

Public Assessment Report Scientific discussion

Ibuprofen Brill Ibuprofen

SE/H/1275/01-03/DC

This module reflects the scientific discussion for the approval of Ibuprofen Brill. The procedure was finalised at 2014-04-29. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Bristol Lab has applied for a marketing authorisation for buprofen Bril 200 mg, 400 mg and 600 mg film coated tablets claiming essential similarity to Brufen 400 mg film coated tablets, authorised in DK since 1972, with Abbot Scandinavia as the marketing authorisation holder.. The product contains Ibuprofen as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Brufen, 600 mg tablets marketed by Abbott Laboratories Limited in UK.

II. QUALITY ASPECTS

II.1 Introduction

Ibuprofen Bril is presented in the form of film-coated tablets containing 200 mg, 400 mg, or 600 mg of ibuprofen respectively . The excipients are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal anhydrous silica, polyvinyl povidone, maize starch, sodium lauril sulphate, magnesium stearate, hydroxypropyl cellulose, hypromellose, macrogol and titanium dioxide. The tablets are packed in/filled in Opaque PVC/Al blisters or HDPE bottles with polypropylene cap.

II.2 Drug Substance

Ibuprofen has a monograph in the Ph Eur.

Ibuprofen is a white or almost white, crystalline powder or colourless crystals which is practically insoluble in water. The structure of ibuprofen has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Ibuprofen Bril film-coated tablets is formulated using excipients described in the current Ph Eur. All raw materials used in the product are of vegetable origin/has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Ibuprofen is rapidly absorbed from the gastrointestinal tract with peak serum levels observed after 1-2 hours. The plasma protein binding is very high, approximately 99%. The plasma half-life is about 2 hours. Ibuprofen demonstrates marked stereoselectivity in its pharmacokinetics. Substantial unidirectional inversion of the R(-) to the S(+) enantiomer occurs *in vivo*.

A bioequivalence study with an achiral bioanalytical method was submitted in the original application. This study was not accepted since ibuprofen is a racemate of two enantiomers with different pharmacokinetic and pharmacodynamic properties and publications by Garcia-Arieta and Torrado show that a difference in absorption rate can modify the exposure ratio of the enantiomers. In addition, t_{max} of test and reference differed in this study and the confidence interval of C_{max} was wide and shifted to the lower end of the acceptance range. When combining these facts, it cannot be excluded that the S-enantiomer is non-bioequivalent. Therefore, a non-stereospecific analysis was not accepted for Ibuprofen Bril.

A new bioequivalence study with a chiral analytical method was submitted. Bioequivalence was evaluated in this single-dose, two-way crossover study conducted in 23 healthy male volunteers, comparing Ibuprofen, 600 mg, tablets with Brufen, 600 mg, tablets under fasting conditions. The study was conducted at Synchron Research Services Pvt. Ltd., Ahmedabad, India between 18th July and 24th July 2013. Blood samples were collected pre-dose and up to 14 hours post-dose. Plasma concentrations of S-ibuprofen and R-ibuprofen were determined with an adequately validated LC-MS/MS method. For AUC_{0-t} and C_{max} of both S-ibuprofen and R-ibuprofen, the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% and bioequivalence was demonstrated.

From a pharmacokinetic point of view, absence of studies with the additional strengths (200 mg and 400 mg) is acceptable, as the pharmacokinetics of ibuprofen is approximately linear between 200 mg and 600 mg.

Based on the submitted bioequivalence study, Ibuprofen Bril is considered bioequivalent with Brufen.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The results of the conducted bioequivalence study can be extrapolated to other strengths since the criteria for biowaiver for additional strengths are fulfilled according to the Guideline on the Investigation of Bioequivalence.

The risk/benefit ratio is considered positive and Ibuprofen Bril 200 mg, 400 mg and 600 mg film coated tablets are recommended for approval.

VI. APPROVAL

The Decentralised procedure for Ibuprofen Bril 200 mg, 400 mg and 600 mg film coated tablets was successfully finalised on 2014-04-29.

Public Assessment Report – Update

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)