ACECLOFENAC 100MG TABLETS

PL 04416/0591

UKPAR

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ACECLOFENAC 100MG TABLETS

PL 04416/0591

LAY SUMMARY

The MHRA granted Sandoz Limited a Marketing Authorisation (licence) on the 7th February 2006, for Aceclofenac 100mg Tablets. This Prescription Only Medicine (POM) is used for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

Aceclofenac 100mg Tablets contain the active ingredient aceclofenac which is a non-steroidal anti-inflammatory drug that reduces pain and inflammation.

The clinical data presented to the MHRA, pre-licensing demonstrated that Aceclofenac 100mg Tablets is essentially similar, or equivalent to the approved product, Preservex Tablets 100mg and, as such, can be used interchangeably.

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

ACECLOFENAC 100MG TABLETS

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for Aceclofenac 100mg Tablets to Sandoz Limited on 7th February 2006. The product is a Prescription Only Medicine (POM).

The application was submitted as an abridged application according to article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to the original product Preservex Tablets 100mg.

The product contains the active ingredient aceclofenac and is indicated for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

Aceclofenac is a widely used non-steroidal anti-inflammatory drug. It is a phenylacetic acid derivative and is similar to diclofenac although it appears to have a lower tendency to cause gastro-intestinal effects.

PHARMACEUTICAL ASSESSMENT

1. INTRODUCTION

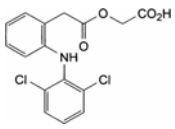
This is an abridged application for Marketing Authorisation in the UK submitted under Article 10.1(a)(iii) of Directive 2001/83 (as amended), first paragraph so called generic application.

The original product is listed as Airtal 100mg tablets licensed in May 1991 in Spain. The reference medicinal product marketed in the UK is listed as Preservex 100mg tablets, with the marketing authorisation held by Almirall Prodesfarma, PL 16973/0001 granted 22nd May 2000. This licence was a change of ownership from PL 08448/0001 granted 24th April 1995, which was held by Prodesfarma. The medicinal products used in the bioequivalence studies were Preservex 100mg tablets sourced from the UK.

2. ACTIVE SUBSTANCE

2.1. General information

The active substance has a DMF and a letter of access has been provided for use with PL 04416/0591. Aceclofenac has a European Pharmacopoeia monograph.

Structure: 

Description: White to almost white crystalline powder

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

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

Relative molecular mass: 354.2

2.2. Manufacture

Manufacturing process

A flow diagram detailing the process has been provided. A detailed description of the process has also been included.

The yields from each step have been detailed.

Control of starting materials

Specifications, sampling procedures and methods have been provided for the raw materials, solvents, reagents, catalyst and sundry chemicals. Certificates of analysis have also been provided from the active substance manufacturer and the material supplier. These materials are adequately controlled. Acceptable justifications for the specifications have been provided, with data from at least two batches to support the justification.

Adequate certification has been provided detailing that none of the materials used are derived from an animal source.

Demineralised water used in the production process is produced on site. Adequate test methods and specifications have been provided for the water. Demineralised water is assessed on appearance, acidity & alkalinity, pH, ammonium, calcium and magnesium, heavy metals, chloride, nitrate, sulphate, oxidisable substances, residue on evaporation, carbon dioxide, total viable count and total pathogens.
Chemical analysis is performed daily with micobiological analysis weekly. An analytical report for one sample has been provided with all parameters within specification, the total viable count is less than 10 cfu/ml with the absence of Escherichia coli, salmonella sp, Staphylococcus aureus and Pseudomonas aeruginosa.

Specifications, sampling procedures and methods have been provided for diclofenac sodium. Diclofenac sodium is manufactured on site and a certificate of suitability has been provided. Full details of the manufacturing process and certificates of analysis have also been provided.

Control of intermediates

The structure of the intermediates have been confirmed by IR and H-NMR. Certificates of analysis have been provided which include the specifications. Adequate details of the test methods have been provided.

Process validation

Process validation has been completed on four batches. The critical stages of each of the steps have been identified and verified that the chosen parameters reproducibly achieve the set limits.

2.3 Evidence of structure

Structure has been demonstrated by elemental analysis, mass spectrum, NMR, UV and IR. This is acceptable.

Polymorphism was shown not to be present by re-crystallising from a ether, alcoholic, hydro carbon, ketonic and chloroform solvents. The IR spectrums of these were superimposable to the aceclofenac CRS. DSC and X-ray diffraction data has also been presented to support these conclusions.

2.4 Impurities

To control the potential impurities arising from the raw materials, acceptable limits of purity have been set.

The potential impurities in diclofenac have not been listed. They are stated as being controlled to the European Pharmacopoeia. There is an acceptable limit for diclofenac in the aceclofenac benzyl ester.

The presence of inorganics remaining in the product as impurities is monitored by the sulphated ash test with a limit of not more than 0.1%, which is acceptable.

The catalyst is stated as being controlled by the process.

The process also reduces the potential carry over of residual solvents. The limits set for the solvents are in-line with the guidelines.

Data have been provided investigating the presence of the related impurities detailed in the European Pharmacopoeia. Three batches were analysed, with the identification of only 3 of the 9 listed impurities. The others were below the detection limit. The detected impurities were well within specification. Representative chromatograms have been provided for the investigation on the European Pharmacopoeia listed impurities.

2.5 Control of drug substance

Specification

Aceclofenac has a European Pharmacopoeia monograph. The specifications for aceclofenac are taken from the manufacturers certificate of analysis, which covers the European pharmacopoeia tests. In addition there are internal standards for the catalyst and the residual solvents, which are in compliance with the guidance on residual solvents.

