

ACECLOFENAC 100 MG FILM-COATED TABLETS

PL 16924 / 0041

UKPAR

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ACECLOFENAC 100 MG FILM-COATED TABLETS

PL 16924/0041

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Qualiti (Burnley) Limited a Marketing Authorisation (licence) for the medicinal product Aceclofenac 100 mg Film-Coated Tablets (Product Licence number: 16924/0041). This product is only available on prescription.

Aceclofenac belongs to a group of medicines called the non-steroidal anti-inflammatory drugs (NSAIDs). It works by preventing the production of prostaglandins, chemicals that are produced in response to injury or certain diseases, that can lead to pain, swelling and inflammation.

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 a Marketing Authorisation has been granted.

ACECLOFENAC 100 MG FILM-COATED TABLETS

PL 16924/0041

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Aceclofenac 100 mg Film-Coated Tablets (PL 16924/0041) to Qualiti (Burnley) Limited on 3 January 2007. This product is a Prescription Only Medicine (POM).

The application was submitted as an abridged application according to Article 10.1 of EC Directive 2001/83. The cross reference product is Preservex 100mg tablets (PL 16973/0001), granted to Almirall Prodesfarma on 22 May 2000. This licence was a change of ownership from PL 08448/0001, granted 24 April 1995 to Prodesfarma. As the cross-reference product was granted prior to the introduction of current legislation, no Public Assessment Report (PAR) was generated for it.

PHARMACEUTICAL ASSESSMENT REPORT

1. INTRODUCTION

This is an abridged application for Marketing Authorisation in the UK submitted under Article 10.1 of Directive 2001/83 (as amended), first paragraph, a so called generic application.

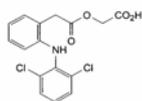
The original product is listed as Aceclofenac 100 mg tablets, licensed to Almirall Prodesfarma in Portugal on the 19 March 1990.

The reference medicinal product marketed in the UK is listed as Preservex 100 mg tablets, with the marketing authorisation held by Almirall Prodesfarma (PL 16973/0001), granted 22 May 2000. This licence was a change of ownership from PL 08448/0001, granted 24 April 1995 to Prodesfarma. The medicinal product used in the bioequivalence studies was AirTal 100 mg tablets, sourced from Spain.

2. ACTIVE SUBSTANCE

2.1 General information

The active substance has a certificate of suitability granted March 2005. The current version has been provided, which has an acceptable declaration of access.



Structure:

Description: White to almost white crystalline powder

Chemical name: [[[2-[(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]acetic acid

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

Relative molecular mass: 354.2

2.2 Manufacture

2.2.1 Manufacturer

The manufacturer of the active substance is suitably qualified.

2.3 Control of active substance

2.3.1 Specification

The specification from the active substance manufacturer and the finished product manufacturer for the active substance has been provided. It is in compliance with the European Pharmacopoeia monograph and the certificate of suitability.

Upon receipt of the active substance, the finished product manufacturer will confirm that it complies to the requirements of the European Pharmacopoeia.

2.3.2 Analytical test methods

Relevant details of the test methods used by the finished product manufacturer have been supplied and are considered acceptable.

2.3.3 Analytical test method validation

No validation has been performed for the analytical methods that are described in the pharmacopoeia, this is acceptable. The non-pharmacopoeial methods are suitably validated.

2.3.4 Batch analyses

Certificates of analysis have been provided from the active substance manufacturer and finished product manufacturer for batches of the active substance, demonstrating comparable results between batches and between the two test sites. All parameters are well within specification, with very low levels of impurities.

2.3.5 Reference standards

Details of the reference standards used are provided.

2.3.6 Container closure system

The active substance is packed in a suitable container. Relevant specifications for the container have been provided, along with certification of compliance with the food contact requirements described in Directive 2002/72/EC.

3. DRUG PRODUCT

3.1 Composition

The composition of the product is summarised as follows. The product is a white or off white, round and slightly convex film coated tablet, packed in Opa-Aluminium-PVC/Aluminium blister packs.

Name of ingredient		Function	Reference Standards
Aceclofenac		Active	Ph. Eur.
Microcrystalline cellulose		Diluent	Ph. Eur.
Povidone		Binder	Ph. Eur.
Stearic acid		Lubricant	Ph. Eur.
Croscarmellose sodium		Disintegrant	Ph. Eur.

