

Public Assessment Report

Scientific discussion

**Ibuprofen 400 mg/100 ml solution for infusion &
Ibuprofen 600 mg/100 mL solution for infusion**

Ibuprofen arginine

ES/H/0390/001/DC

ES/H/0392/001/DC

Applicant: B. Braun Melsungen AG

Registration number in Spain:xxx

This module reflects the scientific discussion for the approval of **Ibuprofen 400 mg/100 mL and Ibuprofen 600 mg/100 mL solution for infusion**. The procedure was finalised on January 2017. For information on changes after this date please refer to the module -Updateø



INTRODUCTION

This decentralised application concerns a hybrid application according to the Article 10(3) of Directive 2001/83/EC as amended of ibuprofen arginine, under Ibuprofen 400 mg/100 ml solution for infusion and Ibuprofen 600 mg/100 ml solution, trade names claiming essential similarity with the innovator product Dalsy film-coated tablets by Abbot Laboratories, S.A. Dalsy film-coated tablets have been registered since October 1979 in Spain.

With Spain as the Reference Member State in this Decentralized Procedure, B. Braun Melsungen AG. is applying for the Marketing Authorisations for Ibuprofen 400 mg/100 ml solution for infusion and Ibuprofen 600 mg/100 ml solution for infusion in:

- ES/H/0390/001/DC and ES/H/0392/001/DC: AT, BE, BG, CZ, DE, DK, EE, FI, FR, HU, IE, IT, LT, LU, LV, NL, NO, PL, PT, RO, SE, SI, SK and UK.

The efficacy and safety of ibuprofen has been demonstrated in several studies conducted with the reference product as well as with its use experience after placed in the market. Ibuprofen 400 mg/100 ml solution for infusion and Ibuprofen 600 mg/100 ml solution for infusion for infusion are submitted under an abridged application and no studies regarding pharmacology, pharmacokinetic, security and efficacy has been carried out besides the bioequivalence studies against the reference product.

The indication is for the short-term symptomatic treatment of acute moderate pain, and for the short-term symptomatic treatment of fever in adults, when administration by intravenous route is clinically justified when other routes of administration are not possible.

A comprehensive description of the product information is given in the SmPC.

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for **Ibuprofen 400 mg/100 ml solution for infusion and Ibuprofen 600 mg/100 ml solution for infusion.**

I. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

Drug substance

The active substance Ibuprofen is described in Ph. Eur. and covered by a CEP.

Ibuprofen is a white or almost white, crystalline powder or colourless crystals, practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates. BCS Classification: Class II (Low solubility ó High permeability).

Drug Product

The finished product is formulated as a clear and colorless to pale yellow medicated solution for infusion, free of foreign particles, containing Ibuprofen (arginate) as active substance at the concentrations of:

- 4 mg per ml (Ibuprofen 400 mg/100 ml solution for infusion).
- 6 mg per ml (Ibuprofen 600 mg/100 ml solution for infusion).

The development of the product has been adequately described. The choice of excipients is justified.

The compatibility of the drug substance with the excipients has been analyzed.



All the manufacturers involved in the different steps of the drug product manufacture have been included.

The industrial batch size of both strengths and the manufacturing formulae are detailed.

A flow chart and a narrative description of the manufacturing process, indicating in process controls, have been included. Critical steps are identified and in-process controls adequate. Process validation on industrial batches is presented.

Excipients are adequate and correct for their function in the formulation. Their specifications are according their respective Ph. Eur. monographs. Documentation presented guarantees the absence of TSE/BSE risk.

Drug product specifications are considered appropriate. They include critical parameters and limits are adequately justified.

Analytical methods are adequate for the parameters to control, correctly described and their validation is according to ICH. Analytical data from three industrial batches are presented and they fulfil specifications. Proposed reference material is adequately certified. Impurities reference standards have been presented.

Proposed packaging material is adequate for the proposed dosage form and coincides with the one used in the stability studies.

Stability data are in accordance with ICH guidelines. The proposed shelf-life can be accepted.

II-2 Non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology of the active substance has been provided, which is based on up-to-date and adequate scientific literature.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate and the Member States agreed that no further non-clinical studies are required.

Environmental Risk Assessment (ERA)

Environmental Risk Assessment of ibuprofen based on publications and studies (phase I and II) were presented. The applicant concluded that ibuprofen is not expected to have any environment risk

II.3 Clinical aspects

Introduction

Ibuprofen arginine is a well-known drug with established efficacy and safety.

