SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Raplon 12.5mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 12.5mg diclofenac potassium.

Excipient(s) with known effect:
Each tablet contains 70.5mg lactose monohydrate and 0.17mg lecithin (contains soya oil).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
White, capsule shaped biconvex tablets with dimensions 5x10 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatic pain, muscular pain, headache, dental pain, symptomatic treatment of primary dysmenorrhea, acute low back pain, cold and flu symptoms, including fever relief, sore throats and colds.

This product in indicated for use in adults and children aged 14 years and over.

4.2 Posology and method of administration

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

Adults and children aged 14 years and over
Initially two tablets, followed by one tablet every 4 to 6 hours as needed. No more than 6 tablets (75 mg) should be taken in any 24 hour period.
Raplon is intended for short-term use, up to 5 days for relief of pain and 3 days for relief of fever.

Paediatric population
Raplon 12.5mg film-coated tablets are not recommended for use in children under 14 years of age.

Elderly
Elderly patients should be treated with the lowest effective dose (see section 4.4).

Renal impairment
Raplon 12.5 mg is contraindicated in patients with severe renal impairment or renal failure (see section 4.3).

No specific studies have been conducted in patients with impaired renal function, therefore, no specific dose adjustment can be recommended. Caution is recommended when Raplon 12.5 mg is administered to patients with mild to moderate renal impairment (see section 4.4).

Hepatic impairment
Raplon 12.5 mg is contraindicated in patients with severe hepatic impairment or hepatic failure (see section 4.3).
No specific studies have been conducted in patients with impaired hepatic function, therefore, no specific dose adjustment can be recommended. Caution is recommended when Raplon 12.5 mg is administered to patients with mild to moderate hepatic impairment (see section 4.4).

Method of administration
For oral administration.
The tablets should be swallowed whole with water, preferably before meals.

4.3 Contraindications

Hypersensitivity to the active substance, soya oil, peanut oil or to any of the excipients listed in section 6.1.
Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease.
Active gastric or intestinal ulcer, gastrointestinal bleeding or perforation.
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).
Last trimester of pregnancy (see section 4.6).
Severe hepatic or renal failure (see section 4.4).
As with other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.
Patients with cerebrovascular bleeding or other active bleeding or bleeding disorders.
Patients with blood dyscrasias.
Patients with bone marrow depression.

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 and GI and cardiovascular risks below).

Concomitant use of other NSAIDs including selective cyclo-oxygenase-2 (COX-2) inhibitors should be avoided due to lack of evidence of synergistic beneficial effect and risk of addition of adverse reactions.

From a general medical point of view, caution is indicated in elderly. In particular it is recommended to use the lowest possible dose in frail elderly or elderly with low body weight. Elderly patients are more likely to have impaired renal, cardiovascular or hepatic function, therefore close monitoring is required.

As with other NSAIDs allergic reactions including anaphylactic/anaphylactoid reactions may also occur in rare cases without previous exposure to diclofenac. 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.

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

Medication overuse headache
Prolonged use of any type of painkiller for headaches can make the headache worse and more frequent (headache due to excessive use of painkillers). If this situation is experienced or suspected, the physician must be consulted regarding discontinuation of headache therapy. The diagnosis of medication overuse headache should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

Diclofenac should be administered with caution to patients with systemic lupus erythematosus and MCTD (mixed connective tissue disease).

Fertility
Use of diclofenac can reduce fertility and it is for this reason not recommended in women attempting to conceive. In women having difficulties in getting pregnant or who are examined for infertility, discontinuation of diclofenac should be considered (see section 4.6).

Gastrointestinal effects
Gastrointestinal bleedings, ulceration or perforation which can be fatal, have been reported with all NSAIDs and may occur at any time during treatment with or without warning symptoms or a history of gastrointestinal problems. They generally have more serious consequences in elderly patients than in younger patients. When gastrointestinal bleeding or ulceration occurs in patients receiving diclofenac, treatment should be discontinued.

As with all NSAIDs, close medical surveillance is imperative and caution should be exercised when prescribing diclofenac in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see section 4.8). The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation. Older people have more frequent side effects of NSAIDs, especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).

