Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

ACECLOFENAC 100 MG FILM-COATED TABLETS

UK/H/3717/001/DC
UK Licence No: PL 23088/0008

ASTRON RESEARCH LIMITED

LAY SUMMARY

On 14th September 2011, the UK granted Astron Research Limited a Marketing Authorisation (licence) for Aceclofenac 100 mg film-coated Tablets.

Aceclofenac Tablets belong to a group of medicines called non-steroidal anti-inflammatory drugs or NSAIDs.

Aceclofenac 100 mg film-coated Tablets are used to relieve pain and inflammation in patients suffering from:

- arthritis of the joints (osteoarthritis). This commonly occurs in patients over the age of 50 and causes the loss of the cartilage and bone tissue next to the joint.

- autoimmune disease that causes chronic inflammation of the joints (rheumatoid arthritis).

- arthritis of the spine which can lead to the fusion of the vertebrae (ankylosing spondylitis).

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Aceclofenac 100 mg film-coated Tablets outweigh the risks; hence this Marketing Authorisation has been granted.

TABLE OF CONTENTS

Module 1

Product Name	Aceclofenac 100 mg film-coated Tablets
Type of Application	Generic application, Article 10.1
Active Substance	Aceclofenac
Form	Film-coated Tablets
Strength	100 mg
MA Holder	Astron Research Limited Sage house, 319 Pinner Road, North Harrow HA1 4HF, Middlesex United Kingdom
Reference Member State (RMS)	UK
Concerned Member States (CMS)	Belgium (BE), Greece (EL), Italy (IT), Latvia (LV), Portugal (PT) and the Slovak Republic (SK)
Procedure Number	UK/H/3717/001/DC
End of Procedure	Day 210: 19th August 2011

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Aceclofenac 100 mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 100 mg Aceclofenac.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
White to off-white, round shaped, biconvex, film-coated tablet debossed with "100" on one side and plain on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Aceclofenac is indicated for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

4.2 Posology and method of administration
Aceclofenac film-coated tablets are supplied for oral administration and should be swallowed whole with a sufficient quantity of liquid.

To be taken preferably with or after food. When Aceclofenac was administered to fasting and fed healthy volunteers only the rate and not the extent of aceclofenac absorption was affected. Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

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.

Paediatric population
There are no clinical data on the use of Aceclofenac in children and therefore it is not recommended for use in children under 18 years of age.

Elderly
The elderly, who are more likely to be suffering from impaired renal, cardiovascular or hepatic function and receiving concomitant medication, are at increased risk of serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

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

Renal insufficiency
There is no evidence that the dosage of Aceclofenac needs to be modified in patients with mild renal impairment, but as with other NSAIDs caution should be exercised (see Section 4.4).

Hepatic insufficiency
There is some evidence that the dose of Aceclofenac should be reduced in patients with hepatic impairment and it is suggested that an initial daily dose of 100 mg be used.

4.3 Contraindications
Hypersensitivity to Aceclofenac or to any of the excipients.

Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

NSAIDS are contraindicated in patients who have previously shown hypersensitivity reactions (eg. Asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.

Severe heart failure, hepatic failure and renal failure (see section 4.4).

History of gastrointestinal bleeding or perforation, related to previous NSAIDS therapy.

Aceclofenac should not be prescribed during pregnancy, especially during the last trimester of pregnancy, unless there are compelling reasons for doing so. The lowest effective dosage should be used (see section 4.6).

4.4 Special warnings and precautions for use

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 use of Aceclofenac with concomitant NSAIDs including cyclooxygenase- 2 selective inhibitors should be avoided (see section 4.5).

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).

Respiratory disorders:
Caution is required if administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

Cardiovascular, Renal and Hepatic Impairment:
The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see also section 4.3).

Renal:
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 Aceclofenac Tablets.

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), Aceclofenac Tablets should be discontinued. Close medical surveillance is necessary in patients suffering from mild to moderate impairment of hepatic function. Hepatitis may occur without prodromal symptoms.
Use of Aceclofenac Tablets in patients with hepatic porphyria may trigger an attack.

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).

Gastrointestinal bleeding, ulceration and perforation:
GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

Close medical surveillance is imperative in patients with symptoms indicative of gastro-intestinal disorders, with a history suggestive of gastro-intestinal ulceration, with ulcerative colitis or with Crohn's disease, bleeding diathesis or haematological abnormalities.

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 section 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 antiplatelet agents such as aspirin (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving aceclofenac, 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 these conditions may be exacerbated (see section 4.8).

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).

Dermatological:
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 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. Aceclofenac Tablets should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Impaired female fertility:
The use of Aceclofenac Tablets 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 Tablets should be considered.

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

Haematological:
Aceclofenac Tablets may reversibly inhibit platelet aggregation (see anticoagulants under 'Interactions').

Long-term treatment:
All patients who are receiving NSAIDs should be monitored as a precautionary measure e.g. renal failure, hepatic function (elevation of liver enzymes may occur) and blood counts.