Acceptable justification for the specification limits set have been provided, with data from three batches to support the justification.

The finished product manufacturer will test all new batches of active substance to the full specification.

Analytical methods

Where relevant the test methods used are those described in the European Pharmacopoeia. The HPLC method for residual solvents is fundamentally similar to that described in the pharmacopoeia. The GC method for determination of residual solvents has been provided.

The test methods used by the finished product manufacturer are those described in the pharmacopoeia. Particle size is determined by laser light diffraction, full details of the method have been supplied.

Analytical test method validation

The validation data for the particle size analysis method has been provided demonstrating that the method is specific, precise and robust, this is acceptable.

2.7 Batch analyses

Certificates of analysis have been supplied for batches, with accompanying relevant data, all of which comply with the specifications.

2.8 Container closure system

The product is filled into a polyethylene bag, which is bagged in a second polyethylene bag (black), which is packed into a blue HDPE round drum. The specifications for the packaging material have been supplied. Certificates of analysis from the active substance manufacture and packaging material suppliers have been supplied. Appropriate certification has also been supplied regarding the suitability of the contact material.

2.9 Stability

Stability data has been presented on laboratory batches and scale up batches, stored under accelerated conditions. Data has also been presented for the scale up batches under long term conditions. All batches are packed into the proposed packaging.

The stability is assessed by assay, related substances, loss on drying and description.

All batches remain in specification at all conditions. There is a slight decrease in assay under accelerated conditions over 6 months, with a corresponding increase in the total impurities. However the difference is small and would not be considered as significant.

The suggested re-test period of 24 months is acceptable based on these results.

Forced degradation studies (heat, acid, alkali, oxidation and light) demonstrated the suitability of the HPLC method for stability.

3. DRUG PRODUCT

3.1 Composition

The qualitative composition of the tablets is summarised in table 1. The tablets are white film coated, circular tablets, with ‘LG’ embossed on one side and ‘100’ embossed on the other. The tablets are packed into aluminium – aluminium blister packs.

Table 1

Formulation	Function	Reference
Aceclofenac	Active	Ph. Eur.
Microcrystalline cellulose	Diluent/Filler	Ph. Eur.
Croscarmellose sodium	Disintegrant	Ph. Eur.
Povidone K-30	Binder	Ph. Eur.
Glyceryl Distearate (type 1)	Lubricant	Ph. Eur.
Opadry-Y-1-7000	Coating agent	In-house

3.2 Pharmaceutical Development

3.2.1 Components

The product is a film coated tablet containing excipients which are commonly used and are similar to those present in the original product, referenced from the SPC. Consequently compatibility between the active substance and excipients has not been investigated. Due to the poor solubility, particle size has been highlighted as a potential issue in formulation. The function of each of the excipients has been listed.

3.2.2 Formulation development

Particle size of the active substance was identified as a key parameter in formulation. Particle size was assessed using a range of processed materials.

The solubility of the smallest and largest particle size active substance was assessed over a range of pH.

Batches formulated from active substance with different particle size ranges were analysed. The data presented for particle size on these batches is laser light diffraction data. There is a conclusive difference in dissolution profiles for which individual tablet data has been supplied and shows a reasonable degree of comparability. This is used as a justification for the discriminatory nature of the method. UV analysis has been shown to produce comparable results to the HPLC analysis.

The development of the product was based on producing a product comparable to the original in terms of appearance, consequently the target was an 8mm round tablet.

Compatibility of the active substance with the excipients has been assumed on the basis that they are the same as the innovator product.

3.3 Manufacture

3.3.1 Manufacturer(s)

An inspection report and an assessment of compliance to the EU guide to GMP has been included for the production, assembly and QC site.

The additional assemblers have been included. Manufacturers Assembly Licences have been supplied. These are alternative primary and secondary packaging sites.

3.3.2 Batch formula

The batch formula has been presented.

Overages have been included for the Opadry coat. The reason has been stated as process loss, relevant data has been provided to justify this.

3.3.3 Manufacturing process and process controls

A flow diagram detailing the manufacturing process has been provided. A written summary of the process is also included.

Bulk coated tablets are stored in HDPE containers lined with double poly bag at controlled conditions (temperature not more than 25°C). Data from two batches after two years has been presented and is well within the specifications.

It has been confirmed that the determination of the expiry date is from the beginning of the manufacturing process.

3.3.4 In-process controls

In-process controls are presented and suitable limits have been supplied for the the tests. Details have been provided on the frequency of testing. Relevant details have been supplied on the methods and sample quantities and selection.

3.3.5 Control of critical steps and intermediates

The critical steps have been identified and tests performed have been stated. Relevant details have been supplied on the methods and sample quantities and selection.

3.3.6 Process validation or evaluation

Data have been provided for three pilot scale batches at 10% of the proposed final batch size. These have been analysed to the in-process testing schedule. The finished product was tested to the release specification. A protocol has been provided.

The dissolution data presented shows very comparable profiles between batches and with the original product. Certificates of analysis have been provided for the tablet cores and the finished product, with all three batches being within specification.

The data provided does demonstrate a process under control.

3.4 Control of materials

3.4.1 Control of excipients

Microcrystalline cellulose, croscarmellose sodium, povidone and glyceryl distearate (type 1) have monographs in the Ph. Eur. Certificates of analysis are provided from the finished product manufacture and the excipient manufacturer. Relevant certification on TSE and residual solvents have also been supplied.

The finished product manufacturer has confirmed that all new batches of excipients are tested to the specifications of the European Pharmacopoeia monograph.

The in-house specifications for the Opadry have been provided, with accompanying methods. Certificates of analysis have been provided from the finished product manufacturer and the excipient manufacturer.

