LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Brufen
(ibuprofen)

SE/H/912/01-03/MR

This module reflects the scientific discussion for the approval of Brufen. The procedure was finalised at 2009-10-26. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

Abbott Scandinavia has applied for a marketing authorisation for Brufen film-coated tablets 200, 400 and 600 mg. The active substance is ibuprofen which belongs to the group of NSAIDS. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Brufen is presented in the form of tablets containing 200, 400 and 600 mg of ibuprofen, respectively. The excipients are microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, anhydrous colloidal silica, sodium laurilsulphate, magnesium stearate, hypromellose, talc and titanium dioxide E171. The tablets are packed in blister of PVC/Al or PVC/PVdC/Al or bottles of HDPE with polypropene closures.

II.2 Drug Substance

Ibuprofen has a monograph in the Ph Eur.

Ibuprofen is a white, crystalline powder or colourless crystals which is practically insoluble in water. Reference is made to two Certificates of Suitability regarding the drug substance.

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 film-coated tablet is formulated using excipients described in the current Ph Eur. Raw materials used in the product are of vegetable origin or has in the case of lactose monohydrate 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 (EMEA/410/01).

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, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The application for Brufen is based on literature in the public domain, in accordance with Article 10.1.(a).ii of Directive 2001/83/EC.

Brufen contains ibuprofen, 200, 400 and 600 mg tablets. The pharmacodynamic, pharmacokinetic and toxicological properties of ibuprofen are considered well known. As ibuprofen 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.

III.2 Ecotoxicity/environmental risk assessment

No ERA was submitted, however Brufen is not considered to increase the risk to the environment beyond or above the risk that may be caused by other ibuprofen-containing products.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ibuprofen is an non-steroidal anti-inflammatory drug (NSAID), which in numerous clinical trials has shown anti-inflammatory, analgesic and antipyretic activity. The efficacy and safety profiles for ibuprofen are well established and ibuprofen is often used active (analgetic) reference comparator in pain trials. Ibuprofen was introduced on the market 1969.

IV.2 Pharmacokinetics

The pharmacokinetics of ibuprofen has been extensively studied; however there are a limited number of studies performed by the MAH. This is considered acceptable, given the extensive use of this product for decades.

The absorption is rapid and almost complete, due to the lipophilic nature of ibuprofen and because of a low first metabolism in addition, the bioavailability is high, approximately 80-90%. The peak serum levels are reached after 1-3 hours after administration of regular ibuprofen tablets. Food slows down the absorption, and it has also been observed that the S/R ratio for AUC and Cmax increases. The product information recommends ibuprofen to be administered with food, the main reason being to decrease upper gastric adverse events.

Ibuprofen has a small volume of distribution, a high degree of protein binding being approximately 99.5 %. Due to a saturation of the protein at higher doses, non-linear pharmacokinetics has been observed.

The metabolism of ibuprofen is via hepatic oxidation and glucuronidation. After oxidation, two major and two minor inactive metabolites are formed (2-hydroxy-ibuprofen and carboxy ibuprofen are major) and 1-hydroxy ibuprofen and 3-hydroxyibuprofen are minor). CYP2C8 and CYP2C9 have been identified as equally important for the transformation of the S-enantiomer and CYP2C8 most important for the R-enantiomer. Depending on the relative expression of these two enzymes (polymorphism), adds variability to the clearance of the two enantiomers. After glucuronidation, ibuprofen acylglucuronides are formed.

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. The total recovered amount is approximately 80 %.

Special populations

Children

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.

Elderly

The pharmacokinetic properties in elderly are comparable to young subjects, given that no renal or liver disease is present. In elderly subjects with mild renal impairment, an increase in the unbound concentrations of approximately 45 % has been observed.

Renal impairment

The mean free fraction in patients with severe renal impairment is 3 % but variable. The mean free fraction is approximately 1% in healthy subjects. The mean unbound concentration is increased compared with healthy subjects.

Hepatic impairment

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.

Interactions

Ibuprofen has been associated with interaction for the following groups or substances (examples, not a complete list): Anticoagulants, antihypertensives (such as ACE-inhibitors, angiotensin II antagonists, betablockers, diuretics), corticosteroids, cardiac glycosides, cyclosporine, lithium salts and methotrexate, tacrolimus, anti-platelet agents and selective serotonin reuptake inhibitors, aminoglycosides, magnesium hydroxide, Ginkgo biloba, COX-2

inhibitors, other NSAIDs and aspirin. Also pharmacokinetic interactions due to inhibition of CYP2C9 may occur.

IV.3 Pharmacodynamics

NSAIDs inhibit cyclooxygenase (COX), thereby inhibiting prostaglandin production, Two COX isoenzyrnes are known to be involved in prostaglandin synthesis, COX-l and COX-2. COX-l is constitutively expressed and generates prostaglandins believed to be involved in GI mucosal protection, whereas at sites of inflammation throughout the body, COX-2 is induced to generate prostaglandins believed to mediate inflammation and pain. The anti-inflammatory effects of nonselective NSAIDs therefore seem to be mediated via inhibition of COX-2, whereas the deleterious effects in the GI tract are believed to occur primarily via inhibition of COX-1. It is stated in the literature that the S-enantiomer of ibuprofen has approximately a two-fold potency over the racemate.

In common with other NSAIDs, ibuprofen possesses platelet anti-aggregatory properties by virtue of its prostaglandin synthesis-inhibiting properties.

IV.4 Clinical efficacy

Studies showing satisfactorily efficacy in rheumatoid arthritis, osteoarthritis, dysmenorrhoea with no organic cause, pain of mild moderate intensity in doses according to the product information have been presented.

IV.5 Clinical safety

Clinical studies (a selection of these are cited in the efficacy section above) and clinical experience of ibuprofen has shown this NSAID to be comparatively well tolerated in short-term as well as long-term use. Adverse events reported from clinical trials and post-marketing experience have mainly been gastrointestinal in nature and include nausea and vomiting, diarrhea, dyspepsia and abdominal pain. Other adverse events less commonly reported affect the nervous system (headache, dizziness), the immune system (allergic reactions including rash, pruritus and urticaria) or the renal system.

There are data suggesting that the use of ibuprofen in high doses in long term treatments may be associated with arterial trombotic events.

A large epidemiological study in the US (Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. JAMA 1995;273:929-933) included 27948 children treated with ibuprofen 5mg/kg and 27837 children treated with ibuprofen 10 mg/kg. The authors conclusion was that there were no increased risk of hospitalization for gastrointestinal bleeding, renal failure, or anaphylaxis was not increased following short-term use of ibuprofen in children. These data, however, did not provide any information on the risks of less severe outcomes or the risks of prolonged ibuprofen use.

Relevant safety information is included in the product information of Brufen.

Risk management plan

Ibuprofen is a well known substance with clinical experience since the end of 1960s. Routine pharmacovigilance is considered sufficient for this known active substance. No additional pharmacovigilance activities or risk minimization activities are planned, which is endorsed.

DDPS

The RMS considers that the Pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

IV.6 Discussion on the clinical aspects

Ibuprofen is one of the most widely used NSAIDs and its efficacy level in treating mild to moderate pain conditions and fever is well documented. Being an NSAID it possesses the ability to elicit all the adverse reactions related to its class but in clinical practice it has shown to be comparatively well tolerated.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Numerous studies and long clinical experience has demonstrated that ibuprofen effective in treating pain and fever both in the paediatric and adult population. However, belonging to the NSAID group of drugs there are a number of condition where such drug must be used with care. These are adequately covered in the proposed Brufen SPC. For short term use and in low doses ibuprofen can be considered to have one of the more benign safety profile of all available NSAIDs.

User testing of the package leaflet has been performed and is acceptable.

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

VI. APPROVAL

The Mutual recognition for Brufen 200, 400 and 600 mg film-coated tablets was successfully finalised on 2009-10-26.

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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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se