4.5 Interaction with other medicinal products and other forms of interaction
Other analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4.4).

Anti-hypertensives: Reduced anti-hypertensive effect.

Diuretics: Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs. 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.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR (glomerular filtration rate) and increase plasma glycoside levels.

Lithium: Decreased elimination of lithium.

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

Ciclosporin: Increased risk of nephrotoxicity.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

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 anti-coagulants and Aceclofenac Tablets therapy should be undertaken.

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).
Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

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 Aceclofenac Tablets, consideration should be given to adjustment of the dosage of hypoglycaemic agents.

Other NSAIDs: Concomitant therapy with aspirin or other NSAIDs may increase the frequency of adverse reactions, including the risk of GI bleeding.

4.6 Fertility, Pregnancy and lactation

Pregnancy:

Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriosus) and on the possible risk of persistent pulmonary hypertension of the new born, use in the last trimester of pregnancy is contraindicated. The regular use of NSAIDs during the last trimester of pregnancy may decrease uterine tone and contraction. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child (see section 4.3). NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

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 foetuses.

Lactation:
In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding.

See section 4.4 Special warnings and precautions for use, regarding female fertility.

The use of Aceclofenac Tablets should therefore be avoided in pregnancy and lactation unless the potential benefits to the other outweigh the possible risks to the foetus.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate 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) have been reported following administration. Less frequently, gastritis has been observed. Pancreatitis has been reported very rarely.

Hypersensitivity:
Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angiodema and, more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Cardiovascular:
Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Other adverse reactions reported less commonly include:

Renal:
Nephrotoxicity in various forms, including interstitial nephritis, nephritic syndrome and renal failure.

Hepatic:
abnormal liver function, hepatitis and jaundice.

Neurological and special senses:
Visual disturbances, optic neuritis, headaches, paraesthesia, reports of aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (See section 4.4) , depression, confusion, hallucinations, tinnitus, vertigo, dizziness, malaise, fatigue and drowsiness.

Haematological:
Thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia.

Dermatological:
Bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (very rare). Photosensitivity.

Within the system organ classes, undesirable effects are listed under headings of frequency, using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare/ isolated reports (<1/10,000)
Blood and lymphatic system disorders			Anaemia	Granulocytopenia Thrombocytopenia Neutropenia Haemolytic anaemia
Immune system disorders			Anaphylactic reaction (including shock) Hypersensitivity	
Metabolism and nutrition disorders				Hyperkalemia
Psychiatric disorders				Depression Abnormal dreams Insomnia
Nervous system disorders	Dizziness			Paraesthesia Tremor Somnolence Headache Dysgeusia (abnormal taste)
Eye disorders			Visual disturbance	
Ear and labyrinth disorders				Vertigo
Cardiac disorders				Palpitations
Vascular disorders				Flushing Hot flush
Respiratory, thoracic and mediastinal disorders			Dyspnoea	Bronchospasm Stridor
Gastrointestinal disorders	Dyspepsia Abdominal pain Nausea Diarrhoea	Flatulence Gastritis Constipation Vomiting Mouth ulceration	Melaena	Stomatitis Haematemesis Gastrointestinal haemorrhage Gastric ulcer Pancreatitis
Hepatobiliary disorders				Hepatitis Jaundice
Skin and subcutaneous tissue disorders		Pruritus Rash Dermatitis Urticaria	Face oedema	Purpura Dermatitis bullous
Musculoskeletal and connective tissue disorders				Cramps in the leg

Renal and urinary disorders				Renal insufficiency Nephrotic syndrome
General disorders and administration site conditions				Oedema Fatigue Cramps in legs
Investigations	Hepatic enzyme increased	Blood urea increased Blood creatinine increased		Blood alkanine phosphatase increased Weight increase

4.9 Overdose

a) Symptoms

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal irritation, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, hypotension, respiratory depression, fainting, occasionally convulsions. In cases of significant poisoning acute renal failure and liver damage are possible.

b) Therapeutic measure :

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Specific therapies such as dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism. Good urine output should be ensured.

Renal and liver function should be closely monitored. Patients should be observed for at least four hours after ingestion of potentially toxic amounts. In case of frequent or prolonged convulsions, patients should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition.

Management of acute poisoning with NSAIDs essentially consists of supportive and symptomatic measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: M01A B16

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 to 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

Core Tablet:
Cellulose microcrystalline
Croscarmellose sodium
Povidone K-30
Glyceryl palmitostearate

Tablet coating:
Hypromellose 15 cps
Macrogol 400
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years.

6.4 Special precautions for storage

"Store below 25°C".

6.5 Nature and contents of container

Aceclofenac Tablets 100 mg are packed in aluminium -aluminium blister packs.
The aluminium blister foil is soft temper, plain, one side bright, dull side lacquer laminated to 25 µm OPA, bright side lacquer laminated to 60 µm PVC.

