

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0968/003/001

Case No: 2043804

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Laboratorios Almirall S.A.

General Mitre, 151, 08022, Barcelona, Spain

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Airtal 100mg Film-coated Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **12/08/2008** until .

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Airtal 100mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Aceclofenac 100mg

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablet

White, round, film-coated tablet, 8mm in diameter, with an 'A' embossed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Airtal[®] is indicated for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

4.2 Posology and method of administration

Airtal[®] tablets are supplied for oral administration and should be swallowed whole with a sufficient quantity of liquid. When Airtal[®] was administered to fasting and fed healthy volunteers, only the rate and not the extent of aceclofenac absorption was affected and as such Airtal[®] can be taken with food.

Route of administration

Oral

Recommended dosage

Adults

The recommended dose is 200 mg daily, taken as two separate 100 mg doses, one tablet in the morning and one in the evening.

Children

There are no clinical data on the use of Airtal[®] in children.

Elderly

The pharmacokinetics of Airtal[®] are not altered in elderly patients, therefore it is not considered necessary to modify the dose or dose frequency.

As with other non-steroidal anti-inflammatory drugs (NSAIDs), caution should be exercised in the treatment of

elderly patients, who are generally more prone to adverse reactions, and who are more likely to be suffering from impaired renal, cardiovascular or hepatic function and receiving concomitant medication.

Renal insufficiency

There is no evidence that the dosage of Airtal[®] needs to be modified in patients with mild renal impairment, but as with other NSAIDs caution should be exercised.

Hepatic insufficiency

There is some evidence that the dose of Airtal[®] should be reduced in patients with hepatic impairment and it is suggested that an initial dose of 100 mg be used.

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

4.3 Contraindications

Airtal[®] should not be administered to patients with a history of gastrointestinal bleeding or perforation, related to previous NSAID therapy. Airtal[®] is also contraindicated in patients with an active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

Airtal[®] should not be given to patients with moderate to severe renal impairment.

Airtal[®] should not be given to patients with severe heart failure.

Airtal[®] should not be prescribed during pregnancy, unless there are compelling reasons for doing so. The lowest effective dosage should be used.

Airtal[®] should not be administered to patients previously sensitive to aceclofenac or in whom aspirin or NSAIDs precipitate attacks of asthma, acute rhinitis or urticaria or who are hypersensitive to these drugs.

4.4 Special warnings and precautions for use

Warnings

The use of Airtal[®] with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

Gastrointestinal bleeding, ulceration and perforation

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events. In the rare instances where gastro-intestinal bleeding or ulceration occurs in patients receiving Airtal[®], the drug should be withdrawn.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and 4.5).

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

Caution should be advised 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 or anti-platelet agents such as aspirin (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Airtal, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8 Undesirable effects).

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for aceclofenac.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease should only be treated with aceclofenac after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Skin reactions

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 (see section 4.8). Patients appear to be at 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. Airtal® should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Elderly

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

Hepatic

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

Hypersensitivity reactions

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug.

Drug-induced pancreatitis is uncommon. Nevertheless pancreatitis has been reported in relation with NSAIDs.

Precautions:

Renal

Patients with mild renal or cardiac impairment and the elderly should be kept under surveillance, since the use of NSAID's may result in deterioration of renal function. The lowest effective dose should be used and renal function monitored regularly.

The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, those being treated with diuretics or recovering from major surgery. Effects on renal function are usually reversible on withdrawal of Airtal®.

Hepatic

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

Use of Airtal® in patients with hepatic porphyria may trigger an attack.

Haematological

Airtal® may reversibly inhibit platelet aggregation (see anticoagulants under 'Interactions').

Female fertility

The use of Airtal®, as with any drug known to inhibit cyclo-oxygenase / prostaglandin synthesis, 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 aceclofenac should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Lithium and digoxin: Airtal®, like many NSAIDs, may increase plasma concentrations of lithium and digoxin.

Diuretics: Airtal®, like other NSAIDs, may inhibit the activity of diuretics. Although it was not shown to affect blood pressure control when co-administered with bendrofluazide, interactions with other diuretics cannot be ruled out. When concomitant administration with potassium-sparing diuretics is employed, serum potassium should be monitored.

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4). Close monitoring of patients on combined anticoagulant and Airtal® therapy should be undertaken.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).

Antidiabetic agents: 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. Thus with Airtal®, consideration should be given to adjustment of the dosage of hypoglycaemic agents.

Methotrexate: Caution should be exercised if NSAIDs and methotrexate are administered within 24 hours of each other, since NSAIDs may increase methotrexate plasma levels, resulting in increased toxicity.

Other NSAIDs and steroids: Concomitant therapy with aspirin, other NSAIDs and steroids may increase the frequency of side effects.

Cyclosporin: Cyclosporin nephrotoxicity may be increased by the effect of NSAIDs on renal prostaglandins.

Quinolone antimicrobials: Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving a NSAID.

4.6 Pregnancy and lactation

Pregnancy: There is no information on the use of Airtal® during pregnancy. The regular use of NSAIDs during the last trimester of pregnancy may decrease uterine tone and contraction. NSAID use may also result in premature closure of the fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn, delay onset and increase duration of labour.

Animal studies indicate that there was no evidence of teratogenesis in rats although the systemic exposure was low and in rabbits, treatment with aceclofenac (10 mg/kg/day) resulted in a series of morphological changes in some fetuses.

