SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT

AIRTAL 100 mg film-coated tablets

2. QUALITATIVE AND CUANTITATIVE COMPOSITION

Airtal 100 mg film-coated tablets: each tablet contains 100 mg of aceclofenac.

See section 6.1. for full list of excipients.

3. PHARMACEUTICAL FORM

Airtal 100 mg film-coated tablets: white circular biconvex film-coated tablets, approximately 8 mm in diameter.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Airtal is indicated in the treatment of inflammatory and painful processes such as backache, toothache, scapulohumeral periarthritis and extra-articular rheumatism, as well as for chronic treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

4.2. Posology and method of administration

Airtal film-coated tablets is supplied for oral administration.

The tablets should be taken whole with sufficient liquid.

When Airtal was given to healthy volunteers, during meals or fasted, only the speed but not the degree of absorption of aceclofenac was altered. Airtal may therefore be taken with food.

Adults

The recommended dose is 200 mg daily, taking 100 mg twice, one tablet in the morning and another in the evening.

Paediatric population

There are no clinical data for use of Airtal in children.

Elderly patients

The pharmacokinetics of aceclofenac is unaltered in elderly patients, so it is not considered necessary to modify the dose or the frequency of administration.

However, as with any other non-steroidal anti-inflammatory drug, precautions should be taken when treating elderly patients, who are generally more likely to present secondary effects, and who are more likely to present cardiovascular and renal or hepatic function alterations, as well as to be receiving concomitant medication.

Renal impairment

There is no evidence to support modifying the dose of Airtal in patients with slight renal impairment (see section 4.4).

Hepatic impairment

Some evidence indicates that the dose of this medication should be reduced in patients with hepatic impairment, suggesting the use of the dose of 100 mg/day.

Adverse reactions can be minimised by using the lowest efficacious dose over the shortest possible treatment period to control symptoms (see section 4.4. Special warnings and precautions for use).

4.3. Contraindications

Hypersensitivity to aceclofenac or to any of the excipients included in section 6.1.

Aceclofenac should not be administered to patients with a history of gastrointestinal bleeding or perforation associated with previous treatment with NSAIDs, peptic ulcer / active or repeated gastrointestinal bleeding (two or more different proven episodes of ulceration or bleeding).

It should not be administered in patients with active bleeding or bleeding disorders.

This medication should not be administered to patients with serious renal or hepatic impairment.

Airtal should not be administered to patients with established congestive cardiac impairment (NYHA classification II-IV), ischaemic cardiopathy, peripheral arterial pathology and/or cerebrovascular illness.

Aceclofenac should not be prescribed in the third trimester of pregnancy. Airtal should not be administered during the first and second trimesters of pregnancy unless considered strictly necessary. In this case the dose and duration of treatment should be reduced as far as possible (see section 4.6).

Aceclofenac should not be prescribed during lactation (see section 4.6).

Airtal should not be administered in patients in whom acetylsalicylic acid or non-steroidal anti-inflammatory drugs trigger asthma attacks, acute rhinitis or urticaria, or in patients with hypersensitivity to these compounds.

4.4. Special warnings and precautions for use

Adverse reactions can be reduced by using the lowest efficacious dose for the least possible time to control symptoms.

As well, concomitant administration of this medication with other NSAIDs should be avoided, including selective cyclo-oxygenase-2 (Coxib) inhibitors.

Gastrointestinal risks:

Monitoring is required in patients with the following disorders, since they could be exacerbated (see section 4.8):

- Symptoms indicative of gastro-intestinal disorders affecting the upper or lower digestive tract.
- History suggesting gastro-intestinal ulcer, bleeding or perforation.
- Ulcerous colitis
- Crohn’s disease
- Haematological abnormalities

Gastrointestinal bleeding, ulcers and perforations: During treatment with non-steroidal anti-inflammatory drugs (NSAIDs), among which aceclofenac is included, there have been notifications of gastrointestinal bleeding, ulcers and perforations (which could be lethal) at any time, with or without previous alerting symptoms and with or without previous history of serious gastrointestinal events.

The risk of gastrointestinal bleeding, ulcer or perforation is greater when using increasing doses of NSAIDs in patients with a history of ulcer, especially if the ulcers were complicated by bleeding or perforation (see section 4.3), and elderly patients. These patients should begin treatment with the lowest possible dose. It is recommended to prescribe these patients concomitant treatment with protective agents (e.g. misoprostol or proton pump inhibitors); said combined treatment should also be considered in the case of patients who require a low dose of acetylsalicylic acid or other medications which could increase gastrointestinal risk (see below and section 4.5).

