Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Aceclofenac 100mg Film-coated Tablets

(aceclofenac)

Procedure No: UK/H/5948/001/DC

UK Licence No: PL 30306/0648

Actavis Group PTC ehf.

LAY SUMMARY
Aceclofenac 100mg Film-coated Tablets
(aceclofenac)

This is a summary of the public assessment report (PAR) for Aceclofenac 100mg Film-coated Tablets (PL 30306/0648; UK/H/5948/001/DC). It explains how Aceclofenac 100mg Film-coated Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Aceclofenac 100mg Film-coated Tablets.

These products will be referred to as Aceclofenac 100mg Film-coated Tablets throughout the lay summary, for ease of reading.

For practical information about using Aceclofenac Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Aceclofenac Tablets and what are they used for?
Aceclofenac Tablets is a generic medicine. This means that Aceclofenac Tablets are similar to a 'reference medicine' already authorised in the UK called Preservex® 100 mg film-coated tablets (Almirall S.A.; PL 16973/0001).

Aceclofenac Tablets are used to relieve pain and inflammation in adult 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).

How are Aceclofenac Tablets used?
Aceclofenac Tablets are taken by mouth. The whole tablet should be swallowed, without crushing or chewing, with plenty of water and should be taken with or after food.

The recommended dose in adults is 200 mg (two Aceclofenac tablets) daily, taken as one 100 mg tablets in the morning and one in the evening.

Elderly patients will be prescribed the lowest effective dose over the shortest duration of time as they are more likely to experience serious side effects.

Aceclofenac Tablets can only be obtained on prescription from a doctor.

For further information on how Aceclofenac Tablets are used, please see the Summary of Product Characteristics and package leaflet available on the MHRA website.

How do Aceclofenac Tablets work?
The active substance in Aceclofenac Tablets, aceclofenac, belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). Aceclofenac works by blocking the production of chemicals called prostaglandins, which are released at the sites of injury, tissue damage and immune reactions.

How have Aceclofenac Tablets been studied?
Because Aceclofenac Tablets is a generic medicine, studies in patients have been limited to tests to determine that they are bioequivalent to the European Union (EU) reference product, Cartrex® 100 mg Film-coated Tablets (Almirall S.A.S, France), which is equivalent to Preservex® 100 mg film-coated tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of Aceclofenac Tablets?
As Aceclofenac Tablets is a generic medicine of the reference medicine, Cartrex® 100 mg Film-coated Tablets, their benefits and risks are taken as being the same as those for Cartrex® 100 mg Film-coated Tablets.

Why are Aceclofenac Tablets approved?
It was concluded that, in accordance with EU requirements, Aceclofenac Tablets have been shown to have comparable quality and are bioequivalent to Cartrex® 100 mg Film-coated Tablets. Therefore, the view was that, as for Cartrex® 100 mg Film-coated Tablets the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Aceclofenac Tablets?
A risk management plan has been developed to ensure that Aceclofenac Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Aceclofenac Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Aceclofenac Tablets
Hungary, Poland, Romania, Slovak Republic and the UK agreed to grant a Marketing Authorisation for Aceclofenac Tablets (PL 30306/0648; UK/H/5948/001/DC) on 17th September 2015. A Marketing Authorisation was granted in the UK on 16th October 2015.

The full PAR for Aceclofenac Tablets follows this summary. For more information about treatment with Aceclofenac Tablets, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in November 2015.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) considered that the application for Aceclofenac 100mg Film-coated Tablets (PL 30306/0648; UK/H/5948/001/DC) indicated for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis in adults, is approvable.

The application was submitted using the Decentralised Procedure (DCP) with the UK as the RMS and Hungary, Poland, Romania and Slovak Republic as CMSs. The application was submitted under Article 10.1 of Directive 2001/83/EC, as amended, and cross referred to Preservex® 100 mg Film-coated Tablets, which was first licensed to Prodesfarma SA (PL 08448/0001) on 24th April 1995. This reference licence underwent a change of ownership procedure to the current Marketing Authorisation Holder, Almirall S.A. (PL 16973/0001), on 22nd May 2000. The reference product used for the bioequivalence study was Cartrex® 100 mg Film-coated Tablets (Almirall S.A.S, France), which is considered to be in the same global Marketing Authorisation as the originator product, Preservex® 100 mg Film-coated Tablets.

The active substance, 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.

