

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Almiral 25mg gastro-resistant tablets

Almiral 50mg gastro resistant tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Almiral tablets contain either 25mg or 50mg of diclofenac sodium

Excipients with known effect: lactose, sunset yellow (FCF) aluminium lake (E110), tartrazine aluminium lake (E102).

For the full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Gastro resistant tablets

Almiral tablets are orange, round, convex, for oral administration.

### 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:

- Arthritic conditions, rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, psoriatic arthritis, arthritis due to crystal deposition, acute gout.
- Acute musculo-skeletal disorders, such as periarthrititis (e.g. frozen shoulder), tendinitis, tenosynovitis, bursitis
- Other painful conditions as a result of trauma, such as fracture, back pain, sprains and strains, dislocations, orthopaedic, dental and other minor surgical procedures, renal colic, migraine attacks and primary dysmenorrhea.

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*Children (aged 1 - 12 years):*

*Almiral 25mg tablets:*

- Treatment of juvenile chronic arthritis

## **4.2. Posology and method of administration**

Dosage is individualized and depends on the patient's condition, indication, and response.

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

### Posology

#### *Adults*

The usual starting dose is 75mg - 150mg daily in two or three divided doses.

The recommended maximum daily dose of diclofenac is 150mg.

Chronic maintenance administration is 50 to 100 mg daily in divided doses and its duration is determined by the treating physician depending on the patient's response. For the treatment of acute conditions, which require short-term treatment, pharmaceutical forms with rapid absorption are preferred.

#### *Elderly*

Although the pharmacokinetics of diclofenac 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 should be used, in frail elderly patients or those with a low body weight (see also section 4.4) and the patient should be monitored for GI bleeding during NSAID therapy.

#### *Paediatric population*

*Children (1 - 12 years):*

Almiral 25mg tablets only: 1mg - 3mg/kg/day, in divided doses, by oral administration.

#### *Renal impairment*

Diclofenac is contraindicated in patients with severe renal impairment (see section 4.3). No specific studies

have been carried out in patients with renal impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering diclofenac to patients with mild to moderate renal impairment (see section 4.3 and 4.4).

#### *Hepatic impairment*

Diclofenac is contraindicated in patients with severe hepatic impairment (see section 4.3). No specific studies have been carried out in patients with hepatic impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering diclofenac to patients with mild to moderate hepatic impairment (see section 4.3 and 4.4).

#### Method of administration

For oral administration.

Almiral tablets should be swallowed whole, with a little water if desired.

### **4.3. Contraindications**

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active, gastric or intestinal ulcer, bleeding or perforation
- History of gastrointestinal bleeding or perforation, relating to previous NSAID 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, renal or cardiac failure.
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contraindicated in patients in whom attacks of asthma, angioedema, urticaria or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs.
- 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 Warnings**

#### **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).

The concomitant use of diclofenac 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).

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).

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). 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 may mask the signs and symptoms of the infection due to its pharmacodynamics properties.

### **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 will 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). 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. The elderly have increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).

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).

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 oral, corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors (SSRIs) or anti-platelet agents such as acetylsalicylic acid (see section 4.5).

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).

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 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), diclofenac 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). 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 diclofenac (see section 4.8). 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.

### **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).

### **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.

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 consistently point towards 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.

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.

### **Haematological effects**

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

Diclofenac may reversibly inhibit platelet aggregation (see anticoagulants in section 4.5). 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 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 4.6).

### **Excipients with known effect**

Almiral tablets also contain lactose, sunset yellow (FCF) aluminium lake (E110), tartrazine aluminium lake (E102).

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

Sunset yellow (FCF) aluminium lake (E110) and tartrazine aluminium lake (E102) may cause allergic reactions.

## **4.5. Interactions with other medicinal products and other forms of interaction**

The following interactions include those observed with diclofenac gastro-resistant tablets and/or other pharmaceutical forms of diclofenac.

**Lithium:** If used concomitantly, diclofenac may increase plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

**Digoxin:** If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

**Diuretics and antihypertensive agents:** Like other NSAIDs, concomitant use of diclofenac 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).