Patients with a history of gastrointestinal toxicity, especially elderly patients, should be warned to inform their physician immediately of any infrequent abdominal symptom (especially gastrointestinal bleeding) during treatment, in particular in the early stages.

Particular caution should be recommended to those patients receiving concomitant treatments which could increase the risk of ulcer or gastrointestinal bleeding, such as dicumarinic-type oral anticoagulants like warfarin, and platelet anti-aggregant medications like acetylsalicylic acid (see section 4.5). Also, some caution should be exercised in the concomitant administration of systemic corticoids and the selective serotonin reuptake inhibitor (SSRIs) antidepressants (see section 4.5).

If gastro-intestinal bleeding or ulcer were to occur in patients treated with Airtal, treatment should be suspended immediately.

Cardiovascular and cerebrovascular risks:

Exercise special caution in patients with a history of hypertension and/or slight or moderate cardiac impairment, since liquid retention and oedema have been notified in association with treatment with NSAIDs.

Patients with congestive cardiac impairment (NYHA-I) and patients with cardiovascular risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smokers) should be treated with aceclofenac only after careful consideration. Given that the cardiovascular risks of aceclofenac could increase with the dose and duration of treatment, the lowest efficacious daily dose should be used with the shortest possible treatment duration. The need to continue treatment and response to treatment should be revaluated periodically.

Aceclofenac should be administered with caution and under strict medical surveillance in patients with a history of cerebral bleeding.

Risk of serious cutaneous reactions:

Serious skin reactions, some lethal, have been described associated with the use of NSAIDs (see section 4.8). These include exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis. These are very rare, presenting in less than 1 case in every 10,000 patients. It appears that patients have a greater risk of suffering these reactions at the beginning of treatment: the onset of said adverse reaction occurs in most cases during the first month of treatment. Administration of Airtal should be suspended immediately at the first symptoms of erythema, mucosal lesions or other signs of hypersensitivity.

Exceptionally, chicken pox can trigger serious skin complications and soft tissue infections. To date the contribution of NSAIDs to the worsening of these infections cannot be ruled out. For this reason the use of aceclofenac should be avoided in cases of chicken pox.

Risk of allergic reactions:

As with any other non-steroidal anti-inflammatory drug, allergic reactions could occur, including anaphylactic /anaphylactoid reactions with no previous exposure to the drug (see section 4.8).

Elderly patients:

Elderly patients present a greater incidence of adverse reactions to NSAIDs, particularly gastrointestinal bleeding and perforation, which could be lethal (see section 4.2).

Patients with renal impairment:

Administration of a NSAID can cause a dose-dependent reduction in prostaglandin formation and trigger renal impairment. The importance of prostaglandins in the maintenance of renal blood flow should be borne in mind in patients with cardiac or renal impairment, hepatic impairment, patients treated with diuretics or in recovery after a major intervention, and in elderly patients.

Patients with slight or moderate renal impairment should be monitored, since the use of NSAIDs can cause deterioration of renal function. Administration of the minimum efficacious dose is recommended, with regular monitoring of renal function. The effects on renal function are reversed on suspension of treatment with Airtal.

Patients with hepatic impairment:

Patients with slight or moderate hepatic impairment should undergo suitable monitoring of hepatic function analytic parameters and begin treatment with 100 mg once daily (see section 4.2).

Administration of Airtal should be suspended in any patient if hepatic function controls worsen or do not normalise (with or without previous alterations in hepatic function). This also applies in the case of onset of symptoms or other manifestations (e.g. eosinophilia, exanthema) which could suggest hepatic pathology. Hepatitis can appear without the presentation of prodromal symptoms (see section 4.8), so the establishment of trimestral hepatic function controls is recommended in long-term treatments.

The administration of this medication in patients with hepatic porphyria could trigger an attack.

Haematological risks:

Airtal could reversibly inhibit platelet aggregation (see section 4.5).

Respiratory disorders:

Administer with caution in patients who present or have a history of bronchial asthma, since notifications exist of NSAIDs causing bronchospasm in these patients.