The purified water is produced on site using potable water. The potable water is analysed weekly for complete chemical and microbiological quality. The pre-treatment system, purified water generation system and storage tank are analysed on a weekly basis for chemical and microbiological specifications so each sampling point is covered at least once in a three to four week period. All 10 user points of the purified water distribution loop are analysed for chemical and microbiological specification as per the European Pharmacopoeia monograph on a weekly basis. Acceptable testing reports have been provided.

3.5 Control of drug product

3.5.1 Specification

The finished product specification has been supplied and is aceptable.
Microbiology is currently tested on each batch.

The specification for diclofenac is somewhat high in relation to the data presented, as this is a pro-drug and non toxic in nature this is considered acceptable.

3.5.2 Analytical procedures

All the details have been provided for the pharmacopoeia and non-pharmacopoeia methods. The methods for assay and impurities and related degradation products are both HPLC methods.

3.5.3 Validation

The UV method for analysis of blends and cores has been validated. Linearity has been shown. The method has been shown to be accurate and precise. Specificity has been shown in relation to placebo and diclofenac. Robustness has been demonstrated. The test solutions were shown to be stable for up to 24 hours.

The assay for aceclofenac has been validated. Linearity has been demonstrated. The method has been shown to be accurate and precise. Specificity has been shown in relation to placebo and the known impurities and stressed samples (acid, base, heat, oxidation and UV). Robustness has been demonstrated. The test solutions were shown to be stable for up to 24 hours.

The assay for impurities and degradation products has been validated for the major impurity diclofenac. Linearity has been demonstrated. The method has been shown to be accurate and precise. Specificity has been shown in relation to the aceclofenac peak, placebo and two of the other known impurities and stressed samples (acid, base, heat, oxidation and UV). It has been stated that there are no co-eluting peaks which has been supported with acceptable peak purity data. Robustness has been demonstrated.

The UV analysis used in dissolution has been validated. Linearity has been demonstrated. The method has been shown to be accurate and precise. Specificity has been shown in relation to placebo and diclofenac. Robustness has been demonstrated. The stability of the test solutions has been shown for up to 24 hours.

Validation data in relation to the microbiology methods used to assess the quality of the tablets has been presented for dilution and validity of counting method.

3.5.4 Batch analyses

Certificates of analysis have been provided for the three batches produced at pilot scale. The dissolution data provided details the minimum, maximum and average %release for the three batches. All comply with the specification limit. However, there is a great deal of variability between the minimum and maximum over the first 10 to 15 minutes. The variability between the minimum and maximum is reasonably consistent across the three batches. These are also comparable to the innovator product.

3.6 Container closure system

The packaging consists of aluminium-aluminium blisters. The cold forming blister foil is composed of three layers, polyamide, aluminium and PVC. The plain aluminium foil is hard tempered coated with VMCH. The specifications of the foils have been provided with test methods. It has been confirmed that the tests listed are those performed by the finished product manufacturer on receipt of new batches of foil.

Certificates of analysis have been provided from the foil suppliers.

Certification demonstrating compliance to the directive 90/128/EEC on contact materials from the suppliers of the foils has been provided.

3.7 Stability

Stability data have been provided for pilot scale batches packed in the aluminium-aluminium blisters, stored under long term, intermediate and accelerated conditions.

Long term testing is planned up to 36 months and accelerated testing up to 6 months. The samples were tested for appearance, hardness, disintegration, loss on drying, dissolution, assay, related substances and microbiology.

The methods used are those used on release.

The data presented for the batches remains in specification for 6 months under accelerated conditions and for 24 months under long term conditions and 12 months under intermediate conditions. Representative chromatograms and the dissolution profiles have been presented.

Across the three batches at the various conditions there is fluctuation in the hardness, though it does remain in specification. The main variation is the increase in diclofenac under long term and accelerated conditions.

A shelf-life of 24 months has been proposed with storage conditions to store below 25°C. The intention is to increase this to 36 months with real time data.

Post approval stability commitment has been made for the first 3 production scale batches at long term and accelerated conditions and in addition at least one batch per year will be put on long term stability.

3.8 Other information

3.8.1 Bioanalytical methods

The validated method is based on HPLC-UV. Both the method and validation report have been supplied. Linearity demonstrated. The LLOQ has been calculated. The method has also been shown to be accurate and precise. The method uses internal standards, calibration standards and quality control samples as an acceptable method check.

3.8.2 Bioavailability/Bioequivalence

The bioequivalence study was an open label, randomised, balanced, two-period, cross-over, single dose study. Comparing the Aceclofenac 100mg tablets with Preservex 100mg tablets from UCB Pharma Ltd, sourced from the UK, in healthy adults under fasting conditions, at a dose of 100mg. Twenty four subjects were enrolled in the study. Data were analysed for twenty four.

One 100mg tablet was given for each of the medications. Samples were taken predose (0 hours) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12 and 24 hours post dose. The washout period was at least 7 days.

Bioequivalence was determined using the 90% confidence interval of the relative mean Cmax, AUC 0-t and AUC∞ of the test to reference formulation, which should be 80% to 125%.

The batch of Aceclofenac 100mg tablets (BN 025901002) is at least 1/10 of the proposed maximum batch size.

The 90% confidence intervals for the log-transformed pharmacokinetic parameters were

	Aceclofenac
AUC 0-t	94.68% - 104.48%
AUC∞	95.06% - 104.62%
Cmax	101.09% - 126.56%

The confidence intervals derived are within the 80% to 125% acceptance range of the Notes for Guidance on Bioavailability and Bioequivalence for AUC0-t and AUC∞. The Cmax is marginally outside the top end of the limits but is considered acceptable in this instance. For further information see the medical assessment report.