The aluminium foil is 0.025 mm thick aluminium alloy hard temper foil with mat finish.
The blisters are further pack in to carton along with leaflet in pack sizes of 10, 20, 30, 40, 60 and 100 tablets per pack.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Astron Research Limited
Sage house, 319 Pinner Road,
North Harrow HA1 4HF, Middlesex
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 23088/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/09/2011

10 DATE OF REVISION OF THE TEXT

14/09/2011

Module 3
Patient Information Leaflet

Astron Research Ltd.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Aceclofenac 100 mg film-coated Tablets

Aceclofenac

Read all of this leaflet carefully before you start taking this medicine
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Aceclofenac Tablets are and what they are used for

Aceclofenac Tablets belongs to a group of medicines called non-steroidal anti-inflammatory drugs or NSAIDs.

Aceclofenac Tablets is used to relieve pain and inflammation in patients suffering from:
- arthritis of the joints (osteoarthritis). This commonly occurs in patients over the age of 50 and causes the loss of the cartilage and bone tissue next to the joint.
- autoimmune disease that causes chronic inflammation of the joints (rheumatoid arthritis).
- arthritis of the spine which can lead to the fusion of the vertebrae (ankylosing spondylitis).

2. Before you take Aceclofenac Tablets

Do not take Aceclofenac Tablets if;

- If you are allergic to aceclofenac or any of the other ingredients of Aceclofenac Tablets
- If you are pregnant (unless considered essential by your doctor).
- If aspirin or other NSAIDs have caused asthma, rhinitis (running nose) or urticaria (skin rash) or other allergic reaction.
- If you have a peptic ulcer (ulcer in your stomach or duodenum) or bleeding in your stomach, or have had two or more episodes of peptic ulcers, stomach bleeding or perforation.
- If you have severe kidney disease
- If you have severe heart disease
- If you have severe liver disease

Take special care with Aceclofenac Tablets

Tell your doctor before taking Aceclofenac tablets if:
- You have ever experienced stomach discomfort or pain, vomiting of blood or heartburn after taking aspirin or other nonsteroidal anti-inflammatory drugs.
- You suffer from any other form of kidney or liver disease.
- You suffer from asthma or any other breathing problems.
- You have suffered from any blood- clotting problem (if you bleed easily).
- You have recently undergone major surgery.
- You are breast-feeding.
- You are suffering from Crohn's disease (chronic inflammatory bowel disease) or ulcerative colitis (inflammatory bowel disease).
- You suffer from a blood disorder known as porphyria.
- You have heart problems, previous stroke or think that you might be at risk of these conditions (for example if you have high blood pressure, diabetes or high cholesterol or are a smoker) you should discuss your treatment with your doctor or pharmacist.

Medicines such as Aceclofenac Tablets may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke.
Any risk is more likely with high doses and prolonged treatment.
Do not exceed the recommended dose or duration of treatment.
Aceclofenac Tablets may make it more difficult to become pregnant. You should inform your doctor if you are planning to become pregnant or if you have problems becoming pregnant.

Taking other medicines:
Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicines, including medicines obtained without a prescription.
- Anticoagulants (drugs that alter the rate of blood clotting) like warfarin.
- Diuretics (drugs used to increase the rate of urine excretion) such as furosemide, hydrochlorothiazide or triamterene.
- Antidiabetic drugs (medicines used to lower blood sugar levels).
- Methotrexate (used to treat cancer, arthritis)
- Steroids.
- Ciclosporin and Tacrolimus (drugs used to suppress the immune system)
- Anti infectives (Such as quinoline antibiotics)
- Zidovudine (drug used to treat HIV)
- Other non-steroidal anti-inflammatory agents (NSAIDs) like aspirin, ibuprofen
- SSRIs and lithium (used to treat depression or manic depression)
- Medicines used to treat high blood pressure (antihypertensives)
- Cardiac glycosides like digoxin (used to treat heart failure and irregular heart beats)

You should not take Aceclofenac Tablets for 8-12 days after taking mifepristone (drug used to terminate pregnancy).

Taking Aceclofenac Tablets with food and drink:
Aceclofenac Tablets should be taken preferably with or after food.

Pregnancy and breast-feeding:
Do not take Aceclofenac Tablets if you plan to become pregnant, are pregnant or breast-feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines:
As a precaution, you should refrain from driving or operating machinery if you feel dizzy or sleepy when you take Aceclofenac Tablets. Do not perform any of these actions until the effects wear off.

3. How to take Aceclofenac Tablets

Always take Aceclofenac Tablets exactly as your doctor has told you. You will be prescribed the lowest effective dose over the shortest duration to reduce side effects. You should check with your doctor or pharmacist if you are not sure.

Adults:
The recommended dose in adults is 200 mg a day. One 100mg tablet should be taken in the morning and one in the evening (1 tablet every 12 hours).

Children:
Aceclofenac Tablets is not recommended for use in children under the age of 18.

Elderly
If you are elderly, you are more likely to experience serious side effects (listed in section 4 'Possible Side Effects). If your doctor prescribes Aceclofenac Tablets for you, you will be given the lowest effective dose over the shortest duration.