No new clinical efficacy or safety studies were conducted, which is acceptable for this abridged application. A clinical overview has been provided, which is based on scientific literature. The Member States agreed that no further clinical studies are required.

For this application, the MAH has submitted a bioequivalence study, which is discussed below.

Biowaiver

In vivo bioequivalence was investigated between Ibuprofen Farmalider 100 mg/ml concentrate for solution for infusion after dilution of 6 ml of this product in an infusion bag of 100 ml versus Espidifen 600 mg granulate for oral solution. The evidence obtained in that study is extrapolated to the applied product Ibuprofen Farmalider 600 mg/100 mL solution for infusion, which facilitates the administration since it does not need to be diluted before administration.

Ibuprofen Farmalider 600 mg / 100 ml has the same qualitative composition and the same route of administration as Ibuprofen Farmalider 100 mg/ml concentrate for solution for infusion that



tested in the submitted bioequivalence study. Therefore, there are no excipients which may alter the pharmacokinetic or pharmacodynamic profile of ibuprofen. The pH and osmolarity properties are not affected significantly as compared to Ibuprofen Farmalider 100 mg/ ml concentrate for solution for infusion.

The only difference between these two products (Ibuprofen Farmalider 100 mg/ml concentrate for solution for infusion and Ibuprofen Farmalider 600 mg/100 mL solution for infusion) is concentration at the time of administration. After dilution in 100 mg of injectable solution, the final concentration is 600 mg in 106 ml (5.66 mg/ml), while the concentration in the products subject of this application is 6 mg/mL. However, the strength is the same, i.e. 600 mg, and the time of the infusion is also the same (30 min). Therefore, the bioavailability is the same.

The second strength that is applied, Ibuprofen Farmalider 400 mg/100 mL solution for infusion, is waived based on its composition proportionality since it is considered to be equivalent to the reference product Espidifen 400 mg granulate for oral solution

Therefore, the results of the bioequivalence study are also applicable to Ibuprofen 400 mg and 600 mg solution for infusion.

Bioequivalence

To support the application, the Applicant has submitted one bioequivalence study òa Phase I clinical trial, single dose, randomised, open label, two treatments, two periods, two sequences cross-over design after a single dose administration to healthy fasted volunteersö.

As the metabolic profile of ibuprofen is the same irrespective of the route of administration, intravenous or oral, the demonstration of pharmacokinetic bioequivalence could be considered sufficient for the approval of this product.

The assessment of the active metabolites would be necessary since this is a different route of administration but none is considered active (please refer to Adams SS, Bough RG, Cliffe EE, et al. Some aspects of the pharmacology, metabolism and toxicology of ibuprofen. *Rheumatol Phys Med* 1970; Suppl. 9: 9-26 and Neal M. Davies. *Clinical Pharmacokinetics of Ibuprofen (The First 30 Years)*. *Clin Pharmacokinet* 1998 Feb; 34 (2): 101-154). Therefore, minor differences in the metabolic exposure are considered irrelevant.

In conclusion, the approach employed by the applicant based on a single dose study in fasting state study showing bioequivalence for the parent drug is acceptable because the administration of the reference product is irrespective of food intake. Therefore, a single dose study under fasting conditions is considered the most sensitive design to detect differences between the applied product and the reference product.

The Clinical part of the study was performed from January 17th, 2014 to February 04th, 2014 at the Clinical Trials Unit, Hospital Central de la Defensa Gómez Ulla. Glorieta del Ejército, 1, Madrid, Spain.

The analytical portion was conducted at Bioanalysis and Metabolism Department of Kymos Pharma Services S.L. C/Bardiri i Reixac, 10-12. Parc Científic de Barcelona. 08028 Barcelona from February 07th, 2014 to February 27th, 2014.

Design

Phase I clinical trial, single dose, randomised, open label, two treatment, two period, two sequence cross-over design in healthy, adult, human subjects under fasting with a wash-out period of at least 3 days

The study design as a single dose study is acceptable to compare an intravenous product to an oral immediate release formulation (granules for oral solution) since it is more sensitive to detect differences than multiple dose studies. In addition, the administration of the reference product is irrespective of food intake. Therefore, a single dose study under fasting conditions is considered acceptable.



The measurement of the parent drug only is considered enough because the metabolic profile of ibuprofen is known to be similar by both routes of administration and ibuprofen does not have active metabolites.

The wash-out period of at least 3 days (more than five times the half-lives) is considered adequate since the drug has a half-life of approximately 2 hours.

Considering the expected time to peak concentration and the elimination half-life, the sampling schedule and the sampling time period of 12 hours seems long enough to estimate PK parameters.