Lactation: There is no information on the secretion of Airtal[®] to breast milk: there was however no notable transfer of radio-labelled (¹⁴C) aceclofenac to the milk of lactating rats.

The use of Airtal[®] should therefore be avoided in pregnancy and lactation unless the potential benefits to the mother outweigh the possible risks to the fetus.

4.7 Effects on ability to drive and use machines

Patients suffering from dizziness, vertigo, or other central nervous system disorders whilst taking NSAIDs should refrain from driving or handling dangerous machinery.

4.8 Undesirable effects

Gastrointestinal: The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4 Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed.

The majority of side effects observed have been reversible and of a minor nature and include, gastro-intestinal disorders (dyspepsia, abdominal pain, nausea and diarrhoea) and occasional occurrence of dizziness. Dermatological complaints including pruritus and rash and abnormal hepatic enzyme levels and raised serum creatinine have occasionally been reported.

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

Bullous reactions including Stevens-Johns on syndrome and toxic epidermal necrolysis (very rare).

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

If serious side-effects occur, Airtal[®] should be withdrawn.

The following is a table of adverse reactions reported from clinical trials and post-authorisation use, grouped by system-Organ Classes and estimated frequencies.

MeDRa SOC	Common <10%->1%	Uncommon <1%->0.1%	Rare <0.1%->0.01%	Very rare/ isolated reports <0.01%
Blood and lymphatic system disorders			Anaemia	Granulocytopenia Thrombocytopenia
Immune system disorders			Anaphylactic reaction (including Shock) Hypersensitivity	
Metabolism and nutrition				Hyperkalemia
Psychiatric disorders				Depression Abnormal dreams Insomnia
Nervous system disorder	Dizziness			Paraesthesia Somnolence Headache

				Dysgeusia (Abnormal taste) Tremor
Eye disorders			Visual disturbance	
Ear and labyrinth disorders				Vertigo
Cardiac disorders			Cardiac failure	Palpitations
Vascular disorders			Hypertension	<?xml:namespace prefix = st1 ns = "urn:schemas- microsoft- com:office:smartrtags" /><st1:place w:st="on">Flushing</st1:place> Hot flush
Respiratory thoracic and mediastinal disorders			Dyspnoea	
Gastrointestinal disorders	Dyspepsia Abdominal pain Nausea Diarrhoea	Flatulence Gastritis Constipation Vomiting Mouth ulceration	Melaena Gastrointestinal perforation	Stomatitis Haematemesis Peptic ulcer Gastrointestinal haemorrhage Hyperkalaemia
Skin and subcutaneous Tissue disorders		Pruritus Rash Dermatitis Urticaria	Face oedema	Purpura Serious mucocutaneous skin reactions
Renal and urinary disorders				Nephritic Syndrome
General disorders and administration site conditions				Oedema Fatigue
Investigations	Hepatic enzyme increased	Blood urea increased Blood creatinine increased		Blood alkaline phosphatase increased Weight increase Hyperkalaemia

4.9 Overdose

Management of acute poisoning with non-steroidal anti-inflammatory drugs essentially consists of supportive and symptomatic measures.

There are no human data available on the consequences of Airtal[®] overdose. The therapeutic measures to be taken are: absorption should be prevented as soon as possible after overdose by means of gastric lavage and treatment with activated charcoal; supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal irritation, and respiratory depression; specific therapies such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating non-steroidal anti-inflammatory drugs due to their high rate of protein binding and extensive metabolism.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

The mode of action of aceclofenac is largely based on the inhibition of prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclo-oxygenase, which is involved in the production of prostaglandins.

5.2 Pharmacokinetic properties

After oral administration, aceclofenac is rapidly and completely absorbed as unchanged drug. Peak plasma concentrations are reached approximately 1.25 to 3.00 hours following ingestion. Aceclofenac penetrates into the synovial fluid, where the concentrations reach approximately 57% of those in plasma. The volume of distribution is approximately 25 L.

The mean plasma elimination half-life is around 4 hours. Aceclofenac is highly protein-bound (> 99%). Aceclofenac circulates mainly as unchanged drug. 4'-Hydroxyaceclofenac is the main metabolite detected in plasma. Approximately two-thirds of the administered dose is excreted via the urine, mainly as hydroxymetabolites.

No changes in the pharmacokinetics of aceclofenac have been detected in the elderly.

5.3 Preclinical safety data

The results from preclinical studies conducted with aceclofenac are consistent with those expected for NSAIDs. The principal target organ was the gastro-intestinal tract. No unexpected findings were recorded.

Aceclofenac was not considered to have any mutagenic activity in three in vitro studies and an in vivo study in the mouse.

Aceclofenac was not found to be carcinogenic in either the mouse or rat.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Croscarmellose Sodium
Glyceryl palmitostearate
Povidone

Film coating

Sepifilm 752 White

Consisting of:

Hypromellose
Microcrystalline cellulose
Macrogol 40 stearate
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

The immediate container for Airtal 100mg Film-coated Tablets is a laminated aluminium/aluminium foil pack. Each foil strip contains 10 tablets. One or six foil strips (10 or 60 tablets) will be provided with a patient information leaflet inside a carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Laboratorios Almirall S.A.
General Mitre, 151 08022
Barcelona
Spain

8 MARKETING AUTHORISATION NUMBER

PA 968/3/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th January 1996

Date of last renewal: 8th January 2006

10 DATE OF REVISION OF THE TEXT

August 2007