Method and route of administration:
Swallow the tablet whole with a glass of water. Do not crush or chew the tablets. Never change the dose of your medicine without talking to your doctor first. Continue to take your tablets for as long as your doctor recommends.

If you take more Aceclofenac Tablets than you should:
If you take more Aceclofenac tablets than you have been told to take, or if someone else accidentally takes your medicine, immediately see a doctor or go to a hospital straight away.

If you forget to take Aceclofenac Tablets:
If you forget to take your medicine at any time, take it as soon as you remember; then continue to take it at the usual times. Do not take a double dose to make up for a forgotten dose.

If you stop taking Aceclofenac Tablets:
Do not stop taking your tablets even if you are feeling well, unless your doctor tells you.
If you have any further question on the use of the product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Aceclofenac tablets can cause side effects, although not everybody gets them.

If you experience any of the following side effects, tell your doctor IMMEDIATELY:

- medicines such as Aceclofenac tablets may be associated with a small increased risk of heart attack, ("myocardial infarction") or stroke
- severe allergic reaction (anaphylactic shock). Symptoms may include difficulty breathing, wheezing, abnormal pain and vomiting
- swelling of the face
- kidney failure

If you suffer from any of the following at any time during your treatment STOP TAKING the medicine and seek immediate medical help:

- Pass blood in your faeces (stools/motions)
- Pass black tarry stools
- Vomit any blood or dark particles that look like coffee grounds.

STOP TAKING the medicine and tell your doctor if you experience:
- Indigestion or heartburn
- Abdominal pain (pains in your stomach) or other abnormal stomach symptoms.

If any of the below side effects get serious, or if you notice any other side effects not listed in this leaflet, please tell your doctor or pharmacist.
Common (occur in more than 1 in 100 patients but in less than 1 in 10 patients):
- dizziness
- nausea (feeling sick)
- diarrhoea
- increased liver enzymes in the blood

Uncommon (occur in more than 1 in 1,000 patients but in less than 1 in 100 patients):
- wind (flatulence)
- inflammation or irritation of the lining of the stomach (gastritis)
- constipation
- vomiting
- mouth ulcers
- itching
- rash
- inflammation of the skin (dermatitis)
- raised circular red itchy, stinging or burning patches on the skin (hives)
- increase in blood urea levels
- increase in blood creatinine levels

Rare (occur in more than 1 in 10,000 patients but in less than 1 in 1,000 patients):
- low levels of iron in the blood
- hypersensitivity (allergic reaction)
- visual disturbance
- shortness of breath

Very Rare (occur in less than 1 in 10,000 patients):
- low white blood cells levels
- low platelets levels in the blood
- abnormal breakdown of red blood cells (anemia)
- high potassium levels in the blood
- depression
- strange dreams
- inability to sleep
- tingling, pricking or numbness of skin
- uncontrollable shaking (tremor)
- drowsiness
- headaches
- abnormal taste in the mouth
- sensation of spinning when standing still
- heart pounding or racing (palpitations)
- hot flushes
- difficulty breathing
- high pitched noise when breathing
- inflammation of the mouth
- stomach ulcer
- inflammation of the pancreas (pancreatitis)
- inflammation of the liver (hepatitis)
- yellowing of the skin (jaundice)
- spontaneous bleeding into the skin (appears as a rash)
- blisters
- water retention and swelling
- tiredness
- leg cramps
- increased blood alkaline phosphatase levels
- weight gain

If any of the below side effects get serious, please tell your doctor or pharmacist.

Other side effects that have been reported with this type of drug (NSAIDs) are:
- bone marrow failure
- hallucinations
- confusion
- blurred, partial or complete loss of vision
- painful movement of the eye
- ringing in the ears
- aggravated asthma
- ulcers
- perforation of either the stomach, large intestine or bowel wall
- blistering and peeling of the top layer of skin
- mild, itchy pink/redness of the skin
- reddening or scaling of skin
- skin irritation (eczema)
- skin reaction to sunlight
- inflammation of the kidneys
- generally feeling unwell
- aseptic meningitis
- exacerbation of colitis and Crohn's disease
- hypertension (high blood pressure)
- cardiac failure
- bone marrow depression

5. How to store Aceclofenac Tablets

- Keep out of the reach and sight of children.
- Store below 25°C.
- Do not use the medicine after the expiry date, which is stated on the carton after (EXP). The expiry date refers to the last day of that month.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What Aceclofenac Tablets contain:
The active substance is aceclofenac. Each tablet contains 100 mg of Aceclofenac.
The other ingredients are:
Core tablet: cellulose microcrystalline, croscarmellose sodium, povidone K-30, glyceryl palmitostearate.
Film-coating: Hypromellose 15 cps, macrogol 400 and titanium dioxide (E171).

What Aceclofenac Tablets looks like and content of the pack:
Aceclofenac Tablets are white to off-white, round shaped, biconvex, film-coated tablet debossed with "100" on one side and plain on the other side.

Aceclofenac Tablets are available in boxes of 10, 20, 30, 40, 60 and 100 tablets.