Test product: Ibuprofen 600 mg/ 6 mL concentrate for solution for infusion manufactured by Braun Medical, S.A., Spain. Batch number: LP-01. Batch size: 500 litres. Proposed batch size: 500-2,000 litres. Expiry date (Retest day): May 2014. Assay (content): 99.2% of label claim.

Reference product: Espidifen 600 mg granules for oral solution manufactured by Zambon, S.A.U. from the Spanish market. Batch number: 325746. Expiry date: August 2016. Assay (content): 98.17% of label claim.

The reference product is adequate with regards to expiry date, content and it was obtained from Spanish market.

All batches were tested before expiry date and a similar content of active substance is shown. Therefore, content correction is not necessary.

A total of twenty four (24) subjects (12 men and 12 female) were enrolled and randomised to a treatment sequence in accordance with the study protocol. All of them completed the study and were included in the pharmacokinetic and safety analysis.

For test treatment (Ibuprofen [arginate] IV), after fasting for at least 10 hours, the drug was administered intravenously after its dilution in saline solution (by an infusion pump) during 30 minutes, and fasting for 5 hour after administration started.

For reference treatment (Espidifen) after fasting for at least 10 hours, the drug was administered orally, dissolved in 240 ml of water. The volunteers were under fasting condition for 5 hours after administration.

The study population is considered acceptable with regards to demographic characteristics. The inclusion and exclusion criteria are considered to be acceptable.

Analytical methods

The analytical method has been adequately validated before the conduct of the study and during the analysis of the subject samples. Therefore, the analytical method is considered acceptable for analysis of the plasma samples.

Pharmacokinetic data analysis

Pharmacokinetic parameters were calculated using a non-compartmental method with acceptable software. AUC was calculated by the trapezoidal rule. The methods used in this study for the pharmacokinetic calculations are considered acceptable.

According to the Guideline on investigation in bioequivalence, the evaluation of bioequivalence was based upon measured concentrations of both analytes (R- and S-ibuprofen) as the following conditions are fulfilled: (1) the enantiomers exhibit different pharmacokinetics (2) the enantiomers exhibit pronounced difference in pharmacodynamics (3) the exposure (AUC) ratio of enantiomers is modified by a difference in the rate of absorption.

Statistical analysis

The pharmacokinetic data were analysed by the statistical package integrated in the PROC GLM of WinNonlin Professional Software Version 2.0 using the analysis of variance (ANOVA) of the logarithmically transformed kinetic parameters AUC and C_{max} and the application of 90% confidence intervals. This ANOVA takes 4 factors into account: sequence, subjects (sequence), period and formulation.



Following EMA criteria, the two formulations were classified as bioequivalent if the standard 90% confidence intervals of the pharmacokinetic parameters (AUC_{0-t} and C_{max}) with log transformation are within the 80.00-125.00 range.

Results

The 90% confidence intervals mean treatment T/R ratios are shown in the following table (N=24):

	Ibuprofen (arginate) IV vs Espidifen®			
	R-Ibuprofen		S-Ibuprofen	
	Ratio	CI 90%	Ratio	CI 90%
$\ln AUC_{0-\infty}$	92.79	84.29 - 102.13	90.56	85.42 - 96.01
$\ln AUC_{0-t}$	92.80	84.29 - 102.18	90.36	85.17 - 95.87
$\ln C_{max}$	93.00	82.99 - 104.22	98.55	87.94 - 110.45
$\ln t_{1/2}$	102.14	95.26 - 109.52	101.77	94.63 - 109.45

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference with respect to the extent and rate of absorption/exposure as for ibuprofen the 90% confidence intervals for the ln-transformed C_{max} and AUC_{0-t} are within the acceptance range of 80-125%.

Risk Management Plan

A risk management plan in accordance with the requirements of Directive 2001/83/EC as amended has been submitted.

No additional risk minimization activities were required beyond those included in the product information.

Discussion on the clinical aspects

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference product.

Efficacy and safety of the active substance ibuprofen is well documented for the reference medicinal product. The design of the submitted bioequivalence study is adequate and the results allow us to conclude bioequivalence with the reference.

III OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bioequivalence has been shown to be in compliance with the requirements of European Union guidance documents.

The SmPC, PIL and labelling are considered satisfactory and consistent with the information for the reference medicinal product. The user testing of the Package Information Leaflet has been tested in accordance with Article 59(3) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.



The benefit/risk balance was considered to be positive.

Agreement between Member States was reached during the procedure. The decentralised procedure was finalised with a positive outcome in January 2017.