Other warnings:

Exercise caution when administering aceclofenac simultaneously with the following medications: lithium, digoxin, anticoagulants, oral antidiabetics, other anti-inflammatory drugs, since they could increase the frequency of adverse reactions or it could be necessary to adjust the dose of Airtal or these medications.

Long-term treatment:

As a precautionary measure there should be follow-up of all patients receiving long-term treatment with non-steroidal anti-inflammatory drugs (for example, renal and hepatic function and haemogram).

Warnings about excipients
Airtal 100 mg powder for oral suspension contains sorbitol. Patients with hereditary fructose intolerance should not take this medication.

4.5. Interaction with other medicinal products and other forms of interaction

Lithium and digoxin: Many non-steroidal anti-inflammatory drugs inhibit renal clearance of lithium and digoxin, increasing serum concentrations of both. Combined treatment should be avoided unless lithium and digoxin levels can be monitored frequently (see section 4.4).

Diuretics: Animal studies indicate the possibility that aceclofenac, like other non-steroidal anti-inflammatory drugs, could interfere with the natriuretic action of the diuretics. This property could be important in hypertensive patients or those with compromised cardiac function.

No effects of Airtal were observed on blood pressure control when it was administered together with bendroflumethiazide, although interaction with other diuretic drugs cannot be ruled out.

Serum potassium levels should be monitored when administering concomitantly with potassium sparing diuretics.

Antihypertensive drugs: NSAIDs could reduce the effect of antihypertensive agents. The risk of acute renal impairment, which is normally reversible, could increase in some patients with compromised renal function (e.g. dehydrated patients or elderly patients) when ECA inhibitors or angiotensin II receptor antagonists are combined with non-steroidal anti-inflammatory drugs. For this reason concomitant administration should be performed with caution, especially in elderly patients. Patients should be duly hydrated and renal function control should be considered after initiating the concomitant treatment. These controls should be regular thereafter.

Anticoagulants: As with other non-steroidal anti-inflammatory drugs, aceclofenac could increase the effects of dicumarinic-type anticoagulants due to a possible inhibitory action on platelet aggregation. Patients in combined treatment with anticoagulants and Airtal should be suitably monitored (see section 4.4).

Platelet antiaggregants: platelet antiaggregants increase the risk of gastrointestinal bleeding (see section 4.4).

Oral antidiabetics: Clinical trials have evidenced that aceclofenac can be administered jointly with oral antidiabetics without altering their clinical effect. However, isolated cases of hypoglycaemia and hyperglycaemia have been notified. The possibility of adjusting the dose of hypoglycaemic agents should be borne in mind when administering Airtal (see section 4.4).

Methotrexate: The possible interaction between non-steroidal anti-inflammatory drugs and methotrexate should be borne in mind when using low doses of methotrexate, especially in patients with renal impairment. In the case of combined treatment, renal function should be controlled. Exercise caution when administering non-steroidal anti-inflammatory drugs and methotrexate with an interval between them of less than 24 hours, because non-steroidal anti-inflammatory drugs could increase plasma concentrations of methotrexate, causing greater toxicity.

Corticoids: Corticoids could also increase the risk of ulcer or gastrointestinal bleeding (see section 4.4).

Other anti-inflammatory drugs: Concomitant treatment with acetylsalicylic acid and other non-steroidal anti-inflammatory drugs could increase the frequency of secondary effects (see section 4.4).

SSRIs: Selective serotonin reuptake inhibitors (SSRIs) could also increase the risk of gastrointestinal bleeding (see section 4.4).

Cyclosporine, tacrolimus: It is believed that concomitant administration of non-steroidal anti-inflammatory drugs and cyclosporine or tacrolimus increases the risk of nephrotoxicity due to decreased prostacyclin synthesis in the kidney. For this reason, it is important to carry out strict follow-up of renal function during combined treatment.

Zidovudine: Joint administration of zidovudine and NSAIDs could increase the risk of haematological toxicity. There are signs of increased risk of haemoarthrosis and haematomas in HIV (+) haemophiliacs receiving joint treatment with zidovudine and ibuprofen.

4.6. Fertility, pregnancy and lactation

Pregnancy
There is no information regarding the use of aceclofenac during pregnancy.

1) First and second trimester of pregnancy
The inhibition of prostaglandin synthesis could have a negative effect on pregnancy and/or the development of the embryo/foetus. Data from epidemiological studies suggest an increased risk of miscarriage and cardiac malformations and gastroschisis after using a prostaglandin synthesis inhibitor in the early stages of pregnancy. The absolute risk of cardiac malformations increased from less than 1% to approximately 1.5%. It appears that the risk increases with the dose and duration of treatment.

