IPAR

HEALTH PRODUCTS REGULATORY AUTHORITY

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion
Vitafen 100mg film-coated tablets
Aceclofenac
PA1113/009/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Vitafen 100mg film-coated tablets from Phoenix Healthcare Limited on the 10th of April 2015 for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

The submission is made under Article 10(1) of Directive 2001/83/EC and is made as a national application.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product: Vitafen Name(s) of the active substance(s) (INN): Aceclofenac Pharmacotherapeutic classification (ATC code): Pharmaceutical form and strength(s): 100mg film-coated tablets Marketing Authorisation Number(s) in Ireland (PA): PA1113/009/001 Marketing Authorisation Holder: Phoenix Labs

II QUALITY ASPECTS

II.1. Introduction

This application is for Vitafen 100mg film-coated tablets.

II.2 Drug substance

The active substance is aceclofenac, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Vitafen are white to off-white, round shaped, biconvex, film-coated tablet debossed with "100" on one side and plain on the other side.

Each tablet contains 100mg aceclofenac. The other excipients of the tablet core are cellulose microcrystalline, croscarmellose sodium, povidone and glyceryl distearate (Type 1). The film-coating excipients are hypromellose, titanium dioxide and polyethylene glycol 400

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented as aluminium/aluminium blisters in packs of 10, 20, 30, 40, 60, and 100 tablets.

Evidence has been provided that blisters complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 4 years when stored in the original package in order to protect from light and below 25°C.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Vitafen 100mg film-coated tablets.

III NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Airtal 100mg Tablets on the European market. No new preclinical data have been submitted.

Pharmacodynamic, pharmacokinetic and toxicological properties of Aceclofenace are well known. As Aceclofenace is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate from this type of application.

The non-clinical overview has been written by Dr Rajendra C. Rane who has over 22 years experience with clinical pharmacology and new product development. The report refers to 13 publications up to year 2005.

III.2 Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment has not been performed as this product is intended for generic substitution and therefore will not result in an increase of risk to the environment during use, storage and disposal.

III.3 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological 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. Overview based on literature review is, thus, appropriate.The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. Non-clinical findings are adequately mentioned in the appropriate sections of the SmPC.

IV CLINICAL ASPECTS

IV.1 Introduction

Aceclofenac is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product.

For this generic application, the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Aceclofenac is compared with the pharmacokinetic profile of the reference product Airtal.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Aceclofenac tablets 100 mg (Intas Pharmaceuticals Limited) was compared to the reference product Airtal tablets 100 mg (Almirall Prodesfarma, S.A - Spain). Based on the pharmacokinetic parameters of aceclofenac, the reference tablet and test tablet (Airtal) are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Absorption: After oral administration, aceclofenac is rapidly absorbed and the bioavailability is almost 100%. Peak blood levels are reached approximately 1.25 to 3 hours after taking the tablet. Maximum concentration is delayed with concomitant food intake whereas the degree of absorption is not influenced.
Distribution: Aceclofenac is highly protein-bound (>99.7%). Aceclofenac penetrates into the synovial fluid, where the concentrations reach approximately 60% of those in plasma.
Elimination: The mean plasma elimination half-life is 4 - 4.3 hours. Clearance is estimated to 5 litres per hour. Approximately two-thirds of the administered dose is excreted via the urine. Only 1% of an oral single dose is excreted unchanged. Aceclofenac is probably metabolized in the liver.

No changes in the pharmacokinetics of aceclofenac have been detected in the elderly. A slower rate of elimination of aceclofenac has been detected in patients with decreased liver function after a single dose of aceclofenac. In a multiple dose study using 100 mg once daily, there was no difference in the pharmacokinetic parameters between subjects with mild to moderate liver cirrhosis and normal subjects. In patients with mild to moderate renal impairment no clinically significant differences in the pharmacokinetics were observed after a single dose.

IV.3 Pharmacodynamics

Aceclofenac is a Non Steroidal Anti-inflammatory Drug known to exhibit multifactor mechanism of action. Aceclofenac blocks inflammatory substances at the site of inflammation

IV.4 Clinical Efficacy

Aceclofenac has been shown to be effective in the treatment of rheumatoid arthritis and osteoarthritis.
In short-term (1 to 6 months) controlled trials in patients of both sexes with active rheumatoid arthritis or osteoarthritis, aceclofenac was an effective and safe (mainly regarding gastrointestinal tolerability) NSAID for treatment of these diseases.

In a placebo-controlled study, aceclofenac showed significant improvements in patients with active rheumatoid arthritis.
Aceclofenac was effective in a double blind, multicentre randomised study in patients with acute low back pain suffering from degenerative spinal disorders and also showed acceptable safety and effectiveness in the treatment of adult patients with active ankylosing spondylitis (AS),

IV.5 Clinical Safety

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.

IV.6 Discussion on the clinical aspects

This application is based on a bioequivalence study which shows that Vitafen is similar to a comparator (Airtal aceclofenac) which has been fully tested and assessed, and thus avoids the need for unnecessary repetition of studies.

V OVERALL CONCLUSIONS

From a quality perspective the overall assessment outcome of Vitafen 100mg film-coated tablets is positive

Vitafen 100mg film-coated tablets is a generic form of Airtal 100mg Tablets. Airtal 100mg tablets is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Vitafen 100mg film-coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.