**Anticoagulants and anti-platelet agents:** Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4). Although clinical investigations do not appear to indicate that Almira has an influence on the effect of anticoagulants, there are isolated reports of an increased risk of haemorrhage with the combined use of diclofenac and anticoagulant therapy (see section 4.4). Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other non-steroidal 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).

**Selective serotonin reuptake inhibitors (SSRIs):** Concomitant administration of SSRI's may increase the risk of gastrointestinal bleeding (see section 4.4).

**Antidiabetics:** Clinical studies have shown that diclofenac can be given together with oral antidiabetic 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.

*CYP2C9 inducers:* Caution is advised when diclofenac is co-prescribed with CYP2C9 inducers (such as rifampicin). This could result in a significant reduction in plasma concentrations and exposure to diclofenac.

#### **4.6. Fertility, pregnancy and lactation Pregnancy**

##### 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. If diclofenac is used by a woman attempting to conceive, or during the 1st trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

From the 20th week of pregnancy onward, diclofenac 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 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, diclofenac is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

#### Breast-feeding

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).

#### 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 also section 4.4 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: ( $>1/10$ ); common ( $\geq 1/100$ ,  $<1/10$ ); uncommon ( $\geq 1/1,000$ ,  $<1/100$ ); rare ( $\geq 1/10,000$ ,  $<1/1,000$ ); 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.

| <b>Blood and lymphatic system disorders</b> |   |
|---|---|
| Very rare                                   | Thrombocytopenia, leucopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis. |
| <b>Immune system disorders</b>              |   |
| Rare  | Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).       |
| Very rare                                   | Angioneurotic oedema (including face oedema).   |

|  |  |
|--|--|
| <b>Psychiatric disorders</b>                           |  |
| Very rare  | Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.   |
| <b>Nervous system disorders</b>                        |  |
| Common   | Headache, dizziness.   |
| Rare   | Somnolence, tiredness.   |
| Very rare  | Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.  |
| Not known  | Confusion, hallucinations, disturbances of sensation, malaise.   |
| <b>Eye disorders</b>                                   |  |
| Very rare  | Visual disturbance, vision blurred, diplopia.  |
| Not known  | Optic neuritis.  |
| <b>Ear and labyrinth disorders</b>                     |  |
| Common   | Vertigo.   |
| Very rare  | Tinnitus, hearing impaired.  |
| <b>Cardiac disorders</b>                               |  |
| Very rare  | Palpitations, chest pain, cardiac failure, myocardial infarction.  |
| Not known  | Kounis syndrome  |
| <b>Vascular disorders</b>                              |  |
| Very rare  | Hypertension, hypotension, vasculitis.   |
| <b>Respiratory, thoracic and mediastinal disorders</b> |  |
| Rare   | Asthma (including dyspnoea).   |
| Very rare  | Pneumonitis.   |
| <b>Gastrointestinal disorders</b>                      |  |
| 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  |
| <b>Hepatobiliary disorders</b>                         |  |
| Common   | Transaminases increased.   |

|   |  |
|---|--|
| Rare  | Hepatitis, jaundice, liver disorder.   |
| Very rare   | Fulminant hepatitis, hepatic necrosis, hepatic failure.  |
| <b>Skin and subcutaneous tissue disorders</b>               |  |
| 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, Henoch-Schonlein purpura, pruritus. |
| <b>Renal and urinary disorders</b>                          |  |
| Very rare   | Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.  |
| <b>General disorders and administration site conditions</b> |  |
| Rare  | Oedema.  |
| <b>Reproductive system and breast disorders</b>             |  |
| 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).

#### 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:

ADR Reporting Website: [www.medicinesauthority.gov.mt/adrportal](http://www.medicinesauthority.gov.mt/adrportal)

## **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, diarrhoea, dizziness, disorientation, excitation, coma, drowsiness, tinnitus, fainting, or convulsions. In the cases of

significant poisoning acute renal failure and liver damage are possible.

### *Treatment*

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 haemo-perfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to 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***

Pharmacotherapeutic group: Antiinflammatory and antirheumatic products, Nonsteroidal ATC code: M01AB05.