3.8.3 Essential similarity

Dissolution data comparing the Aceclofenac 100mg tablets with Preservex 100mg tablets in phosphate buffer pH6.8 have been shown to be similar for the biobatch of Preservex with the three pilot scale batches. Individual tablet data has been presented demonstrating intra and inter batch comparability.

Comparative impurity data have been presented for Aceclofenac 100mg tablets and Preservex 100mg tablets. This was part of the stability study. Under long term and accelerated conditions, the Preservex has an increased level of diclofenac and total other impurities.

Overall the two products are considered to be comparable.

4. PRODUCT LITERATURE

4.1 SPC

The SPC is in compliance with the quality section and the relevant guidelines and is considered to be acceptable.

4.2 PIL

The PIL is in compliance with the SPC and the relevant guidelines and is considered acceptable.

4.3 LABEL

The label is in compliance with the SPC and the relevant guidelines and is considered acceptable.

5. ADMINISTRATIVE

5.1 MAA form

The MAA form is complete and in compliance with the SPC and relevant guidelines and is considered acceptable.

5.2 Quality overall summary

The report is a summary of the module and has been completed by a suitable person.

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 a national abridged complex application for a marketing authorisation for Aceclofenac 100 mg Tablets, PL 04416/0591. The applicant claims essential similarity to Airtal 100 mg tablets, licensed to Almirall Prodesfarma SA and first granted in the EU (Spain) in May 1991. It was first granted in the UK in 1995 and it is currently marketed under the name PRESERVEX Tablets 100 mg (PL 16973/001) being the marketing authorisation holder Almirall Prodesfarma SA. UCB Pharma Ltd UK is the company responsible for placing the product in the UK.

The application is made under article 10.1(a)(iii) of EC Directive 2001/83.

2. BACKGROUND

Aceclofenac is a widely used non-steroidal anti-inflammatory drug which has been licensed in the EU for over 10 years. It is a phenylacetic acid derivative and is similar to diclofenac although it appears to have a lower tendency to cause gastro-intestinal effects.

3. INDICATIONS

Aceclofenac 100mg Tablets are indicated for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

4. DOSE & DOSE SCHEDULE

Aceclofenac tablets are supplied for oral administration and should be swallowed whole with a sufficient quantity of liquid. Aceclofenac should be taken preferably with or after food.

Adults

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

Children

There are no clinical data on the use of Aceclofenac in children and therefore it is not recommended for use in children.

Elderly

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

As with other non-steroidal anti-inflammatory drugs (NSAIDs), caution should be exercised in the treatment of elderly patients, who are at increased risk of the serious consequences of adverse reactions, and who are more likely to be suffering from impaired renal, cardiovascular or hepatic function and receiving concomitant medication. If an NSAID is considered necessary, the lowest effective dose should be used for the shortest possible duration. The elderly should be monitored regularly for GI bleeding during NSAID therapy

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 also Precautions).

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.

5. TOXICOLOGY

No new preclinical data have been submitted and none are required for this application.

6. CLINICAL PHARMACOLOGY

6.1 PHARMACOKINETICS

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.

6.2 PHARMACODYNAMICS

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

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

6.3 BIOEQUIVALENCE

A single dose phase 1 bioequivalence study has been performed to compare the proposed new presentation with the reference product.

Study design & methods

This was a single-dose, open label, balanced, randomised, two-period, crossover study to compare the rate and extent of absorption of test and reference formulations of aceclofenac 100 mg tablets in healthy, fasting male and female volunteers aged between 18 and 50 years.

The clinical part of the study took place between 7th August 2003 and the 3rd October 2003.

The study medications were:

Test: Aceclofenac tablets 100 mg; Batch Number 025901002: dose one tablet orally.
Reference: Preservex® Tablets 100 mg (aceclofenac 100 mg); Batch Number R7: dose one tablet orally. The company responsible for placing product on the Market is UCB Pharma Ltd.UK.

Before the study began, ethics approval was obtained for the protocol. The study was conducted in compliance with the requirements of Good Clinical Practice.

24 volunteers were randomised, 16 female and 8 male. All subjects were admitted to the clinical unit on the night before the study to ensure compliance with a 10 hour pre-dosing fasting period. Water was withheld for 1 hour prior to dosing and for 2 hours afterwards. No food was allowed until 4½ hours after dosing.

Allocation to the test or reference product was according to a pre-determined random table. A single tablet of the allocated study medication was given with a drink or 240 ml water. Subjects were dosed in an upright seated position and were not allowed to lie down for 3 hours afterwards, or take any vigorous exercise for 12 hours.

A pre-dose blood sample was taken followed by further blood samples at these timepoints after dosing: ½, 1, 1½, 2, 2½, 3, 4, 5, 6, 8, 12, 24 hours. Immediately after withdrawal, the samples were kept in a refrigerator for no more than 20 minutes before being spun in a cooled centrifuge to separate the plasma.

After the final 24 hour blood sample was taken the subjects were allowed to leave the clinical unit. There was a washout period between the two doses of at least 7 days after which the subjects returned for the second dosing with the alternate

medication following the same schedule as for the first dosing period. Within 7 days after the end of the study, all the subjects underwent a post-study health check. All subjects completed the study satisfactorily.

The method used for analysis of the blood samples was a validated HPLC method with UV detection and the lower limit of quantitation was 0.1 μg/ml with a linearity range from 0.1 to 60 μg/ml. The laboratory remained blinded to which medication had been administered to each subject during each period.