The administration of a prostaglandin synthesis inhibitor in animals evidenced greater loss pre- and post-implantation and greater mortality of the embryo/foetus. Also, a greater incidence of various malformations was notified, for example cardiovascular, in animals administered a prostaglandin synthesis inhibitor during the organogenesis period. Aceclofenac should not be administered during the first and second trimesters of pregnancy unless considered strictly necessary. If aceclofenac is used when a woman is attempting to conceive, or during the first and second trimesters of pregnancy, the dose and duration of treatment should be reduced as far possible.

2) Third trimester of pregnancy
During the third trimester of pregnancy, all prostaglandin synthesis inhibitors could expose the foetus to:

- Cardio-pulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
- Renal dysfunction, which could lead to renal failure with oligohydroamnios.

At the end of pregnancy the mother and new-born baby could be exposed to:

- Possible prolonging of bleeding, due to an antiaggregant effect which could occur even at very low doses.
- Inhibition of uterine contractions, which could cause delay or prolonging of the birth.

Consequently, aceclofenac is contraindicated in the third trimester of pregnancy (see section 4.3).

Breastfeeding
Airtal should not be administered during breastfeeding. There is no information regarding secretion of Airtal in breast milk; however, there was no notable transfer of radio-labelled (14C) aceclofenac to the milk of lactating rats.

Therefore the use of aceclofenac during pregnancy and breastfeeding should be avoided, except in those cases where the potential benefits for the mother exceed possible risks for the foetus.

Fertility

The use of aceclofenac could alter female fertility and is not recommended in women who are attempting to conceive. In women who have difficulties conceiving, or who are subject to a fertility investigation, suspension of this medication should be considered.

4.7. Effects on ability to drive and use machines

Patients with signs or symptoms of alterations to the central nervous system such as dizziness, vertigo or fainting should not drive or use machinery whilst they in treatment with non-steroidal anti-inflammatory drugs.

4.8. Undesirable effects

The most frequently observed adverse reactions are gastrointestinal. Peptic ulcers, perforation or gastrointestinal bleeding could occur. These are lethal in some cases, especially in the elderly (see section 4.4). There have also been notifications for nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerous stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4). Gastritis has been observed less frequently.

Exceptionally there have been notifications of serious skin complications and soft tissue infections during chicken pox in association with treatment with non-steroidal anti-inflammatory drugs.

Aceclofenac metabolises to diclofenac and is similar to it in structure. There is a large quantity of clinical and epidemiological data associated with the use of diclofenac, consistently indicating increased risk of arterial thrombosis events (myocardial infarction or ictus, particularly at high doses and in long-term treatments). Epidemiological data also demonstrate an increase in the risk of acute coronary syndrome and myocardial infarction associated with the use of aceclofenac (see sections 4.3 and 4.4 on Contraindications and Special warnings and precautions for use).

Administration of Airtal should be suspended if serious adverse reactions occur.

The following adverse effects were observed during all clinical trials, and were later corroborated by post-marketing experience. They are classified by organs, systems and frequencies. The frequencies are defined as: very frequent (≥ 1/10); frequent (≥1/100, < 1/10); infrequent (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000) or very rare (<1/10,000).

Organic systems MedDRa	Frequent ≥ 1/100 to < 1/10	Infrequent ≥ 1/1.000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Very rare < 1/10,000
Blood and lymphatic system disorders			Anaemia	Bone marrow depression Granulocytopaenia Thrombocytopaenia Haemolytic anaemia
Immune system disorders			Anaphylactic reaction (including shock) Hypersensitivity	
Nutritional and metabolic disorders				Hyperpotassaemia
Psychiatric disorders				Depression Interrupted sleep Insomnia
Nervous system disorders	Dizziness			Paresthaesia Drowsiness Headache Dysgeussia (taste disorder) Trembling
Ocular disorders			Deterioration of sight	
Ear and labyrinth disorders				Vertigo Tinnitus
Cardiac disorders			Heart failure	Palpitations