#### **Mechanism of action**

Diclofenac sodium is a nonsteroidal 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 produce a clinical response characterized by marked relief of signs and symptoms such as pain at rest, pain on movement, morning stiffness and joint swelling as well as improvement in function.

In post-traumatic and post-operative inflammation diclofenac rapidly relieves both autogenic pain and pain on movement and reduces inflammatory swelling and wound swelling.

Diclofenac has also been found to provide a strong analgesic effect in moderate to severe pain of non-

rheumatic origin with onset of action occurring in 15 to 30 minutes.

Diclofenac has also been shown to have a beneficial effect on migraine attacks.

## **5.2. Pharmacokinetic properties**

### Absorption

Tablets: 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  $1.48 \pm 0.65 \mu\text{g/ml}$  ( $1.5 \mu\text{g/ml}$   $5 \mu\text{mol/l}$ )).

### Bioavailability

About half of the administered diclofenac is metabolized during its first passage through the liver ("first pass" effect), the area under the concentration 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.

### 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.

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).

### Biotransformation

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  $263 \pm 56$  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.

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**

Preclinical data from acute and repeated toxicity studies, as well as from genotoxicity, mutagenicity and carcinogenicity studies did not show any particular risk for humans at the proposed therapeutic doses. In established preclinical animal studies, there was no evidence of teratogenic potential in the mouse, rat or rabbit. No further relevant information.

Diclofenac had no effect on parental fertility in the rat. Apart from minor effects on fetuses at maternally



toxic doses, the prenatal, perinatal and postnatal development of the offspring was not affected. Administration of NSAIDs (including diclofenac) inhibited ovulation in the rabbit and implantation and placentation in the rat and resulted in premature convergence of the ductus arteriosus in pregnant rats. Maternal toxic doses of diclofenac were associated with dystocia, prolonged gestation, reduced fetal survival and intrauterine growth retardation in rats. The minor effects of diclofenac on reproductive and parturition parameters as well as the convergence of the ductus arteriosus in the uterus are pharmacological consequences of the class of prostaglandin synthesis inhibitors.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1. List of excipients**

Almiral tablets 25mg:

- microcrystalline cellulose,
- lactose monohydrate,
- croscarmellose sodium,
- silica colloidal anhydrous,
- magnesium stearate,
- propylene glycol,
- talc,
- methacrylic acid copolymer,
- simeticone and
- opandry orange OY-3538, (hydroxypropylmethylcellulose, polyethylene glycol 8000, sunset yellow (FCF) aluminium lake (E110), talc and tartrazine aluminium lake (E102).

Almiral tablets 50mg:

- microcrystalline cellulose,
- lactose spray dried,
- croscarmellose sodium,

- colloidal silicon dioxide,
- magnesium stearate,
- methacrylic acid copolymer,
- propylene glycol,
- talc,
- simeticone,
- opandry orange OY-3538 (hydroxypropylmethylcellulose, polyethylene glycol 8000, sunset yellow aluminium lake (E110), talc and tartrazine aluminium lake (E102).

## **6.2. Incompatibilities**

None known.

## **6.3. Shelf Life**

5 years

## **6.4. Special precautions for storage**

Store below 25<sup>0</sup>C, in the original package.

## **6.5. Nature and contents of container**

Almiral 25 mg tablets are supplied in aluminium/polyvinylchloride blisters of ten tablets in packs of three or ten blisters.

Almiral 50 mg tablets are supplied in aluminium/polyvinylchloride blisters of ten tablets in packs of two, three or ten blisters. Polyvinylchloride securitainers of 500 or 1000 tablets are also available.

## **6.6. Special precautions for disposal and other handling**

Not applicable

**7. MARKETING AUTHORISATION HOLDER**

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

**8. MARKETING AUTHORISATION NUMBER**

Almiral 25mg tablets: MA032/02301

Almiral 50mg tablets: MA032/02303

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION**

Date of first authorisation: 18<sup>th</sup> June 2007

Renewal of authorisation: 18<sup>th</sup> July 2011

**10. Date of (Partial) Revision of the Text:**

May 2023