Not all pack sizes may be marketed.

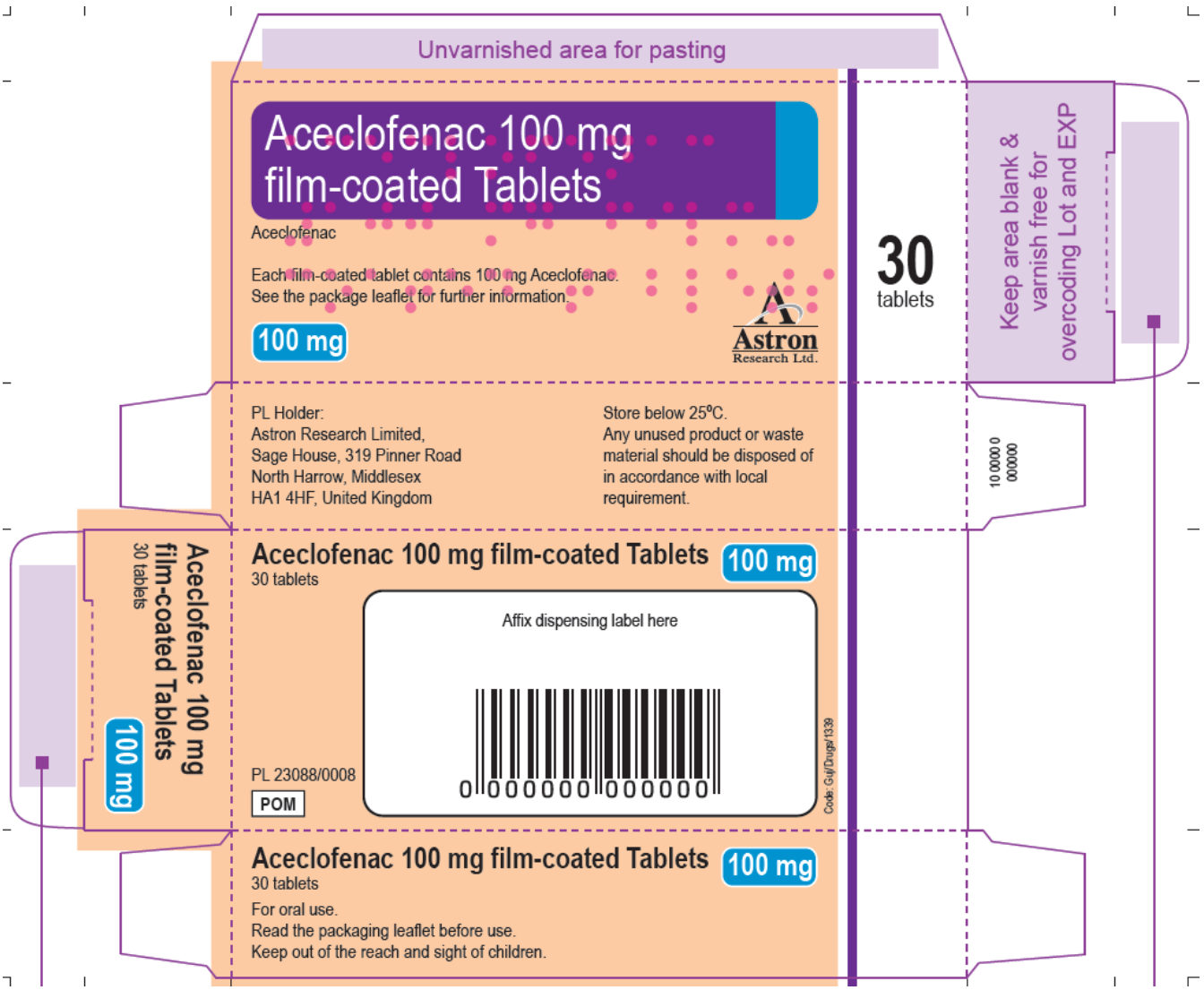
Who has made your medicine?