Organic systems MedDRa	Frequent ≥ 1/100 to < 1/10	Infrequent ≥ 1/1.000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Very rare < 1/10,000
Vascular disorders			Arterial hypertension	Blushing Hot sensation Peripheral oedema Vasculitis
Respiratory, thoracic and mediastinal disorders			Dyspnoea	Whistling in lungs Bronchospasm
Gastrointestinal disorders	Dyspepsia Abdominal pain Nausea Diarrhoea	Flatulence Gastritis Constipation Vomiting Mouth ulcer	Melaena Gastrointestinal bleeding Gastrointestinal ulcer	Stomatitis Pancreatitis Intestinal perforation Exacerbation of Crohn's disease and ulcerous colitis Haematemesis
Hepatobiliary disorders	Raised hepatic enzymes			Hepatic lesion (including hepatitis) Raised alkaline phosphatase in blood
Skin and subcutaneous tissue disorders		Pruritus Exanthema Dermatitis Urticaria	Angioedema	Purpura Serious mucocutaneous reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis).
Muscular-skeletal and conjunctival tissue disorders				Leg cramps
Renal and urinary disorders		Raised blood urea Raised blood creatinine		Nephrotic syndrome Renal failure
General disorders and alterations at the administration site				Oedema Fatigue
Other examinations				Increased body weight

See sections 4.4 and 4.5 for more information on warnings, precautions and interactions.

4.9. Overdose

Treatment for acute intoxication due to non-steroidal anti-inflammatory drugs consists, essentially of support and symptomatic measures for complications such as hypotension, renal impairment, convulsions, gastrointestinal irritation and respiratory depression.

There are no data regarding the consequences of overdose of Airtal in humans. Therapeutic measures to adopt are: in the case of overdose, avoid absorption of the drug as far as possible through gastric lavage and treatment with activated carbon.
Specific treatments such as forced diuresis, dialysis or haemoperfusion probably do not contribute to the elimination of non-steroidal anti-inflammatory drugs due to their high rate of protein binding and extensive metabolism.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Non-steroidal anti-inflammatory and anti-rheumatic products. Derivatives of acetic acid and related substances.
(ATC Code: M01AB16).

Aceclofenac is a non-steroidal agent with notable anti-inflammatory and analgesic properties.

The mechanism of action of aceclofenac is based mainly on the inhibition of prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclooxygenase, which intervenes in the production of prostaglandins.

5.2. Pharmacokinetic properties

Aceclofenac is absorbed rapidly and completely as unaltered product after oral administration. Maximum plasma concentrations are reached approximately 1.25 to 3.00 hours after ingestion. Aceclofenac penetrates the synovial fluid, where concentrations reach approximately 57% of plasma concentrations. The distribution volume is approximately 25 l.

The half-life in plasma is around 4 hours. Aceclofenac binds greatly to proteins (> 99%). Aceclofenac circulates mainly as unaltered product. The main metabolite detected in plasma is 4'-hydroxyaceclofenac. Approximately two thirds of the dose administered is excreted in urine, fundamentally as hydroxymetabolites.

No alterations in the pharmacokinetics of aceclofenac have been observed in elderly patients.

5.3. Preclinical safety data

The results from preclinical studies performed with aceclofenac are congruent with those expected in non-steroidal anti-inflammatory drugs. The main target organ was the gastrointestinal tract. No unexpected findings were recorded.

Aceclofenac was considered not to have any mutagenic activity in three *in vitro* studies and in one *in vivo* study in rats. However, in a study in rabbits treatment with aceclofenac (10 mg/kg/day) caused a series of morphological alterations in some foetuses.

Teratogenesis studies in rats were negative and presented no abnormalities. Aceclofenac was not found to be carcinogenic in mice or rats.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

The following excipients are used in Airtal 100 mg film-coated tablets: microcrystalline cellulose, sodium croscarmellose, glycerol palmitostearate and povidone. Coating components (sepifilm): hypromellose, microcrystalline cellulose, polyoxyl 40 stearate and titanium dioxide (E-171).

6.2. Incompatibilities

None described.

6.3. Shelf-life

4 years.

6.4. Special precautions for storage

Airtal 100 mg film-coated tablets: Store below 30ºC.

6.5. Nature and contents of container

Airtal 100 mg film-coated tablets are presented in cardboard boxes with 20 and 40 coated tablets, packed in aluminium-aluminium blisters with the patient information leaflet.

6.6. Special precautions for disposal

No precautions.

7. MARKETING AUTHORISATION HOLDER

Almirall, S.A.
General Mitre, 151
08022 Barcelona (Spain)

8. LAST TEXT REVISION

July 2014