In order to reduce the risk of gastro-intestinal toxicity in patients with a history of ulcer, in particular when have occurred complications such as bleeding or a perforation, and in the elderly, treatment should be initiated and continued with the lowest effective dose.

Combination therapy with protective agents (e.g. proton pump inhibitors or misoprostol) should be taken into consideration for these patients and also for patients who require concomitant medications which contain a low dose acetylsalicylic acid or other drugs likely to increase gastrointestinal risk.

Patients with a history of GI toxicity, particularly the 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, anti-platelet agents or selective serotonin-reuptake inhibitors (SSRIs) (see section 4.5).

Close medical surveillance should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated (see section 4.8).

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 effects
Close medical surveillance is required when prescribing diclofenac to patients with impaired hepatic function, as their condition may be exacerbated (especially GI bleeding).

As with other NSAIDs, values of one or more liver enzymes may increase. During long-term treatment with diclofenac, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash), diclofenac should be discontinued. Hepatitis may occur without prodromal symptoms. Caution advised 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 NSAID therapy, particular caution is called for in patients with impaired cardiac or renal function, with a history of hypertension, in elderly, in patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery (see section 4.3). Monitoring of renal function is recommended as a precautionary measure when using diclofenac in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

If NSAIDs such as diclofenac are combined with diuretics, ACE inhibitors or angiotensin II receptor antagonists may increase the risk of deterioration of renal function, including possible acute renal failure in some patients, especially if renal function is already impaired (see section 4.5).

Skin reactions
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Steven-Johnson syndrome, and toxic epidermal necrolysis (TEN), have been reported very rarely in association with the use of NSAIDs (see section 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. Treatment with diclofenac should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
In exceptional cases varicella can cause serious infectious complications of skin and soft tissue. Until now the contributing role of NSAIDs in the worsening of these infections cannot be excluded. Therefore, it is advisable to avoid the use of diclofenac in varicella.

Cardiovascular and cerebrovascular effects
Clinical trial and epidemiological data suggest that use of diclofenac, particularly at high dose (150 mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).
Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus and 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
Like other NSAIDs, diclofenac may temporarily inhibit platelet aggregation. Patients with haemostasis defects should be carefully monitored.

Treatment with diclofenac is recommended only for a few days. If, on the other hand diclofenac is administered for a longer period of time, it is recommended, as with other NSAIDs, to have blood tests performed.

Asthma
In patients with asthma, seasonal allergic rhinitis, swelling of nasal mucosa (nasal polyps), chronic obstructive lung disease or chronic infections of the airways (particularly associated with allergic rhinitis-like symptoms), are reactions to NSAIDs such as exacerbation of asthma (so called intolerance to analgesics/analgesic asthma), Quincke's oedema or urticaria more likely to occur than in other patients. Caution is therefore advised in these patients (be prepared for development of critical situation). This also applies to patients who are allergic to other agents, e.g. with skin reactions, pruritus or urticaria.

Raplon contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Raplon contains lecithin.
If a patient is hypersensitive to peanut or soya, do not use this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions have been observed in diclofenac gastro-resistant tablets and/or other pharmaceutical forms of diclofenac.

Lithium: During concomitant use, diclofenac may increase plasma concentrations of lithium. Monitoring of serum lithium levels is recommended.

Digoxin: During concomitant use, diclofenac may increase plasma concentrations of digoxin. Monitoring of serum digoxin level is recommended.

Diuretics and antihypertensive agents: Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive agents may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored.
If NSAIDs such as diclofenac are combined with diuretics, ACE inhibitors or angiotensin II receptor antagonists may increase the risk of deterioration of renal function, including possible acute renal failure (usually reversible) in some patients, especially if renal function is already impaired (e.g. the elderly or dehydrated patients). Therefore this combination should be given with caution, especially in the elderly.
Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.
Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, which should therefore be monitored frequently (see section 4.4).

Other NSAIDs and corticosteroids: Co-administration of diclofenac with other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal adverse reactions (see section 4.4). Co-administration of acetylsalicylic acid reduces the plasma concentration of diclofenac, without influencing the clinical effect.