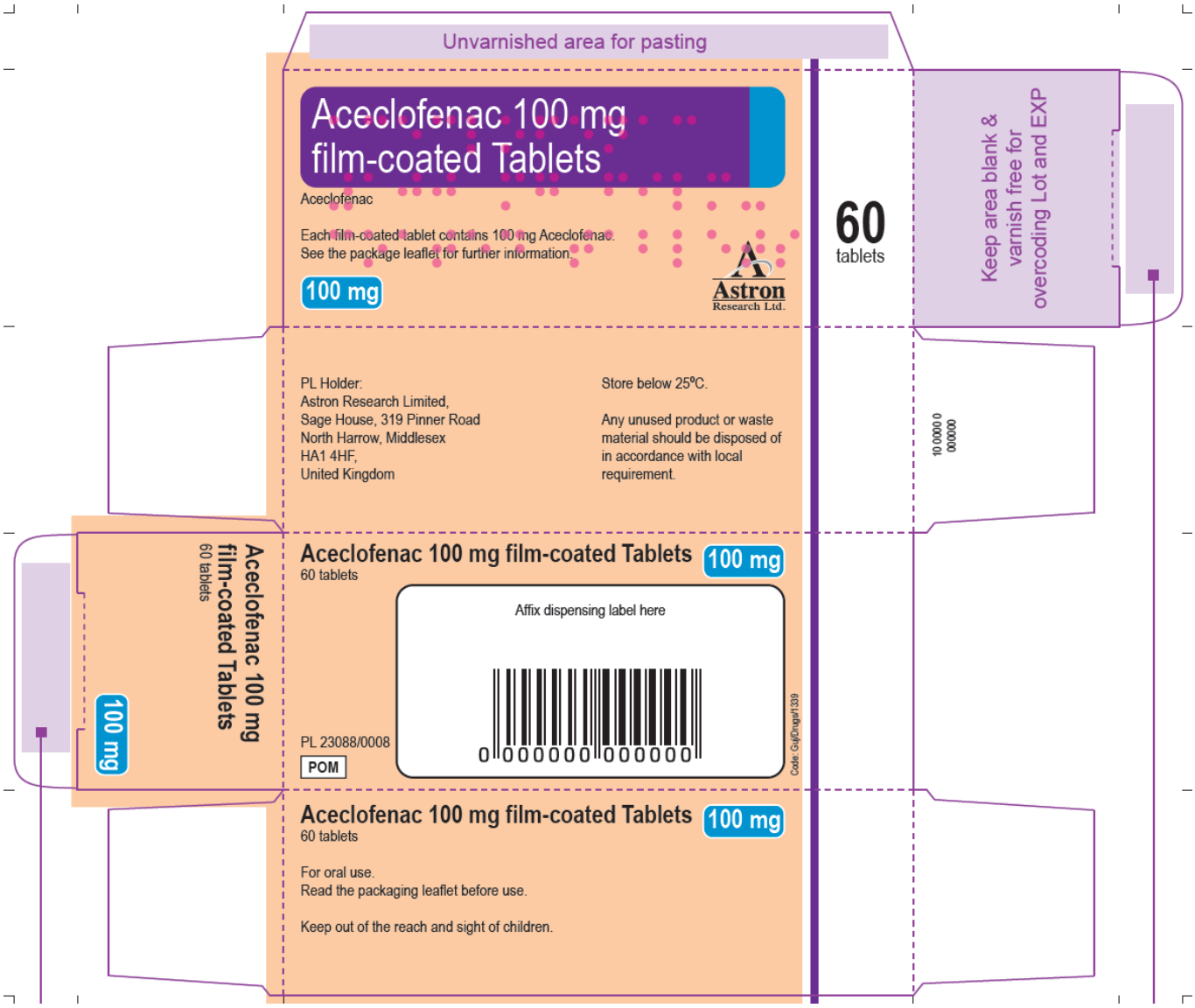
Marketing Authorisation Holder:
Astron Research Limited,
Sage house, 319 Pinner road, North Harrow HA1 4HF, Middlesex, United Kingdom

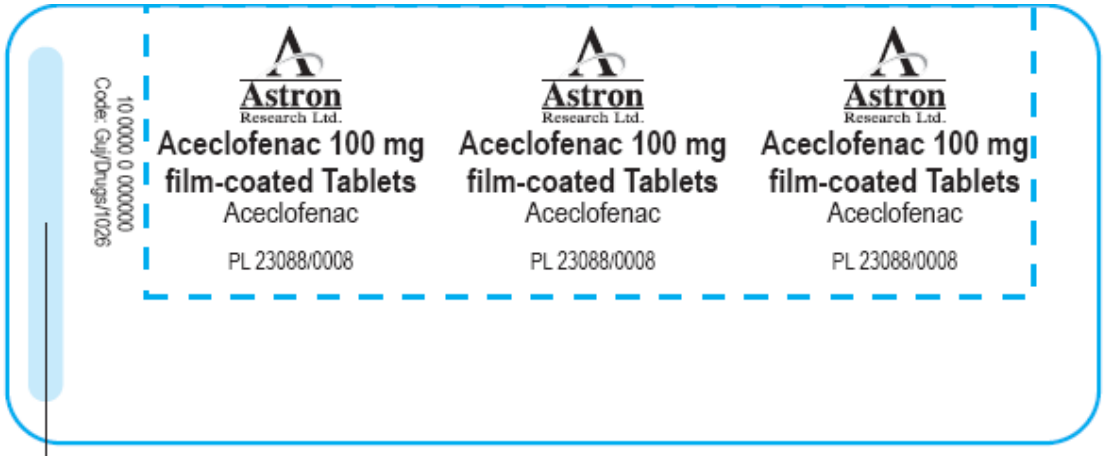
Manufacturer:
Accord Healthcare Limited,
Sage house, 319 Pinner road, North Harrow HA1 4HF, Middlesex, United Kingdom

The leaflet was last approved in 08/2011.