Pharmacokinetic parameters were calculated from plasma concentrations for the test and reference preparations. Analyses of variance (ANOVA) were performed on ln values of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

Results

The summary of the results are shown below.

Aceclofenac Pharmacokinetic Parameters (log-transformed)				
	Geometric Mean Values			**90% Confidence**
	Test	**Ref**	**Ratio T/R**	**Intervals**
C_{max} (mcg/ml)	13.09	11.77	113.11%	101.09-126.56%
AUC $_{0-t}$ (mcg.h/ml)	24.68	24.83	99.46%	94.68-104.48%
AUC $_{0-inf}$ (mcg.h/ml)	25.51	25.62	99.72%	95.06-104.62%
	Mean Values			
T_{max} (h)	1.58	1.98		
$T_{½}$ (h)	2.67	2.35		

As can be seen, the upper confidence interval for the peak concentrations is just outside the 80-125% acceptance range but is consided acceptable in this instance. Although the mean peak value for the test was higher than that for the reference product, aceclofenac is very well tolerated and the slightly higher peak level is unlikely to be of any clinical significance with respect to safety. The AUC values are well within the normal 80-125% acceptance limits. The secondary efficacy criteria of time to peak plasma concentration (T_{max}) and the half-life ($T_{½}$) were similar for both presentations.

During the study, six subjects experienced side effects most of which were classed as mild with one of moderate intensity. The unwanted effects were: headache (1), tendon rupture (1), abdominal pain (1), diarrhoea (1), dizziness (3), urinary tract infection with raised white cell count (1), and a flu syndrome. Four events were considered to be possibly drug related, three unlikely to be related, and two unrelated.
Laboratory results (haematology, biochemistry and urine analysis) and vital signs showed no significant changes.

Conclusion

It can be concluded that on the basis of rate and extent of absorption, the test and reference products have equivalent bioavailability and that the study medication is safe and well tolerated in healthy volunteers at the dose given.

7. EFFICACY

The bioequivalence study submitted has demonstrated that the applicant product is bioequivalent to the reference product and therefore will have essentially the same clinical efficacy.

8. SAFETY

The bioequivalence study submitted has demonstrated that the applicant product is bioequivalent to the reference product and therefore will have essentially the same clinical safety.

9. EXPERT REPORT

A clinical expert report signed by a consultant to the Pharmaceutical Industry has been submitted. The report provides a discusssion on the proposed product including the results of the bioequivalence study and is presented in the new CTD format.

10. SUMMARY OF PRODUCT CHARACTERISTICS

The SPC is satisfactory.

11. PATIENT INFORMATION LEAFLET

The PIL is satisfactory.

12. LABELLING

Mock-ups of all pack sizes have been submitted and are satisfactory.

13. MARKETING AUTHORISATION FORM

This is satisfactory.

14. DISCUSSION

This is a national application for a marketing authorisation for Aceclofenac 100 mg Tablets submitted as essentially similar to Airtal 100 mg tablets, licensed to Almirall Prodesfarma SA and first granted in the EU in 1991. It was first granted in the UK in 1995 and it is marketed under the name PRESERVEX Tablets 100 mg (PL 16973/001).

Aceclofenac 100mg Tablets are indicated for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

A single dose phase 1 bioequivalence study has been performed to compare the proposed new presentation with the reference product. The bioequivalence study has demonstrated that the applicant's product is bioequivalent to the reference product and therefore will have essentially the same clinical efficacy and safety.

15. CONCLUSIONS

The efficacy and safety of Aceclofenac 100 mg Tablets are satisfactory for the grant of a product licence.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Aceclofenac 100mg 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.

PRECLINICAL

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

EFFICACY

Aceclofenac is a well known drug and has been used as an anti-inflammatory for many years. The applicant has demonstrated essential similarity to the marketed product, Preservex tablets 100mg.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's product and the originator product are interchangeable. Extensive clinical experience with aceclofenac is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

ACECLOFENAC 100MG TABLETS

PL 04416/0591

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 27/01/2004.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 13/02/2004.
3	Following assessment of the application the MHRA requested further information relating to the clinical dossier on 10/09/2004.
4	The applicant responded to the MHRA's requests, providing further information relating to the clinical dossier on 21/10/2004.
3	Following assessment of the application the MHRA requested further information relating to the quality dossier on 18/11/2004 and 05/07/2005.
4	The applicant responded to the MHRA's requests, providing further information on 06/06/2005, 27/06/2005 and 23/11/2005.
5	The application was determined on 07/02/2006.

ACECLOFENAC 100MG TABLETS

PL 04416/0591

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

ACECLOFENAC 100MG TABLETS

PL 04416/0591

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Aceclofenac 100 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Aceclofenac 100 mg

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.
White, circular, film-coated tablets with 'LG' embossed on one side and '100' on the other side of the tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Aceclofenac 100 mg Tablets are indicated for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

4.2. Posology and method of administration

Aceclofenac tablets are supplied for oral administration and should be swallowed whole with a sufficient quantity of liquid. Aceclofenac should be taken preferably with or after food.

Adults

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

Children

There are no clinical data on the use of Aceclofenac in children and therefore it is not recommended for use in children.

Elderly

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

As with other non-steroidal anti-inflammatory drugs (NSAIDs), caution should be exercised in the treatment of elderly patients, who are at increased risk of the serious consequences of adverse reactions, and who are more likely to be suffering from impaired renal, cardiovascular or hepatic function and receiving concomitant medication. If an NSAID is considered necessary, the lowest effective dose should be used for the shortest possible duration. The elderly should be monitored regularly for GI bleeding during NSAID therapy

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 also Precautions).

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 any of the constituents.