Magnesium stearate		Lubricant	Ph. Eur.
Opadry white YS-1R-7003		Coating agent	In-house
Ingredients of Opadry white YS-1R-7003			
Titanium dioxide		Opacifier	Ph. Eur.
Hypromellose 3cp		Film-forming agent	Ph. Eur.
Hypromellose 5cp		Film-forming agent	Ph. Eur.
Macrogol 4000		Plasticiser	Ph. Eur.
Polysorbate 80		Suspending agent	Ph. Eur.

3.2 Pharmaceutical Development

The development pharmaceuticals are well presented and the issues addressed included the rationale for the formulation and its subsequent evolution. Details of the manufacturing development are provided as well as the reason for the selection of the container closure system.

3.3 Manufacture

3.3.1 Manufacturer(s)

A manufacturer's licence dated January 2004 and a GMP certificate dated May 2003 have been provided.

3.3.2 Batch formula

The batch formula has been presented for a batch that is the proposed maximum size.

3.3.3 Manufacturing process and process controls

A flow diagram detailing the manufacturing process and in-process control testing has been provided. A written summary of the process has been included.

3.3.4 Control of critical steps (in-process controls)

Appropriate in-process controls are applied.

3.3.5 Process validation or evaluation

Validation has been completed on three batches, two produced at 20% of the planned industrial scale and one batch at 100% of the intended industrial scale. Full details of how the manufacturing process is monitored have been provided and, on the basis of this information, the process is considered controlled and validated. Following approval, the first two industrial scale batches will be validated to the current protocol to supplement the validation, this is considered acceptable.

Relevant details of the sampling plan have been provided for the validation process.

3.4 Control of excipients

3.4.1 Specification

Microcrystalline cellulose, povidone, stearic acid, croscarmellose sodium and magnesium stearate have monographs in the European Pharmacopoeia. Acceptable certificates of analysis have been provided for each of the pharmacopoeia excipients from the finished product manufacturer and excipient manufacturers.

All excipients are tested on conformance to description and identification with an accompanying supplier's certificate of analysis. The analytical methods used to test the excipients are those described in the European Pharmacopoeia. No validation data has been supplied for the pharmacopoeial methods, which is acceptable.

Relevant certification has been supplied from the excipient manufacturers regarding compliance to TSE/BSE requirements.

The in-house specification for Opadry I YS-1R-7003 has been provided from the finished product manufacturer and the excipient manufacturer, with accompanying certificates of analysis. Relevant certification has been provided on compliance to the TSE/BSE requirements.

3.5 Control of drug product

3.5.1 Specification

The finished product specification for release and shelf-life has been provided and is satisfactory.

3.5.2 Analytical procedures

All the details have been provided for the pharmacopoeia and non-pharmacopoeia methods.

3.5.3 Validation

The process was appropriately validated. The data generated were generally consistent and complied with the proposed control specification. The process appears to be under control and provides a reproducible bulk product equivalent to the clinical study batch.

3.5.4 Batch analyses

Batch analyses have been provided for the three validation batches. Two batches are pilot scale and the other is commercial scale. All batches are comparable and within specification. The results for the related substances are very low. Relevant certificates of analysis have been provided.

3.5.5 Characterisation of impurities

Reference has been made to the active substance section on impurities, which references the certificate of suitability.

The applicant has confirmed, from both release and stability data, that no new impurities arise from the finished product that have not already been characterised in the active substance.

3.5.6 Reference standards

Suitable reference standards are used.

3.6 Container closure system

The blister pack consists of OPA-AL-PVC and aluminium.

Relevant specifications, methods and certificates of analysis have been supplied from the finished product manufacturer.

The necessary certification, confirming compliance to the EU requirements on food contact materials as detailed in 2002/72/EC, is provided.

3.7 Stability

Stability data has been presented for the three validation batches. Two batches are pilot scale and the other is commercial scale. The batches have been packed in the proposed commercial packaging.

The batches have been assessed using suitable methods.

All batches have reached 18 months at 25°C/60%RH, 12 months at 30°C/65%RH and 6 months at 40°C/75%RH.