Module 4
Labelling


Unvarnished area for pasting
Aceclofenac 100 mg film-coated Tablets
Aceclofenac
Each film-coated tablet contains 100 mg Aceclofenac.
See the package leaflet for further information.
100 mg
Astron Research Ltd.
30 tablets
Keep area blank & varnish free for overcoding Lot and EXP
PL Holder:
Astron Research Limited,
Sage House, 319 Pinner Road
North Harrow, Middlesex
HA1 4HF, United Kingdom
Store below 25°C.
Any unused product or waste material should be disposed of in accordance with local requirement.
Aceclofenac 100 mg film-coated Tablets
30 tablets
100 mg
Affix dispensing label here
PL 23088/0008
POM
Code: Guy/Drugs/1039
Aceclofenac 100 mg film-coated Tablets
30 tablets
100 mg
Aceclofenac 100 mg film-coated Tablets
30 tablets
100 mg
For oral use.
Read the packaging leaflet before use.
Keep out of the reach and sight of children.


Unvarnished area for pasting
Aceclofenac 100 mg film-coated Tablets
Aceclofenac
Each film-coated tablet contains 100 mg Aceclofenac.
See the package leaflet for further information.
100 mg
Astron Research Ltd.
60 tablets
Keep area blank & varnish free for overcoding Lot and EXP
PL Holder:
Astron Research Limited,
Sage House, 319 Pinner Road
North Harrow, Middlesex
HA1 4HF,
United Kingdom
Store below 25°C.
Any unused product or waste material should be disposed of in accordance with local requirement.
Aceclofenac 100 mg film-coated Tablets
60 tablets
100 mg
Affix dispensing label here
PL 23088/0008
POM
Code: Guj/Drugs/1026
Aceclofenac 100 mg film-coated Tablets
60 tablets
100 mg
Aceclofenac 100 mg film-coated Tablets
60 tablets
100 mg
For oral use.
Read the packaging leaflet before use.
Keep out of the reach and sight of children.


Astron Research Ltd.
Aceclofenac 100 mg film-coated Tablets
Aceclofenac
PL 23088/0008
Astron Research Ltd.
Aceclofenac 100 mg film-coated Tablets
Aceclofenac
PL 23088/0008
Astron Research Ltd.
Aceclofenac 100 mg film-coated Tablets
Aceclofenac
PL 23088/0008
Code: Guj/Drugs/1026

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Belgium, Greece, Italy, Latvia, Portugal, the Slovak Republic and the UK considered that the application for Aceclofenac 100 mg film-coated Tablets could be approved. This prescription only medicine (POM) is indicated for the the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

This application for Aceclofenac 100 mg film-coated Tablets was submitted according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product of Airtal 100 mg Tablets, first authorised in Spain in 1997 to Almirall Prodesfarma S.A.

The UK reference product is Preservex Tablets 100 mg first authorised to Prodesfarma S.A. on 24th April 1995. This licence then underwent a change of ownership to Almirall S.A. on 22nd May 2000 (PL 16973/0001).

Aceclofenac, a phenylacetic acid derivative, is a non-selective NSAID. It inhibits cyclo-oxygenase, which is involved in the production of prostaglandins.

No new non-clinical studies were conducted, which is acceptable given that the product contains a widely-used, well-known active substance. No clinical studies, with the exception of the bioequivalence study, have been performed and none are required for this application as the pharmacology of aceclofenac is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A satisfactory justification has been provided for the absence of a Risk Management Plan.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Aceclofenac 100 mg film-coated Tablets
Name(s) of the active substance(s) (INN)	Aceclofenac
Pharmacotherapeutic classification (ATC code)	Acetic acid derivatives and related substances (M01A B16)
Pharmaceutical form and strength(s)	100 mg film-coated Tablets
Reference numbers for the Decentralised Procedure	UK/H/3717/001/DC
Reference Member State	United Kingdom
Member States concerned	Belgium (BE), Greece (EL), Italy (IT), Latvia (LV), Portugal (PT) and the Slovak Republic (SK)
Marketing Authorisation Number(s)	PL 23088/0008
Name and address of the authorisation holder	Astron Research Limited Sage house, 319 Pinner Road, North Harrow HA1 4HF, Middlesex United Kingdom

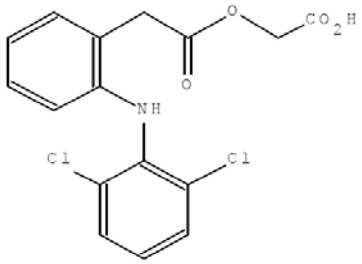
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN name: Aceclofenac
Chemical name: 2-[2-[2-(2, 6-dichlorophenyl) aminophenyl] acetyl] oxyacetic acid

Structural formula:



Molecular formula: $C_{16}H_{13}Cl_2NO_4$

Appearance: A white to almost white crystalline powder.

Molecular weight: 354.2
Solubility: Freely soluble in acetone and soluble in ethanol (96%). Practically insoluble in water.

Aceclofenac complies with its European Pharmacopoeia monograph.

