

Public Assessment Report

Scientific discussion

Brufen 400 mg effervescent granules (ibuprofen)

SE/H/1184/01/DC

Applicant: Abbott Scandinavia AB

This module reflects the scientific discussion for the approval of Brufen, 400 mg, effervescent granules. The procedure was finalised at 2012-12-05. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Abbott Scandinavia AB has applied for a marketing authorisation for Brufen 400mg effervescent granules. The MAH is presently marketing a number of different pharmaceutical forms under the brand name Brufen, and has now applied for an additional pharmaceutical form; effervescent granules. The active substance is ibuprofen. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Brufen is presented in the form of effervescent granules containing 400 mg of ibuprofen. The excipients are anhydrous sodium carbonate, malic acid, sodium saccharin, sodium hydrogen carbonate, sucrose, povidone, orange flavour and sodium lauril sulfate. The effervescent granules are filled in sachets.

II.2 Drug Substance

Ibuprofen has a monograph in the Ph Eur.

Ibuprofen is a white, crystalline powder or colourless crystals which is poorly soluble in water. The structure of ibuprofen has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on chirality is presented. 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

Brufen 400 mg effervescent granules are formulated using excipients described in the current Ph Eur, except for orange flavour which is controlled according to acceptable in house specifications. All raw materials used in the product are of vegetable origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as poor aqueous solubility.

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, when stored below 25°C in the original package in order to protect from light and moisture.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of ibuprofen are well known. As ibuprofen is a widely used, well-known active substance, no further studies were required. Brufen 400 mg effervescent granules is not considered to increase the risk to the environment beyond or above that which may be caused by other ibuprofen-containing products.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ibuprofen is a well known substance used mainly for its analgesic and anti-inflammatory effects.

IV.2 Pharmacokinetics

General information regarding the active substance

The pharmacokinetics of ibuprofen is well known.

Being an asymmetric molecule ibuprofen exists in two optically active isomeric forms, R(-) and S(+) enantiomers. The enantiomers of ibuprofen differ in their pharmacological and pharmacokinetic properties. The S(+) enantiomer is pharmacologically predominantly active as prostaglandin synthesis inhibitor. Incomplete unidirectional inversion of the R(-) to the S(+) enantiomer occurs *in vivo*.

Following oral administration of immediate release ibuprofen formulations, it has been observed that the absorption is rapid and almost complete, due to the lipophilic nature of ibuprofen. Because of a low first pass metabolism in addition, the bioavailability is high, approximately 80-90%. The peak serum levels are reached 1-2 hours after administration of regular ibuprofen tablets. Food slows down the absorption, resulting in lower C_{max} and later t_{max}. The bioavailability is however not significantly affected by food. There are no restrictions with respect to food in the SPC for the effervescent granules.

Ibuprofen has a small volume of distribution (0.12-0.2 l/kg in adults) and a high degree of protein binding of approximately 99 %. Due to a saturation of the protein at higher doses, non-linear pharmacokinetics has been observed with a smaller than expected increase in AUC with increasing dose.

The metabolism of ibuprofen is via hepatic oxidation and glucuronidation. CYP2C8 and CYP2C9 have been identified as equally important for the transformation of the S-enantiomer and CYP2C8 most important for the R-enantiomer. Polymorphism adds variability to the clearance of the two enantiomers. Elimination is rapid, the majority being eliminated renally. Plasma elimination half-lives of approximately two hours have been observed. Less than 10 % is excreted as unchanged drug.

For patients with mild renal impairment increased unbound (S)-ibuprofen, higher AUC values for (S)-ibuprofen and increased enantiomeric AUC (S/R) ratios as compared with healthy

controls have been reported. In end-stage renal disease patients receiving dialysis the mean free fraction of ibuprofen was about 3% compared with about 1% in healthy volunteers.