There is no significant change in assay in any batch under any condition, though there is some evidence of variability. Impurity levels remained satisfactory. There is no evidence of change in disintegration or dissolution. Hardness increases slightly at 40°C/75%RH but, with no change in the disintegration or dissolution, this is not considered to be of relevance. The water content is variable but shows no trends.

The post approval stability commitment covers the continuation of the long term stability study of the current batches according to the stability protocol presented up to 48 months and the first two commercial production batches which will be placed on long term, intermediate and accelerated stability to the current protocol. The applicant also commits to placing one batch per year on long-term stability.

A shelf-life of 3 years has been proposed with the condition for storage: “Do not store above 30°C. Store in original package.” This is acceptable.

3.8 Other information

3.8.1 Bioanalytical method

Aceclofenac is extracted from an aliquot of human EDTA K3 plasma, then injected into a LC system with UV detection.

The method has been validated. Linearity has been demonstrated. Dilution integrity was maintained when diluted two and twenty times in human EDTA K3 plasma prior to sample processing and analysis. The method is accurate and precise. Specificity has been shown on the basis of no significant interferences observed in 6 out of 6 matrices. A suitable lower limit of quantitation has been set. Relevant stability of the solutions has been demonstrated. The method has an adequate system suitability check which uses calibration and quality control samples.

3.8.2 Clinical work

A single dose, open-label, randomised, crossover study was conducted in healthy volunteers under fasted conditions. AirTal 100 mg tablets sourced from Spain have been used as the medicinal reference product.

The batch of Aceclofenac 100 mg tablets used in the clinical study is the proposed commercial formulation and represents the maximum commercial batch size.

The study enrolled and analysed 24 subjects.

Samples were taken at baseline and 20 mins, 40 mins, 1 hour, 1 h 20 mins, 1 h 40 mins, 2 h, 2 h 30 mins, 3 h, 4 h, 6 h, 8 h, 12 h and 24 h post dosing. The washout period was 7 days.

The concentrations ranged from 0 to 18253 ng/ml.

Bioequivalence was determined using the 90% confidence interval of the relative mean C_{max}, AUC_{0-t} and AUC_∞ of the test to reference formulation, and have been shown to be between 80% to 125%.

The 90% confidence intervals of the ln-transformed parameters

	Ratio T/R	90% CI
C _{max}	1.00	90.23% - 111.55%
AUC _{0-t}	0.99	95.32% - 102.55%
AUC _∞	0.99	95.43% - 102.73%

Mean T_{max} (h) Test 1.00 (0.33-2.5) Reference 1.33 (0.66-3.00)

For further information see medical assessment report.

3.8.3 Essential similarity

The data provided by the applicant confirm the essential similarity of this generic product to the reference product.

4. PRODUCT LITERATURE

4.1 SPC

The Summary of Product Characteristics (SPC) for this product is satisfactory.

4.2 PIL

The Patient Information Leaflet (PIL) for this product is satisfactory.

4.3 LABEL

All labelling for this product is satisfactory.

5. ADMINISTRATIVE

5.1 MAA form

The Marketing Authorisation Application (MAA) form for this product is satisfactory.

5.2 Quality Overall Summary

The summary has been done by a suitably qualified expert. The report is a summary of the module.

6. CONCLUSIONS AND ADVICE

A marketing authorisation can be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION

This is an abridged application for Marketing Authorisation in the UK submitted under Article 10.1 of Directive 2001/83 (as amended), first paragraph, a so called generic application.

2. BACKGROUND

The original product is listed as Aceclofenac 100 mg tablets, licensed to Almirall Prodesfarma in Portugal on 19 March 1990. The reference medicinal product marketed in the UK is listed as Preservex 100 mg tablets, with the marketing authorisation held by Almirall Prodesfarma (PL 16973/0001), granted 22 May 2000. This licence was a change of ownership from PL 08448/0001, granted 24 April 1995 to Prodesfarma. The medicinal products used in the bioequivalence studies were AirTal 100 mg tablets sourced from Spain.

3. INDICATIONS

The applicant has submitted the following:

“Aceclofenac is indicated for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.”

This is consistent with that for the innovator product and is acceptable.

4. DOSE & DOSE SCHEDULE

The Applicant has submitted the following:

“Aceclofenac Tablets should be swallowed whole with liquid.