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration may increase the risk of bleeding (see section 4.4). From clinical trials there was no evidence that diclofenac affects the action of anticoagulants. However, there are reports of an increased risk of

haemorrhage with the combined use of diclofenac and anticoagulants. Careful monitoring of such patients is therefore recommended.

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of systemic NSAIDs and SSRIs may increase the risk of gastrointestinal bleeding (see section 4.4).

Antidiabetics: Clinical trials have shown that diclofenac can be administered with oral anti-diabetics without affecting the clinical effect. However, there have been isolated reports of hypoglycaemia and hyperglycaemia that have required dose adjustment of the anti-diabetic during concomitant use with diclofenac. Monitoring of blood glucose levels is therefore recommended as a precaution in case of co-administration.

Methotrexate: Diclofenac can inhibit the tubular renal clearance of methotrexate with the risk of elevated methotrexate exposure. Care should be observed when NSAIDs are administered earlier than 24 hours before or after treatment with methotrexate as the concentration of methotrexate and thus the toxicity of the agent may increase.

Ciclosporins: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Furthermore, is reported that cyclosporin may increase the plasma concentrations of diclofenac with 100%. The dose of diclofenac must therefore be administered in lower doses than usually in patients who are not treated with ciclosporin.

Medicinal products known to cause hyperkalaemia: Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which therefore require regular monitoring (see section 4.4).

Quinolones: There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.

Potent CYP2C9 inhibitors: Caution should be exercised when prescribing diclofenac with potent CYP2C9 inhibitors (such as sulfinpyrazone and voriconazole), which may result in significant increases in peak plasma concentrations and exposure to diclofenac through the 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.

Colestipol and cholestyramine: Colestipol/cholestyramine 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.

Interaction with foods
The rate of absorption of diclofenac is reduced when the tablets are taken with meals. It is not recommended to take the tablets during or immediately after meals.

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 of 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 been 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 organogenesis. Standard preclinical animal studies have shown that there is no evidence to support diclofenac may be teratogenic in mice, rats or rabbits.

From the 20th week of pregnancy onward, d 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, diclofenac should not be given unless clearly necessary. If diclofenac 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 diclofenac for several days from gestational week 20 onward. Diclofenac 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 pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect of thrombocytes which may occur even after very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, diclofenac is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Breast-feeding

Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, diclofenac should not be administered during breast feeding in order to avoid undesirable effects in the infant.

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 have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of diclofenac should be considered.

4.7 Effects on ability to drive and use machines

Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking diclofenac should refrain from driving or using machines.

4.8 Undesirable effects

Adverse drug reactions are ranked by frequency, with the most frequent reactions first, using the following convention: very common (>1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (<1/10000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

The following undesirable effects include those reported with 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 edema (including face oedema).

Psychiatric disorders
Very rare: Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder, anxiety.

Nervous system disorders
Common: Headache, dizziness.
Rare: drowsiness.
Very rare: Paraesthesia, memory impairment, convulsion, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.

Eye disorders
Very rare: Visual impairment, vision blurred, diplopia.

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

Cardiac disorders
Very rare: Palpitations, chest pain, heart failure, myocardial infarction.
Not known: Kounis syndrome.

Vascular disorders
Very rare: Hypertension, 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, hematemesis, diarrhoea haemorrhagic, melena, gastrointestinal ulcer (with or without bleeding or perforation).
Very rare: Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal lesions, intestinal strictures, pancreatitis.

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 reactions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), exfoliative dermatitis, alopecia, photosensitivity, purpura (including 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.

Gastrointestinal:
The most common adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, blood in stool, hematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following diclofenac administration. Gastritis has been less commonly observed.

Cardiovascular:
Clinical trials and epidemiological data suggest that there is a slightly increased risk of arterial thrombosis (e.g. myocardial infarction and stroke) with the use of diclofenac (see section 4.4). This risk is increased with the use of high doses (150 mg per day) and during long-term treatment (see section 4.4).

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.

4.9 Overdose

Symptoms
There is no typical clinical picture resulting from diclofenac over-dosage. Overdose can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhoea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.