Alcoholic liver disease with mild to moderate hepatic impairment did not result in substantially altered pharmacokinetic parameters. In cirrhotic patients with moderate hepatic impairment (Child Pugh's score 6-10) treated with racemic ibuprofen an average 2-fold prolongation of the half-life was observed and the enantiomeric AUC ratio (S/R) was significantly lower compared to healthy controls suggesting an impairment of metabolic inversion of (R)-ibuprofen to the active (S)-enantiomer.

The pharmacokinetic properties in elderly are comparable to young subjects, given that no renal or liver disease is present.

Children 3 months to 2.5 years appeared to have a higher volume of distribution (L/kg) and clearance (L/kg/h) of ibuprofen than did children >2.5 to 12 years of age. The systemic exposure of ibuprofen following weight adjusted therapeutic dosage (5mg/kg to 10 mg/kg bodyweight) in children aged 1 year or over, appears similar to that in adults.

Specific information regarding the applied formulation

The Marketing Authorisation is approved based on a pivotal bioequivalence study.

The study was a randomised, single-dose, four-way, cross-over study comparing the bioavailability of two formulations of effervescent granules of ibuprofen to that of Brufen (ibuprofen) 600 mg film-coated tablets in the fasting state. In addition, the effect of food on the bioavailability of the applied effervescent granules formulation was determined. The use of a different strength than the applied one is considered acceptable from a pharmacokinetic perspective since the pharmacokinetics of ibuprofen could be classified as linear in the interval 400-600 mg. The study was performed in 36 healthy male subjects. Blood samples were collected pre-dose and up to 14 hours post-dose. The study design is considered acceptable. Plasma concentrations of ibuprofen were determined with a validated achiral LC/MS/MS method. The use of an achiral method is considered acceptable for this particular product, since the t_{max} values for test and reference were rather similar and since the confidence interval for C_{max} was quite narrow and not close to the limits 80 and 125 %. When combining these facts it is considered likely that the results would be similar for the active enantiomer as for the racemate.

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for both the new and the previous granule formulation.

Both granules formulations had slightly later t_{max} (approximately 0.5 hour) compared to the tablets, but the median t_{max} is within the range 1-2 hours stated in the SPC for Brufen tablets.

A high-fat meal did not affect the extent of absorption from the new granule formulation, since the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for AUC_{0-t} . However, C_{max} was 34% lower following administration with food and t_{max} was delayed by about 2.3 hours. For Brufen tablets, the SPC states that administration with food results in lower and later C_{max} than in the fasting state, but the bioavailability is not affected. The size of the decrease in C_{max} is not stated in the tablet SPC. In a study by Klueglic et al (2005), administration with food (standardized continental breakfast) resulted in approximately 20 % lower C_{max} for regular ibuprofen tablets. Thus, the results for the granules are largely in line with previous results with the tablet formulation. The food effect may possibly be larger for the granules formulation compared to the tablets, but since this is a between-study comparison and since the type of meal is different, is it not certain that there is a real difference in food effect. Since only

C_{max} and not AUC is affected by food, it is considered acceptable to have similar recommendations regarding administration in relation to food as in the tablet SPC.

The pharmacokinetic documentation is sufficient.

IV.3 Pharmacodynamics

The pharmacodynamic properties of ibuprofen are considered well known and no further studies were required for this application.

IV.4 Clinical efficacy

The clinical efficacy profile of ibuprofen is considered well known and well supported by the literature review and studies provided with this application.

IV.5 Clinical safety

The clinical safety profile of ibuprofen is considered well known and well supported by the literature review and studies provided with this application. No new safety issues were identified not considered covered by routine pharmacovigilance activities.

IV.6 Discussion on the clinical aspects

The clinical efficacy and safety of ibuprofen are considered well known and covered by the documentation provided in the application.

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 risk/benefit ratio is considered positive and Brufen 400 mg effervescent granules, is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Brufen 400 mg effervescent granules was successfully finalised on 2012-12-05.

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)