When aceclofenac was administered to fasting and fed healthy volunteers, only the rate and not the extent of the drug’s absorption was affected. For this reason, aceclofenac may be taken with or after food.

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

Children: There are no clinical data supporting the use of aceclofenac in children therefore its use is not recommended.

Elderly: There are no data to suggest that the dosage should be reduced in elderly, however 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. The elderly should be monitored for GI bleeding for 4 weeks following initiation of NSAID therapy.

Renal insufficiency: There is no evidence to suggest that the dosage needs to be altered for patients with mild renal impairment, however caution should be exercised (see 4.4 Special Warnings and Special Precautions).

Hepatic insufficiency: There is some evidence that the dose of aceclofenac should be reduced in patients with hepatic impairment. It is suggested that an initial daily dose of 100 mg is used.”

This is consistent with that of the innovator product and is acceptable.

5. TOXICOLOGY

No formal data is provided under this heading and none are required for this application. There is a preclinical overview written by an appropriately qualified expert.

6. CLINICAL PHARMACOLOGY

Bioequivalence

A single dose, open-label, randomised, crossover study was conducted in healthy volunteers under fasted conditions. AirTal 100 mg tablets sourced from Spain have been used as the medicinal reference product, this is equivalent to the UK reference product. The batch of Aceclofenac 100 mg tablets used in the clinical study is the proposed commercial formulation and represents the maximum commercial batch size.

The study enrolled and analysed 24 subjects.

Samples were taken at baseline and 20 mins, 40 mins, 1 hour, 1 h 20 mins, 1 h 40 mins, 2 h, 2 h 30 mins, 3 h, 4 h, 6 h, 8 h, 12 h and 24 h post dosing. The washout period was 7 days.

The concentrations ranged from 0 to 18253 ng/ml.

Bioequivalence was determined using the 90% confidence interval of the relative mean C_{max}, AUC_{0-t} and AUC_∞ of the test to reference formulation, and have been shown to be between 80% to 125%.

The 90% confidence intervals of the ln-transformed parameters

	Ratio T/R	90% CI
C _{max}	1.00	90.23% - 111.55%
AUC _{0-t}	0.99	95.32% - 102.55%
AUC _∞	0.99	95.43% - 102.73%

Mean T_{max} (h) Test 1.00 (0.33-2.5) Reference 1.33 (0.66-3.00).

Assessor's Comment

The study is of an adequate design. The limits of the confidence intervals for C_{max} and AUC fall within the limits 80% to 125%. Bioequivalence may be assumed.

7. EFFICACY

No new data are submitted and none are required for this type of application.

8. SAFETY

No formal safety data are presented. The adverse events that can be expected are listed in the SPC and are consistent with those for the reference product.

9. CLINICAL EXPERT REPORT

There is a clinical overview written by an appropriately qualified expert.

10. SUMMARY OF PRODUCT CHARACTERISTICS

The SPC is consistent with that of the innovator product in the UK and is satisfactory.

11. PATIENT INFORMATION LEAFLET

The patient information leaflet is satisfactory

12. LABELLING

All labelling is satisfactory

13. DISCUSSION

This is an abridged application for Marketing Authorisation in the UK submitted under Article 10.1 of Directive 2001/83 (as amended), first paragraph, a so called generic application. The Applicant has provided evidence in the form of a clinical study to demonstrate that their formulation of aceclofenac is bioequivalent to the innovator product Preservex tablets. The results of the bioequivalence study demonstrate that the two products may be considered essentially similar.

14. RECOMMENDATIONS

The efficacy and safety of the product are satisfactory for the grant of a product licence.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of the product 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.

PRECLINICAL

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

EFFICACY AND SAFETY

The efficacy of aceclofenac tablets has been well documented in the past. No new or unexpected safety concerns arise from this application.

The generic formulation, which is the subject of this application, has been shown in the comparative bioavailability study submitted to be bioequivalent to the brand leader with confidence intervals within the required range for C_{max} and AUC pharmacokinetic parameters. Therefore it is reasonable to conclude that the applicant's product will exhibit the same efficacy and safety profile.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit ratio is considered to be positive.