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

Severe hepatic and cardiac failure (See section 4.4 - Special warnings and precautions for use).

Moderate to severe renal failure.

During the last trimester of pregnancy (See section 4.6 - Pregnancy and lactation)

Active or previous peptic ulcer.

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

Use with concomitant NSAIDs including cyclooxygenase 2 specific inhibitors (See section 4.5 Interactions).

4.4. Special warnings and precautions for use

Undesirable effects may be minimised by using the minimum effective dose for the shortest possible duration.

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 - Posology and administration).

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 – Contraindications). Effects on renal function are usually reversible on withdrawal of Aceclofenac.

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.

Caution in patients with a history of hypertension and/or heartfailure as fluid retention and oedema have been reported in association with NSAID therapy.

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.

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 gastrotoxicity or bleeding, such as corticosteroids, or

anticoagulants such as warfarin or anti-platelet agents such as aspirin (See section 4.5 Interactions).

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 – Undesirable effects).

Close medical surveillance is imperative in patients with bleeding diathesis or haematological abnormalities.

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 – Undesirable effects).

Female fertility:
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.

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

Haematological:
Aceclofenac 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 function, hepatic function (elevation of liver enzymes may occur) and blood counts.

4.5. Interactions 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 bendroflumethiazide, 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 - Special warnings and precautions for use). 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 methotrexate 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.

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.

Other analgesics*:* Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (See section 4.3 Contraindications).

Anti-hypertensives*:* Reduced anti-hypertensive effect.

Corticosteroids: Increased risk of GI bleeding (See section 4.4 – Special warnings and precautions for use).

Tacrolimus*:* Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

4.6. 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), use in the last trimester of pregnancy is contraindicated. 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 Contraindications). 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:
There is no information on the secretion of Aceclofenac to breast milk; there was however no notable transfer of radio-labelled (^{14}C) aceclofenac to the milk of lactating rats.

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.

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

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 side-effects 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.

WHO System Organ Class	Common 1 to 10%	Uncommon 0.1 to 1%	Rare or very rare <0.1%

Gastrointestinal System disorders	Dyspepsia Abdominal pain Nausea Diarrhoea	Flatulence Gastritis Constipation Vomiting Ulcerative stomatitis	Melaena Stomatitis Haematemesis Gastrointestinal haemorrhage Gastric ulcer Pancreatitis
Urinary system disorders	-	-	Renal failure Nephrotic syndrome
Central and peripheral nervous system disorders	Dizziness	Vertigo	Paraesthesia Tremor
Psychiatric disorders	-	-	Depression Abnormal dreamimg Somnolence Insomnia
Disorders of the skin and appendages	-	Pruritus Rash Eczema Dermatitis Urticaria	Bullous dermatoses
Liver and Biliary Disorders	Hepatic enzymes increased	-	Hepatitis Jaundice
Metabolic disorders	-	BUN increased Blood creatinine increased	Alkaline phosphatase increased Hyperkalaemia
Cardiovascular disorders	-	-	Oedema in lower limbs Palpitation Cramps in legs Flushing Purpura
Respiratory disorders	-	-	Dyspnoea Stridor Bronchospasm
Haematological disorders	-	-	Anaemia Granulocytopenia Thrombocytopenia Neutropenia Haemolytic anaemia
Body as a whole – General disorders	-	-	Allergic reaction Anaphylactic reactions (including shock) Headache Fatigue Face oedema Hot flushes Weight increase
Others	-	-	Abnormal vision Abnormal taste

Other rare or very rare class-effects reported with NSAIDs in general are:

Gastrointestinal System – Duodenal ulcer, Gastrointestinal perforation
Urinary System – Interstitial nephritis

Central and Peripheral Nervous System – Optic neuritis
Psychiatric – Hallucination, Drowsiness, Confusion
Skin and Appendages – Epidermal necrolysis, Erythema multiforme, Exfoliative dermatitis
Respiratory – Aggravated asthma
Haematological – Aplastic anaemia
Others – Tinnitus, Photosensitivity, Malaise

Other undesirable effects that have been reported are exacerbation of colitis and Crohn's disease, angioedema, 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 and also asthma (See section 4.4 Special warnings and precautions for use).

4.9. Overdose

There are no human data available on the consequences of Aceclofenac overdose.

a) Symptoms
Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, 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.
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.
Frequent or prolonged convulsions should be treated with intravenous diazepam.
Other measures may be indicated by the patient's clinical condition.
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: 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 of prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclo-oxygenase, which is involved in the production of prostaglandins.

5.2. Pharmacokinetic properties

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

The mean (geometrical) plasma elimination half-life is 2.30 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:
Microcrystalline cellulose
Croscarmellose Sodium
Povidone
Glyceryl distearate (type I)

Film-coat:

Hypromellose
Titanium dioxide (E171)
Macrogol 400

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years.

6.4. Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5. Nature and contents of container

Aluminuim/Aluminium blister in packs of 28, 30, 56, 60 and 100.

Not all pack sizes may be marketed.

6.6 Instructions for Use and Handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Sandoz Ltd
Woolmer Way
Bordon
Hants
GU35 9QE
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 04416/0591

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/02/2006

10 DATE OF REVISION OF THE TEXT

ACECLOFENAC 100MG TABLETS

PL 04416/0591

PRODUCT INFORMATION LEAFLET

SANDOZ

PATIENT INFORMATION LEAFLET
Aceclofenac 100mg Tablets

SZ02101LT01A

What you should know about Aceclofenac 100mg Tablets.
Please read this leaflet carefully before you start taking your medicine. This leaflet provides a summary of the information available on your medicine. Keep it so that you can read it again if you need to. If you have any questions or are not sure about anything, ask your doctor or pharmacist. Remember, this medicine is for you only. Only your doctor can prescribe it for you. Never give it to others, even if they have the same symptoms as you, as it may harm them.