Treatment
Management of acute poisoning with NSAIDs consists of supportive measures and symptomatic treatment and should be considered for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Special measures such as forced diuresis, dialysis or hemoperfusion are probably of no help in eliminating NSAIDs 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

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, acetic acid derivatives and related substances, diclofenac, ATC code: M01AB05.

Diclofenac potassium is a non-steroidal analgesic with anti-inflammatory and antipyretic properties.

Diclofenac is suitable for the treatment of acute pain. The mechanism of action is attributed to the inhibition of prostaglandin biosynthesis. Prostaglandins play a major role in causing inflammation, pain and fever.

The effect of diclofenac occurs rapidly. Thus, it is particularly suitable for the treatment of acute pain, and reduction of fever. Diclofenac has an analgesic effect and relieves the pain.

In vitro, the synthesis of prosteoglycan in the tissue is not reduced at concentrations as those achieved in humans.

5.2 Pharmacokinetic properties

Absorption
Diclofenac is rapidly and completely absorbed. Mean plasma concentration (1.9 μmol/l) is achieved within app. 35 minutes (median Tmax) following intake of 2 tablets of 12.5 mg. The amount absorbed is directly proportional to the dose. Approximately half of the amount of diclofenac is metabolised by the liver during the first pass (first-pass effect). The bioavailability after an oral dose is half of the same dose administered parenterally. Pharmacokinetics does not change after repeated administration. No accumulation takes place provided that the recommended dose range is maintained.

Distribution
99.7% of diclofenac binds to serum proteins, mainly to albumin (99.4%). The apparent volume of distribution is 0.12 to 0.17 L/kg. Diclofenac is found in the synovial fluid, where the peak concentrations are measured 2-4 hours following achievement of the peak plasma levels. Half-life of elimination from synovial fluid is 3-6 hours. Two hours after the peak plasma concentrations are achieved the concentrations are higher in the synovial fluid than in plasma and maintain at this level for up to 12 hours.

Biotransformation
The metabolism of diclofenac involves partly glucuronidation of the intact molecule but mainly single and multiple hydroxylation and methoxylation. This results in several phenol metabolites of which the majorities are converted to glucuronide conjugates. Two of these metabolites are biologically active but weaker than diclofenac.

Elimination
Total systemic clearance of diclofenac from plasma is 263±56 mL/min. The terminal half-life in plasma is 1 to 2 hours. Four of the metabolites, including the two active ones, also have shorter plasma half-lives of 1 to 3 hours. A fifth metabolite, 3-hydroxy-4-methoxy-diclofenac, has a much longer plasma half-life. This metabolite is virtually inactive.
About 60% of the administered dose is excreted in the urine as 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.

Special population
No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed.

When the usual dose is administered there seem to be no accumulation of unchanged active substance in patients with renal insufficiency. This conclusion has been drawn from the results from single dose kinetics. At a clearance lower than 10 ml/min the calculated steady-state plasma levels of hydroxyl metabolites are about four times higher than in normal subjects. However, the metabolites are finally excreted through the bile.
In patients with chronic hepatitis or non-symptomatic cirrhosis, the kinetics and metabolism are the same as in patients without liver disease.

5.3 Preclinical safety data

Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, and carcinogenicity studies with diclofenac revealed no specific hazard for humans at the intended therapeutic doses. There was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits.
Diclofenac in rats had no effect on the fertility of the mother animal. The prenatal, perinatal and postnatal development of the new-born was not affected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose monohydrate,
Calcium phosphate,
Sodium starch glycolate type A,
Maize starch,
Povidone K30,
Cellulose microcrystalline 101,
Silica colloidal anhydrous,
Magnesium stearate.

Coating - Opadry White OY-B-28920
Polyvinyl alcohol,
Titanium dioxide (E171),
Talc,
Lecithin (soya) (E322),
Xanthan gum.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container and special equipment for use, administration or implantation

The tablets are packed in cold forming aluminium/push through aluminium OPA-Al-PVC/Al blisters.

Available in packs sizes of 10, 20, 30 and 40 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

MEDOCHEMIE LTD, 1-10 Constantinoupoleos street, 3011 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER(S)

06348/08815/NMR/2021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25/07/2021

Date of latest renewal: N/A

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08/2022