ACECLOFENAC 100 MG FILM-COATED TABLETS

PL 16924/0041

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 25 April 2005
2	Following assessment of the application the MHRA requested further information relating to the quality dossier on 6 September 2005
3	The applicant responded to the MHRA's requests, providing further information on 21 December 2005
4	Following assessment of the response the MHRA requested further information relating to the quality dossier on 21 December 2005
5	The applicant responded to the MHRA's request, providing further information on 9 January 2006
6	Following assessment of the application the MHRA requested further information relating to the clinical and quality dossier on 4 August 2006
7	The applicant responded to the MHRA's requests, providing further information on 29 August 2006
8	The application was determined on 3 January 2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Aceclofenac 100 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Aceclofenac.

Each tablet contains 100 mg aceclofenac.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Circular tablets, white or off-white in colour and slightly convex on both sides, marked “G” on one 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

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

For oral use. Aceclofenac Tablets should be swallowed whole with liquid.

When aceclofenac was administered to fasting and fed healthy volunteers, only the rate and not the extent of the drug’s absorption was affected. For this reason, aceclofenac may be taken with or after food.

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

Children: There are no clinical data supporting the use of aceclofenac in children therefore its use is not recommended.

Elderly: There are no data to suggest that the dosage should be reduced in elderly, however 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. The elderly should be monitored for GI bleeding for 4 weeks following initiation of NSAID therapy.

Renal insufficiency: There is no evidence to suggest that the dosage needs to be altered for patients with mild renal impairment, however caution should be exercised (see 4.4 Special Warnings and Special Precautions).

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

4.3 Contraindications

Aceclofenac must not be used in patients with a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Aceclofenac must not be used in patients with an active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

Aceclofenac must not be used in patients with moderate to severe renal impairment.

Aceclofenac must not be used in patients with severe heart failure.

Aceclofenac must not be administered to patients who are hypersensitive to aceclofenac or any of its constituents, or any other NSAIDs.

Aceclofenac must not be used in patients in whom aspirin or NSAIDs precipitate attacks of asthma, acute rhinitis or urticaria.

Aceclofenac must not be used during pregnancy.

Aceclofenac must not be used in severe heart failure.

4.4 Special warnings and precautions for use

Warnings:

The use of Aceclofenac with concomitant NSAIDs including cyclooxygenase-2-selective inhibitors should be avoided.

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).

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).

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.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID dose, 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 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 their condition may be exacerbated (See section 4.8 – undesirable effects).

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.

The use of aceclofenac 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.

Precautions:

Renal: Patients with mild renal or cardiac impairment and the elderly should be kept under surveillance, since the use of NSAIDs 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 Aceclofenac.

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 should be discontinued. Hepatitis may occur without prodromal symptoms.

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

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

Cardiovascular: Caution is required in patients with a history of hypertension and/or heart failure, as fluid retention and oedema have been reported in association with NSAID therapy.

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).

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.

Use with caution in patients suffering from or with a history of bronchial asthma since NSAIDs have been known to cause bronchospasm in such patients.

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

4.5 Interaction with other medicinal products and other forms of interaction

Lithium: Aceclofenac, like many NSAIDs, may increase plasma concentrations of lithium

Cardiac Glycosides: Through their renal effects, NSAIDs may increase plasma

glycoside (including digoxin) levels, exacerbate cardiac failure and reduce the glomerular filtration rate in patients receiving glycosides.

Diuretics: Aceclofenac, 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. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Anticoagulants: Like other NSAIDs, Aceclofenac may enhance the activity of anticoagulants such as warfarin (See section 4.4). Close monitoring of patients on combined anticoagulant and Aceclofenac therapy should be undertaken.

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, 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 plasma levels, resulting in increased toxicity.

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

Ciclosporin: Ciclosporin 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 Aceclofenac 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 foetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the new born, 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 foetuses.

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

The use of Aceclofenac 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

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

The majority of adverse reactions reported have been reversible and of a minor nature. The most frequent are gastro-intestinal disorders, in particular dyspepsia, abdominal pain, nausea and diarrhoea, and occasional occurrence of dizziness. Dermatological complaints including pruritus and rash and abnormal hepatic enzyme and serum creatinine levels have also been reported with the frequencies indicated in the following table.