In this leaflet:

The name of your medicine is **Aceclofenac 100mg Tablets.**
The Marketing Authorisation Holder and Manufacturer is:
Sandoz Ltd, 37 Woolmer Way, Bordon, Hampshire, GU35 9QE.

1. WHAT ACECLOFENAC TABLETS ARE AND WHAT THEY ARE USED FOR.

The tablets are white, round, film-coated tablets with "LG" embossed on one side and "100" on the other side of the tablet and contain 100mg Aceclofenac.
Other ingredients contained within this medicine are: microcrystalline cellulose, croscarmellose sodium, povidone, glyceryl distearate (type I), opadry Y-1-7000 (containing: hypromellose, titanium dioxide (E171), macrogol 400).
The tablets are available in blister packs of 28, 30, 56, 60 and 100.
Aceclofenac Tablets are used for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.
The active ingredient Aceclofenac belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs) which reduce inflammation and pain.

2. BEFORE YOU TAKE ACECLOFENAC TABLETS.

DO NOT take Aceclofenac Tablets and talk to your doctor if:
- you are allergic to Aceclofenac or to any of the other ingredients in this medicine;
- you have had any breathing problems, a runny nose, skin rash or any other type of allergic reaction after taking ibuprofen, aspirin or any other NSAIDs;
- you are pregnant, may be pregnant, or are breast feeding;
- you have any kidney problems;
- you suffer from severe liver problems;
- you suffer from severe heart problems;
- you are already taking other NSAIDs;
- you have or have ever had peptic ulcers (ulcer in your stomach or duodenom) or bleeding in your digestive tract.

Take special care with Aceclofenac Tablets if:
- you suffer from any bowel disorders, for example, ulcerative colitis or Crohn's disease;
- you suffer from any blood or bleeding disorder;
- you have any liver problems;
- you have heart failure or high blood pressure;
- you have bronchial asthma;
- you suffer from porphyria;
- you suffer from lupus or an immune disorder called mixed connective tissue disease.

If any of these apply to you, talk to your doctor before taking these tablets. In some cases your doctor may ask you to go for regular check-ups whilst you are taking these tablets.
If you suffer from any of the following at any time during your treatment **STOP TAKING** the medicine and *seek immediate 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 pains (pains in your stomach) or other abnormal stomach symptoms.

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 becoming pregnant.
Taking Aceclofenac with food and drink:
Aceclofenac Tablets should be swallowed whole, with sufficient quantity of liquid, preferably with or after food.
Driving and using machines:
You may suffer from dizziness, drowsiness, visual disturbances, fatigue or other similar effects whilst you are taking these tablets. If you are affected, you should avoid driving or operating dangerous machinery.

Taking other medicines:
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed, particularly: any other NSAIDs or aspirin; lithium (for mental illness); digoxin or digitoxin (for the heart); diuretics (water tablets) such as bendroflumethiazide, furosemide or amiloride; anticoagulants (medicines used to thin the blood) such as warfarin; anti-hypertensives (medicines used to treat high blood pressure); medicines for diabetes (such as glibenclamide or metformin); methotrexate (used to treat cancers, rheumatoid arthritis or psoriasis); mifepristone (a medicine used during termination of pregnancy); ciclosporin (used after transplants); steroids such as prednisolone or hydrocortisone; corticosteroids; tacrolimus (used in organ transplants and for eczema); or quinolone antibiotics such as ciprofloxacin, norfloxacin or nalidixic acid.

3. HOW TO TAKE ACECLOFENAC TABLETS.

The usual doses for Aceclofenac Tablets are given below. You should always follow your doctor's instructions on how many tablets to take and how often to take them. The instructions will be stated on the pharmacy label. If you are unsure about anything your pharmacist may be able to help.
Aceclofenac Tablets are taken by mouth and should be swallowed whole with a drink preferably with or after food.
Adults and elderly:
The recommended dose is one tablet in the morning and one in the evening.
If you are elderly your doctor may ask you to go for regular check-ups as you may be more prone to the side effects of this medicine.
Children:
Aceclofenac Tablets are not recommended.
Patients with liver problems:
If you suffer from liver problems your doctor may need to start you on a lower dose.
If you take more Aceclofenac Tablets than you should: contact your doctor or go to the local hospital accident and emergency department immediately and take this leaflet and any remaining Aceclofenac Tablets with you.
If you forget to take Aceclofenac Tablets: If you forget to take a dose, take it as soon as you remember. If it is nearly time for your next dose, just take the next dose. Do not double the next dose to make up for the missed one.