One bioequivalence study was submitted to support this application comparing the test product Aceclofenac 100mg Film-coated Tablets (Rivopharm SA., Switzerland) with the reference product Cartrex® 100 mg Film-coated Tablets (Almirall S.A.S, France) in 35 healthy adult subjects under fasting conditions. The applicant has stated that the bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical studies were conducted, which is acceptable given that the application was based on being generic medicinal product of an originator product that has been licensed for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

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 of 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.

All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 150 – 17th September 2015). After a subsequent national phase, the UK granted a Marketing Authorisation (PL 30306/0648) for this product on 16th October 2015.

II QUALITY ASPECTS

II.1 Introduction

This product is a film-coated tablet and contains 100mg of aceclofenac, as active ingredient. The excipients present are microcrystalline cellulose (E460i), croscarmellose sodium, copovidone (K28), talc (E553b), silica colloidal anhydrous, glicerol distearate (Type I) making up the core, and the film-coating is composed of Opadry O3A0280002 (HPMC 2910/hypromellose 6 mPa·s (E464), microcrystalline cellulose, titanium dioxide (E171) and polyoxyl 40 (macrogol) stearate (Type I)). Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs with the exception of Opadry O3A0280002 which complies with an in-house specification.

The finished product is packaged in aluminium/oriented polyamide (OPA)-aluminium-polyvinylchloride blisters placed into cardboard boxes containing 20, 30, 40, 50, 60, 70, 80, 90, 100 or 180 tablets. Not all pack sizes may be marketed.

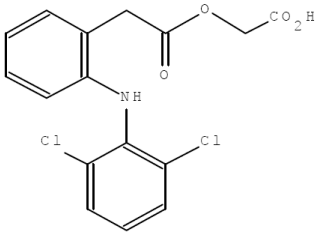
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

INN: Aceclofenac

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

Structure:



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

Molecular weight: 354.2 g/mol

Appearance: White to almost white crystalline powder.

Solubility: Aceclofenac is freely soluble in acetone and soluble in ethanol (96%) and it is practically insoluble in water.

Aceclofenac is the subject of an active substance master file (ASMF).

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been provided, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, film-coated tablets containing 100mg aceclofenac that is bioequivalent to the reference product Cartrex® 100 mg Film-coated Tablets (Almirall S.A.S, France).

Comparative dissolution and impurity profiles have been presented for the proposed and reference products.

Manufacture of the product

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. The Marketing Authorisation Holder has committed to perform process validation on future full scale production batches.

Finished Product Specification

The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the product

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results a shelf-life of 24 months with no special storage conditions is set. This is satisfactory.

Bioequivalence/bioavailability

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

This generic application has been submitted in accordance with Article 10.1 of Directive 2001/83/EC, as amended.

The pharmacodynamic, pharmacokinetic and toxicological properties of aceclofenac are well known. As aceclofenac is a widely used, well-known active substance, no new non-clinical data have been supplied and none are required for applications of this type. The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

III.2 Pharmacology

No new data have been submitted and none are required for applications of this type.

III.3 Pharmacokinetics

No new data have been submitted and none are required for applications of this type.

III.4 Toxicology
No new data have been submitted and none are required for applications of this type.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since the proposed product is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this product from a non-clinical point of view.

IV CLINICAL ASPECTS
IV.1 Introduction
This is a generic application submitted under the Decentralised Procedure according to Article 10.1 of Directive 2001/83/EC, as amended, for Aceclofenac 100mg Film-coated Tablets.

The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of aceclofenac are well known. As aceclofenac is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is considered appropriate.

With the exception of the bioavailability study, no new clinical data have been submitted and none are required for applications of this type. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
In support of this application, the Marketing Authorisation Holder has submitted the following bioequivalence study under fasting conditions.

This is a single centre, randomized, single-dose, open-label, 2-way, crossover bioequivalence study comparing the pharmacokinetics of the test product Aceclofenac 100mg Film-coated Tablets (Rivopharm SA., Switzerland) with the reference product Cartrex® 100 mg Film-coated Tablets (Almirall S.A.S, France) in 35 healthy adult subjects, under fasting conditions.

Blood samples were collected pre-dose and at 0.333, 0.667, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.0 and 12.0 hours post-dose, in each period. The washout period was 7 days.

Pharmacokinetic parameters for aceclofenac (non-transformed values; arithmetic mean ± SD, t_{max} median, range).

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	20270.28 ± 2898.04	20814.17 ± 3042.28	10700.18 ± 1879.29	1.67 (0.667 – 4.00)
Reference	20680.55 ± 3213.58	21270.94 ± 3340.44	10058.71 ± 2564.14	1.00 (0.667 – 4.00)
***Ratio (90% CI)**	98.11% **(95.77 – 100.50%)**	97.92% **(95.68 – 100.22%)**	109.28% **(98.63 – 121.08%)**	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed values*

Conclusion
The 90% confidence intervals for C_{max} and AUC were within the pre-defined acceptance criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test formulation (Aceclofenac 100mg Film-coated Tablets) and the reference formulation (Cartrex 100 mg Film-coated Tablets) under fasting conditions.