If serious adverse reactions occur, Aceclofenac should be withdrawn.

The following is a table of adverse reactions reported during clinical studies and after authorisation, grouped by System-Organ Class and estimated frequencies.

System Organ Class	Common < 10 % - > 1%	Uncommon < 1% - > 0.1%	Rare < 0.1% - > 0.01%	Very rare / isolated reports < 0.01%
Blood and the lymphatic system disorders			Anaemia	Granulocytopenia Thrombocytopenia Neutropenia Haemolytic anaemia
Immune system disorders			Anaphylactic reaction (including shock) Hypersensitivity	
Metabolism and nutrition disorders				Hyperkalaemia

Psychiatric disorders				Depression Abnormal dreaming 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		Pruritus	Face oedema	Purpura

subcutaneous tissue disorders		Rash		Dermatitis bullous
		Dermatitis		
		Urticaria		
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		Blood alkaline phosphatase increased
		creatinine increased		Weight increase

Undesirable effects associated with NSAIDs in general:

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.

Vascular and cardiac disorders: 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 rare or very rare class-effects reported with NSAIDs in general are:

Blood and the lymphatic system disorders– Aplastic anaemia

Psychiatric disorders – Hallucination, Confusional state

Nervous System disorders – Optic neuritis, somnolence

Ear and labyrinth disorders - Tinnitus

Respiratory, thoracic and mediastinal disorders – Aggravated asthma

Skin and subcutaneous tissue disorders – Toxic epidermal necrolysis, Erythema multiforme, Exfoliative dermatitis, photosensitivity reaction

Renal and urinary disorders – Interstitial nephritis
General disorders and administration site conditions –Malaise

4.9 Overdose

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

There are no human data available on the consequences of aceclofenac overdosage. The therapeutic measures to be taken are: absorption should be prevented as soon as possible after overdosage 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, gastro-intestinal irritation, and respiratory depression; specific therapies such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: M01AB16

Group: Anti-inflammatory and antirheumatic products, non steroids
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

Tablet core:

Microcrystalline cellulose

Povidone

Stearic acid

Croscarmellose sodium

Magnesium stearate

Tablet coating:

Titanium dioxide (E171)

Hypromellose 3 cp (E464)

Hypromellose 5 cp (E464)

Macrogol 400

Polysorbate 80 (E433)

6.2 Incompatibilities

Not known.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in original package.

6.5 Nature and contents of container

Opa-Alu-PVC/Aluminium blister packs.

Pack sizes: 10, 20, 30 and 60 tablets. Not all pack sizes may be marketed in all territories.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Qualiti (Burnley) Limited (QBL),
Talbot Street,
Briercliffe,
Burnley,
BB10 2JY

8 MARKETING AUTHORISATION NUMBER(S)

PL 16924 / 0041

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

03/01/2007

10 DATE OF REVISION OF THE TEXT

05/04/2007

PATIENT INFORMATION LEAFLET

ACECLOFENAC 100 mg FILM-COATED TABLETS

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 personally. Do not give it to anyone else. It may harm them, even if their symptoms are the same as yours.

YOUR MEDICINE

Each Aceclofenac Film-Coated Tablet contains 100 mg of the active ingredient aceclofenac. The tablets also contain microcrystalline cellulose, povidone, stearic acid, croscarmellose sodium, magnesium stearate, titanium dioxide (E171), hypromellose 3 cp (E464), hypromellose 5 cp (E464), macrogol 400 and polysorbate (E433). Aceclofenac Film-Coated Tablets are circular and white or off-white in colour, marked "G" on one side. They come in pack types of 60 tablets.

Marketing Authorisation holder: Qualiti (Burnley) Limited (QBL), Talbot Street, Briercliffe, Burnley, BB10 2JY.
Manufacturers: Merck Farma y Química, S.A. Polígono Merck, 08100 Mollet del Vallés (Barcelona), Spain.
Gerard Laboratories, 35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland.
Distributed by: Generics [UK] Limited, Station Close, Potters Bar, Hertfordshire, EN6 1TL.