4. POSSIBLE SIDE EFFECTS.

As with all medicines, you may experience some side effects when taking Aceclofenac Tablets.
If you experience any of the following rare but serious side effects, stop taking these tablets and contact your doctor immediately as you may be allergic to these tablets: severe skin rash or itching, swelling of the face, mouth or lips, difficulty swallowing, difficulty breathing or shortness of breath, chest pain or collapse.
Common side effects (affecting between 1 in 10 and 1 in 100 people) include: indigestion, abdominal pain, nausea (feeling sick), diarrhoea, dizziness, or increase in liver enzymes.
Uncommon side effects (affecting between 1 in 100 and 1 in 1000 people) include: flatulence (wind), gastritis (inflammation of the stomach lining causing stomach pain), constipation, vomiting, ulcers and inflammation inside the mouth, vertigo, skin problems (such as rash, itching, eczema, dermatitis, or nettle rash), or an increase of waste products in the blood.
Rare or very rare side effects (affecting less than 1 in 1000 people) include: black tarry stools, inflammation inside the mouth, blood in the vomit, bleeding in the stomach, stomach ulcers, inflammation of the pancreas, kidney problems (including kidney failure), tingling in the hands and feet, shaking of arms, legs or other muscles, depression, abnormal dreams, tiredness, insomnia, blistering of the skin, inflammation of the liver or jaundice (a yellowing of the skin or whites of the eyes), an increase of potassium or liver enzymes in the blood, swelling of the legs or ankles, cramps in the legs, palpitations (an awareness of the heartbeat), flushing, purple patches on the skin, difficulty breathing, noisy or wheezy breathing, changes in blood such as anaemia (symptoms include tiredness and looking pale) or a reduction in white blood cells (making you more prone to infections), allergic reactions (see above), headache, tiredness, hot flushes, increase in weight, abnormal vision or taste.
Other rare or very rare side effects that have been reported with NSAIDs in general include: duodenal ulcer, gastrointestinal perforation, inflammation of the kidney, pain in the eye, hallucinations, drowsiness, confusion, severe skin reactions (including blistering and flaking of the skin), aggravated asthma, anaemia caused by lack of red blood cells made by bone marrow, ringing in the ears (tinnitus), sensitivity of the skin to sunlight, and a general feeling of unwell.
Other undesirable effects that have been reported or a worsening of the following: abdominal pain and Crohn's disease; flushing; aseptic meningitis with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation; asthma; somnolence; worsening of colitis.
If you think your medicine may be causing any of these effects or any other side-effects that are not mentioned here, talk to your doctor or pharmacist.

5. STORING ACECLOFENAC TABLETS.

Do not store above 25°C. Store in the original package.
Do not use after the expiry date stated on the label. Any out of date or unwanted tablets should be returned to your pharmacist for disposal.
REMEMBER keep all medicines out of the reach and sight of children. Your medicines may harm them.
This leaflet applies to Aceclofenac 100mg Tablets only.
Date of leaflet preparation: December 2006.

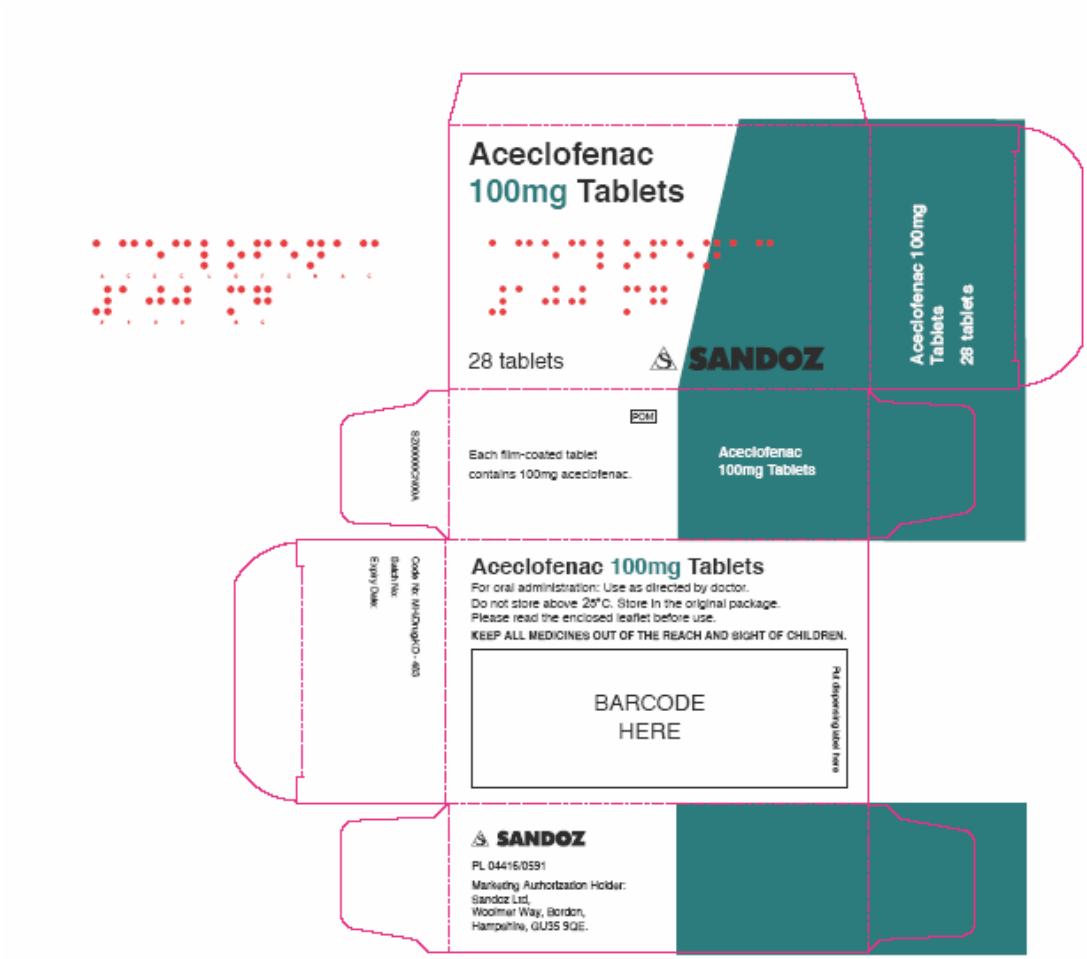
SZ02101LT01A

ACECLOFENAC 100MG TABLETS

PL 04416/0591

LABELLING

CARTON



BLISTER FOIL