drugs (NSAIDs).

Rhumalgan XL 100 contains the prostaglandin synthetase inhibitor diclofenac sodium.

Mechanism of action

Rhumalgan XL 100 is a non-steroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase, (cyclo-oxygenase).

Diclofenac sodium in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings.

In rheumatic diseases the anti-inflammatory and analgesic properties of diclofenac sodium elicit a clinical response, characterised by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness and swelling of the joints, as well as by an improvement in function.

5.2. Pharmacokinetic properties

The summary pharmacokinetic parameters of Rhumalgan XL 100 modified release capsules in healthy volunteers are:

Parameter	Mean value
C _{max} (ng/ml)	508
T _{max} (h)	2.4
AUC _{0-t} (ng/ml*h)	2369
AUC _{0-∞} (ng/mg*h)	2601

Absorption:

Diclofenac sodium is rapidly absorbed from the gut and undergoes first-pass metabolism.

Rhumalgan XL 100 capsules give peak plasma concentrations after approximately 2.5 hours on an empty stomach and after approximately 6 hours after administration after a high fat meal.

Food has no relevant clinical influence on the re-absorption and systemic availability of Rhumalgan XL 100.

Absorption is unaffected by food.

Bioavailability and repeat dose administration

Since about half the active substance is metabolised during its first passage through the liver ('first pass' effect), the bioavailability after oral ingestion is about 50 % of that observed after parenteral administration of an equal dosage.

Pharmacokinetic behaviour does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed.

Distribution:

The active substance is 99.7% protein bound, mainly to albumin (99.4%).

The apparent volume of distribution calculated is 0.12-0.17 l/kg.

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 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.

Diclofenac and its metabolites cross the placenta and traces of diclofenac have been found in the milk of lactating women.

Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose (see section 4.6 Pregnancy and lactation).

Metabolism

The 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 of these phenolic metabolites are biologically active, but to a lesser extent than diclofenac.

Elimination:

The total systemic clearance of diclofenac in plasma is 263 ± 56 ml/min (mean value \pm 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. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac has a much longer plasma half-life. However, this metabolite is virtually inactive.

About 60% of the administered dose is eliminated in the urine in the form of metabolites. Less than 1% is excreted as unchanged substance. The remainder 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 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 < 10 ml/min, the theoretical steady-state plasma levels of 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

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6.1 List of excipients

Capsule contents

Sugar spheres (sucrose, maize starch)

Macrogol 6000

Ammonia methacrylate copolymer Type A

Talc

Lactose monohydrate

Polysorbate 80

Capsule shell

Gelatin

Titanium dioxide (E171)

Red iron oxide

Yellow iron oxide

Printing ink

Shellac

Propylene glycol

Black iron oxide (E172)

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months, as packaged for sale.

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Blister strips made of Poliamide/Aluminium/PVC 25µm/45µm/60µm coupled with an aluminium lid 25 µm in packs of 28 capsules.

6.6 Instructions for use and handling

Not applicable.

7 MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

PL 05146/0002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

8 October 2004

10 DATE OF REVISION OF THE TEXT

18/04/2023