WHAT ACECLOFENAC IS AND WHAT IT IS USED FOR

Aceclofenac belongs to a group of medicines called non-steroidal anti-inflammatory drugs or NSAIDs. Aceclofenac Tablets are used to relieve pain and inflammation that occur with osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

BEFORE YOU TAKE ACECLOFENAC FILM-COATED TABLETS

Before you start to take Aceclofenac Film-Coated Tablets please read the following questions:

- do you have or have you ever had a stomach ulcer or bleeding ?
- do you suffer from problems with your kidneys ?
- do you suffer from heart failure ?
- have you ever had a reaction to any of the ingredients in Aceclofenac Tablets or to any other NSAID eg. Aspirin or Diclofenac ?
- have you ever had difficulty breathing or had a skin rash or runny nose after taking Aspirin or any other NSAIDs ?
- are you pregnant ?

If you answer **YES** to any of the above questions, do not take this medicine until you have spoken to your doctor.

Take special care when taking Aceclofenac Film-Coated Tablets if:

- you suffer from any digestive or bowel problems, particularly bleeding
- you suffer from heart disease or liver problems
- you suffer from high blood pressure
- you suffer from asthma
- you suffer from blood clotting disorders
- you have recently undergone major surgery
- you are trying to become pregnant or are breast feeding
- you are already taking any of the following medicines: * lithium (for depression) * drugs to treat heart failure (eg. Digoxin) * diuretics (water tablets) * anticoagulants (blood thinning drugs eg. Warfarin) * antidiabetic drugs (to control blood sugar) * Methotrexate (for arthritis or psoriasis) * Mifepristone (for termination of pregnancy) * other NSAIDs (eg. Aspirin, Diclofenac) or steroids * Ciclosporin (used to prevent organ or tissue rejection) * medicine to treat an infection (eg. Ciprofloxacin) * SSRIs (often used to treat depression).

If any of the above apply to you, tell your doctor or pharmacist.

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Important information - If you are already taking water tablets your doctor may want to take blood samples to measure the amount of potassium in your blood. Aceclofenac 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 in becoming pregnant.

Driving and using machines - If you feel dizzy whilst taking Aceclofenac you should not drive or operate machinery.

HOW TO TAKE ACECLOFENAC FILM-COATED TABLETS

For oral use. Swallow the tablets whole with a glass of water. Try to take the tablets at the same time every day. Always take Aceclofenac exactly as your doctor has told you to. You should check with your doctor or pharmacist if you are unsure.

Adults & Elderly - The usual dose is 200 mg per day, one tablet in the morning and one tablet in the evening. If you have problems with your liver your doctor may want you to take only one tablet a day to start.

Children - Aceclofenac should not be given to children.

If you forget to take a dose take it as soon as you remember unless it is nearly time for your next dose. Don't take two doses together to make up for the one you have missed.

If you accidentally take more than your prescribed dose, contact your doctor or nearest hospital casualty department immediately. Take any remaining tablets with you.

POSSIBLE SIDE EFFECTS

Like most medicines, Aceclofenac can sometimes cause side effects.

If any of the following happen to you, stop taking Aceclofenac and tell your doctor straight away: • Vomiting blood or passing black

stools • Itchy swollen skin, skin rash, fever, tightness of the chest and difficulty breathing • Itchy skin, yellowing of the skin or whites of the eyes. These side effects are rare but serious. You may need urgent medical attention.

Common side effects include indigestion, nausea, diarrhoea, stomach pain and dizziness. Other less common side effects include wind, constipation, being sick, mouth ulcers and itchy skin rash. Rarely you may notice black stools, difficulty sleeping or falling asleep, depression, unusual dreams, shortness of breath, tiredness, abnormal vision or swelling of the face. Very rare side effects include hallucinations or confusion, depression, pins and needles, shaking, feeling drowsy, headache, abnormal taste, unpleasant sensations of irregular and/or forceful beating of the heart, hot flushes, wheezing, inflamed mouth, bleeding from a stomach ulcer, blisters on the skin or the skin becoming red then yellow, severe skin problems, problems passing urine, swelling or cramp in the legs, weight increase, severe skin problems, ringing in the ears or light sensitivity.

If you have a blood test, make sure that you tell your doctor that you are taking Aceclofenac 100 mg Tablets the results may be affected.

If you suffer from any of the effects mentioned above or any other side effect, tell your pharmacist or doctor.

HOW TO STORE ACECLOFENAC FILM-COATED TABLETS

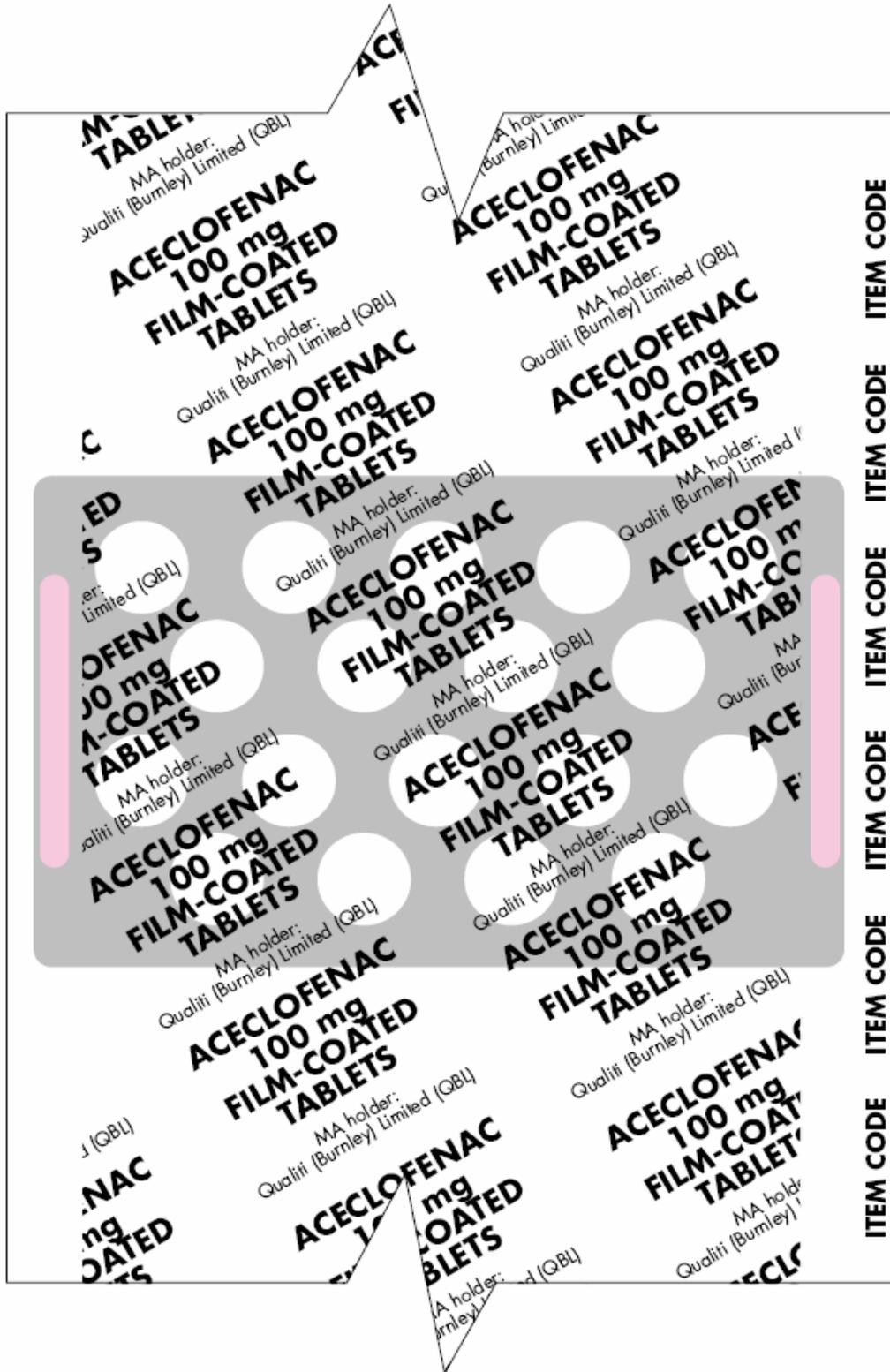
• Keep Aceclofenac out of the reach and sight of children. • Do not store above 30°C. Store in original package. • Do not take this medicine after the expiry date shown on the pack.

Date of leaflet preparation:
May 2006

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LABELLING





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