IV.3 Pharmacodynamics
No new data have been submitted and none are required for applications of this type.

IV.4 Clinical efficacy
No new data on efficacy have been submitted and none are required for applications of this type.

IV.5 Clinical safety
No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP)
The Marketing Authorisation Holder (MAH) has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Aceclofenac 100mg Film-coated Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Peptic ulceration (including bleeding and perforation)	(Proposed) text in SmPC Contraindication in section 4.3. Warning in section 4.4. Interaction with other medicinal product stated in section 4.4 and section 4.5. Listed in section 4.8. Proposed) text in PIL Warning in section 2. Listed in section 4. Other Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Exacerbation of asthma	(Proposed) text in SmPC Warning in section 4.4. (Proposed) text in PIL Precautions recommended in section 2.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Listed in section 4. Other Prescription only medicine	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Renal failure	(Proposed) text in SmPC Warning in section 4.4. Warning in section 4.5 regarding the interaction with antihypertensive medication. Foetus renal dysfunction described in section 4.6. Listed in section 4.8. (Proposed) text in PIL Listed section 4 as possible side effect. Other Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hepatotoxicity	(Proposed) text in SmPC Warning and precaution advice in section 4.4. Listed in section 4.8. (Proposed) text in PIL Warning in section 4 Other Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Anaphylactic reactions and hypersensitivity	(Proposed) text in SmPC Warning in section 4.4. Listed in section 4.8. (Proposed) text in PIL Warning in section 2. Symptoms of severe allergic reactions (anaphylactic shock) are described in section 4. Other Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Aseptic meningitis	(Proposed) text in SmPC Warning in section 4.4. Listed in section 4.8. (Proposed) text in PIL Listed in section 4. Other Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Serious skin reactions (Steven Johnson syndrome and toxic epidermal necrolysis)	(Proposed) text in SmPC Warning and precautions in section 4.4. Listed in section 4.8. (Proposed) text in PIL Recommendation and listedness in section 4. Other Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Haematological reactions (granulocytopenia, thrombocytopenia, neutropenia, haemolytic anemia)	(Proposed) text in SmPC Warning and precautions in section 4.4 Listed is section 4.8. (Proposed) text in PIL Listed in section 4. Other Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Heart failure	(Proposed) text in SmPC Warning and precautions for use in section 4.4. Drug interaction in section 4.5. Listed in section 4.8. (Proposed) text in PIL Listed as an adverse effect in section 4. Other Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Arterial thrombotic events (myocardial infarction, stroke)	(Proposed) text in SmPC Warning and description in sections 4.4 and 4.8. (Proposed) text in PIL Warning in section 2 and 4. Other Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in patients with active bleeding or bleeding diathesis	(Proposed) text in SmPC Contraindication in section 4.3. Warning in section 4.4. Use during pregnancy described in section 4.6. (Proposed) text in PIL Warning in section 2. Other Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in pregnancy	(Proposed) text in SmPC Contraindication in section 4.3 and section 4.6 for aceclofenac use during pregnancy and description of this risk. Preclinical data in section 5.3. (Proposed) text in PIL Warning listed in section 2 Other Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in children	Proposed) text in SmPC Warning in section 4.2. (Proposed) text in PIL Warning in section 2. Use not recommended in section 3. Other	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Prescription only medicine	

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended.

V User consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Aceclofenac 100 mg Film-coated Tablets (UK/H/5382 &5667/001/DC). The bridging report submitted by the applicant is acceptable.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. The data provided by the applicant showed that the test product is comparable to the reference product. Extensive clinical experience with aceclofenac is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Aceclofenac 100mg Film-coated Tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100mg aceclofenac

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

20 film-coated tablets
30 film-coated tablets
40 film-coated tablets
50 film-coated tablets
60 film-coated tablets
70 film-coated tablets
80 film-coated tablets
90 film-coated tablets
100 film-coated tablets
180 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use
Use as directed by your doctor.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA holder
Actavis Group PTC ehf.
Reykjavíkurvegi 76-78
220 Hafnarfjörður
Iceland

12. MARKETING AUTHORISATION NUMBER(S)

PL 30306/0648

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

aceclofenac 100 mg film-coated tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Aceclofenac 100mg Film-coated Tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Actavis logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)