All aspects of the manufacture of the active substance from its starting materials are controlled by a Certificate of Suitability.

All potential known impurities have been identified and characterised.

An appropriate specification with suitable test methods and limits is provided for the active substance. The methods of testing and limits for residual solvents are in compliance with current guidelines. Suitable Certificates of Analysis have been provided for all reference and impurity standards used. Batch analysis data are provided and comply with the proposed specification.

The proposed retest period is in-line with the Certificate of Suitability and is satisfactory.

P. Medicinal Product

Other Ingredients

Other ingredients in the tablet core consist of the pharmaceutical excipients microcrystalline cellulose, croscarmellose sodium, povidone K-30, glyceryl palmitostearate.
Ingredients in the tablets film-coating are hypromellose 15 cps, macrogol 400 and titanium dioxide (E171).

With the exception of glyceryl palmitostearate, all excipients comply with their respective European Pharmacopoeia monographs.

Glyceryl palmitostearate complies with suitable in-house specifications.

None of the excipients used contain material of animal or human origin. The suppliers of the excipients have provided declarations that neither the excipients nor any material used in the production of the excipients pose a TSE risk. The supplier of glyceryl palmitostearate has confirmed that it is of vegetable origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development
The objective of the development programme was to produce a safe, efficacious product containing aceclofenac that could be considered a generic medicinal product of Preservex Tablets 100 mg.

The applicant has provided suitable product development information. Justifications for the use and amounts of each excipient have been provided and are valid.

Comparative *in vitro* impurity and dissolution profiles have been provided for the proposed and reference product.

The reference product used in the bioequivalence study is Airtal 100 mg Tablets, licensed in Spain. This is considered to be pharmaceutically equivalent to the UK reference product.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Satisfactory process validation data on pilot-scale batches have been provided. The applicant has committed to perform process validation on future commercial-scale batches.

Finished Product Specification
The finished product specification is acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
This product is packaged in blister packs made of aluminium. The aluminium blister foil is soft temper, plain with one side bright and one side dull. The dull side is lacquer laminated to 25 µm orientated polyamide (OPA), the bright side lacquer laminated to 60 µm polyvinyl chloride (PVC). The aluminium foil is 0.025 mm thick aluminium alloy hard temper foil with mat finish.
The blisters are further packed into cartons in pack sizes of 10, 20, 30, 40, 60 and 100 film-coated tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 4 years with storage instructions ‘Store below 25°C’, which is satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labelling are pharmaceutically acceptable. A representative sample of the UK PIL and label mock-ups are included in modules 3 and 4 of this report.

User testing results have been submitted for the PIL for this product. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA form
The MAA form is pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application from a quality point of view.

III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of aceclofenac are well-known. As aceclofenac is a widely used, well-known active substance, the applicant has not provided any new non-clinical data and none are required. An overview based on literature review is, thus, appropriate.

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A satisfactory justification has been provided for the absence of an Environmental Risk Assessment.

It is recommended that a Marketing Authorisation is granted for this application from a non-clinical point of view.

III.3 CLINICAL ASPECTS
CLINICAL PHARMACOLOGY

With the exception of the following bioequivalence study, no new pharmacokinetic or pharmacodynamic data were submitted with this application and none were required.

Pharmacokinetics

An open-label, randomised, two-period, two-treatment, two-sequence crossover study to compare the pharmacokinetics of the test product Aceclofenac 100 mg film-coated Tablets versus the reference product Airtal (aceclofenac) 100 mg Tablets (Almirall Prodesfarma S.A.) in healthy subjects under fasted conditions.

Blood samples were taken pre- and up to 24 hours post dose. There was a washout period of at least 3 days (not exceeding 15 days) between each treatment period. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for aceclofenac are presented below as non-transformed values:

Treatment	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/ml)
Test (T)	27.238 ± 7.1904	28.512 ± 7.5395	12.755 ± 3.1214
Reference (R)	27.198 ± 6.6992	28.386 ± 7.0203	11.785 ± 2.4875
T/R Ratio (90% CI)*	100.0 97.72 – 102.28	100.3 98.08 – 102.47	107.2 98.50 – 116.61

*log transformed values

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for aceclofenac lie within acceptable limits. Thus, bioequivalence has been shown between the test and reference products in this study.

EFFICACY
No new efficacy data were submitted with this application and none were required.

SAFETY
With the exception of the data submitted during the bioequivalence study, no new safety data were submitted with this application and none were required. No new or unexpected safety concerns were raised during the bioequivalence study.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPC, PIL and labelling are clinically satisfactory and consistent with those for the reference product, where appropriate.

CLINICAL EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA FORM
The MAA form is clinically satisfactory.

CONCLUSIONS
It is recommended that a Marketing Authorisation is granted for this application from a clinical point of view.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Aceclofenac 100 mg film-coated Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Aceclofenac 100 mg film-coated Tablets and the reference product Airtal 100 mg Tablets.

No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory and consistent with that for the reference product.

BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with aceclofenac is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome