LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Brufen Retard prolonged release tablet 800 mg
Brufen oral suspension 20 mg/ml
(ibuprofen)

SE/H/912/04-05/MR

This module reflects the scientific discussion for the approval of Brufen Retard 800 mg and Brufen oral suspension 20 mg/ml. The procedure was finalised at 2011-05-06. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Abbott Scandinavia AB has applied for a marketing authorisation for Brufen Retard, prolonged release tablets, 800 mg and Brufen oral suspension 20 mg/ml. The active substance ibuprofen is the same as in “Brufen 200, 400 and 600 mg tablets, marketed by “Abbott Scandinavia AB since 1975. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Brufen Retard and Brufen are presented in the form of prolonged release tablets and an oral solution, respectively containing 800 mg respective 20 mg/ml of ibuprofen.
The excipients in the prolonged release tablets are xantahn gum, povidone, stearic acid, colloidal anhydrous silica, isopropyl alcohol, hypromellose, talc, titanium dioxide, purified water and industrial methylated spirit.
The excipients in the oral solution are methyl parahydroxybenzoate, propyl parahydroxybenzoate, citric acid monohydrate, kaolin light, glycerol, sorbitol liquid non crystallising, sucrose ,sodium benzoate, sunset yellow (E110), orange flavour and polysorbate 80.
The prolonged release tablets are packed in opaque PVC/aluminium blisters or white HDPE bottles closed with white polypropylene screw caps.
The oral solution is filled in amber PET bottles closed with a polypropylene cap or an aluminium cap.

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, freely soluble in dichloromethane, ether and methylene chloride. 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

Brufen Retard and Brufen are formulated using excipients described in the current Ph Eur, except for Sunset yellow and the orange flavour in the oral solution. These excipients are controlled according to acceptable in house specifications. The colouring agent Sunset yellow

also complies with the requirements of the UK Colouring Matter in Food Regulations 1973, S.I. 1340, with the EEC specification E110 and the requirements in Commission Directive 95/45/EC. In the prolonged release tablets is industrial methylated spirit controlled according to acceptable BP 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.

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

The tests and limits in the specifications are considered appropriate to control the quality of the finished products 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 for the prolonged release tablets and with no special storage precautions for the oral solution.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Brufen contains ibuprofen, 800 mg prolonged release tablets and oral suspension 20 mg/ml.

III.2 Pharmacology

The pharmacodynamic, pharmacokinetic and toxicological properties of ibuprofen are 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.3 Pharmacokinetics

See Section III.2

III.4 Toxicology

See section III.2.

III.5 Ecotoxicity/environmental risk assessment

Brufen is not considered to increase the risk to the environment beyond or above that which may be caused by other ibuprofen-containing products.

III.6 Discussion on the non-clinical aspects

There are no objections to approval of Brufen Retard 800 mg prolonged release tablets and Brufen oral suspension 20 mg/ml from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

IV.2 Pharmacokinetics

Brufen Retard prolonged release tablets 800 mg

In total 11 studies have been performed to evaluate the absorption of the Ibuprofen Retard 800 mg prolonged release tablet, including steady state pharmacokinetics, influence of food, dose proportionality and possible differences in absorption between batches of different release rates. In addition one study on the pharmacokinetics in elderly and one in the target population was performed. The analytical methods were summarised by the company and although they are old reports, the methods seem to have an acceptable performance. The company states a justification that the formulation manufactured today is the same as used in the pharmacokinetic studies with the exception of the removal of printing ink.

The most important conclusion from the absorption studies are that the prolonged release tablet seem to have a distinct profile apart from the immediate release tablets, justifying the possibility to administer once daily. The specification limits used showed that the fast and slow tablets were bioequivalent. There was likely an inhibition of gastric emptying after intake with food, resulting in higher but more slowly attained peak concentrations. Although little data, the extent of absorption does not seem to be affected with high fat food, although in some subjects, the tablets may remain for a prolonged period in the stomach. No dose or time-dependency in the pharmacokinetics of ibuprofen was evident. The pharmacokinetics of the prolonged release tablet was similar in young and elderly patients, although the elderly group included a limited number of subjects above 75 years of age.

The distribution and elimination section has been investigated since before and is not expected to show any differences compared to tablets. The interaction section proposed in the product information is identical to the one of Brufen tablets.

Brufen oral suspension 20 mg/ml

One four-way cross-over study evaluating the bioavailability of the oral suspension was performed. Bioequivalence between the oral suspension (denoted syrup in the study report) and immediate release 400 mg tablets was shown (90 % confidence interval within 0.8-1.25 for both AUC and Cmax). Bioequivalence is also shown with and without food.

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.

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

IV.4 Clinical efficacy

Brufen Retard prolonged release tablets 800 mg
The use of ibuprofen for symptomatic treatment of rheumatoid arthritis and arthrosis can be considered well established practice. The prolonged released tablet has been demonstrated to have a pharmacokinetic profile that allows a once daily treatment regimen. The recommended posology reflects the doses found effective and safe in clinical studies. The safety is comparable with ibuprofen tablets in the same dose range.

Brufen oral suspension 20 mg/ml
The use of ibuprofen for treatment of rheumatoid arthritis, arthrosis, dysmenorrhoea with no organic cause and general pain of mild to moderate intensity in adults can be considered well established practice. For patients having difficulties taking Brufen tablets, the oral suspension will become a more appropriate alternative.
The use of ibuprofen for treatment of pain and fever in children can be considered well established practice. Both the studies performed during the development program and after its wide-spread approvals in most countries have demonstrated that ibuprofen is at least as effective and safe as paracetamol. Some studies indicate that ibuprofen could be marginally superior.

The oral suspension does not differ in any aspects related to efficacy and safety compared with the tablets. The recommended paediatric doses in this application reflect the effective doses found in clinical studies.

IV.5 Clinical safety

See section IV.4.

IV.6 Discussion on the clinical aspects
The overall benefit/risk of the use of Brufen Retard 800 mg and Brufen oral suspension 20 mg/ml for the proposed indications is considered positive.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Brufen 200 mg, 400 mg and 600 mg film-coated tablets SE/H/912/01-03/MR. The bridging report submitted by the applicant has been found acceptable.

The risk/benefit ratio is considered positive and Brufen Retard 800 mg, prolonged release tablets and Brufen 20 mg/ml oral suspension are recommended for approval.

VI. APPROVAL

The Mutual recognition procedure for Brufen Retard 800 mg, prolonged release tablets and Brufen 20 mg/ml oral suspension was successfully finalised on 20110506.

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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)

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