Public Assessment Report
Scientific discussion

Ibuprofen Idifarma 4 mg/mL solution for infusion

Ibuprofeno

ES/H/0256/001/DC

Applicant: Idifarma, Desarrollo Farmacéutico, S.L.

Registration number in Spain: 79.755

This module reflects the scientific discussion for the approval of **Ibuprofen 4 mg/mL solution for infusion.** The procedure was finalised on March 2015. For information on changes after this date please refer to the module ôUpdateô.

INTRODUCTION

This decentralised application concerns a ñhybrid applicationò according to the Article 10(3) of Directive 2001/83/EC as amended of ibuprofen, under Ibuprofen Idifarma 4 mg mL solution for infusion, trade name claiming essential similarity with the innovator product Nurofen® 200 mg tablets, MAH Reckitt Benckiser Healthcare (UK) Ltd, first authorised in May 06th, 1983 in UK (PL-00327/0004).

With Spain as the Reference Member State in this decentralised procedure, Idifarma, Desarrollo Farmacéutico, S.L. is applying for the Marketing Authorisations for Ibuprofen Idifarma 4 mg/mL solution for infusion in DE.

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 Idifarma 4 mg/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 ï High permeability).

Drug Product

The finished product is formulated as a solution for infusion containing 4 mg/mL Ibuprofen and packed in 100 ml Type I glass vials, with prewashed bromobutyl rubber stopper and flip-off of aluminium cap.

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 and the manufacturing formula 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 at pilot scale is performed, and a commitment on validation of the manufacturing process at commercial scale has been submitted.

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 pilot 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 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
Not applicable as the 4 mg/mL solution for infusion is tested in vivo.

Bioequivalence

To support the application, the Applicant has submitted one bioequivalence study (study report No. IDI-001) ña comparative randomized, open label, multiple dose, two-treatment, two-sequence, two-period crossover study to determine the bioequivalence of two formulations of ibuprofen: Ibuprofen 4 mg/ml solution for infusion vs. Nurofen® Express Soluble 400 mg Oral Powder in healthy volunteers under fasting conditions

The study was also conducted to compare the safety profile of the two formulations in healthy volunteers after multiple doses as this is the dosing regimen generally used to achieve an adequate therapeutic response.

The design of this study was discussed with the AEMPS in a scientific advice meeting held in September 12th, 2012. According to the AEMPS, a multiple-dose comparative bioavailability study was more adequate than a single dose study to demonstrate similar pharmacokinetics of the intravenous Test formulation vs. an orally administered Reference formulation to rule out the probability of drug accumulation with the intravenous formulation and assess the safety of the product in normal conditions of use.

The application concerns a solution for infusion and the BE study has been carried out versus the oral formulation, which can be taken irrespective of food intake; therefore a 2x2 cross-over

study under fasting conditions is considered acceptable to demonstrate bioequivalence with the brand leader.

The use of a dose of 400 mg with this 4 mg/mL unit containing 100 mL (equivalent to an oral dose of 400 mg) is adequate since it is a therapeutic dose and there is no safety concerns. Higher doses exhibit a less than proportional increase due to saturation protein binding with less sensitivity to detect differences between products.

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.

The clinical part of the study was conducted at the Clinical Investigation Unit, Navarra University Clinic, Segunda Planta, Avenida Pío XII, 36, 31008 Pamplona (Spain) between June 12th, 20013 and August 01st, 2013 and the principal investigator was Dr. Belén Sádaba.

Sample analysis was performed at DynaKin, S.L. Parque Tecnológico de Bizkaia. Ed.801-B First floor, 48160 Derio, Bizkaia, (Spain), between August 07th, 2013 and August 27th, 2013.

Design

A comparative randomized, open label, comparative, multiple doses, two-treatment, two sequence, cross-over study to assess comparative bioavailability of two ibuprofen formulations (IV vs. Oral) in healthy volunteers under fasting conditions with a washout period of 12 days.

The wash-out period of at least 12 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 6 hours seems long enough to estimate PK parameters.

Test Product: Ibuprofen 4 mg/mL solution for infusion, manufactured by Solupharm, Germany. Batch number: 10/02B. Batch size: 450 litres. Expiry date (analysis date): August 2013 (as per CoA). Assay (content): 98.3 % of label claim.

Reference Product: Nurofen® Express Soluble 400 mg Oral Powder, manufactured by Farmacodinamicas, S.A. (Fardi; from the UK market). Batch number: 12F236. Expiry date: August 2015. Assay (content): 97.4% of label claim.

The reference product is adequate as it is an IR oral dosage form of an innovator ibuprofen product. The reference product was approved according to article 8.3 (complete dossier) of 2001/83/EC on UK (date of approval of Nurofen® tablet was May 6th, 1983).

Both batches were tested before expiry date and the CoA shows a similar content. Therefore, content correction is not necessary.

Mode of administration

Subjects fasted overnight for at least 10 hours prior to drug administration. The following two investigational medicinal products (IMP) were used in this clinical investigation:

- Test Product: Ibuprofen 4 mg/ml solution for injection. 1 vial of 100 ml equivalent to a dose of 400 mg of ibuprofen was administered as a 1-hour intravenous infusion.
- Reference Product: Nurofen® Express Soluble 400 mg Oral Powder. One sachet was dissolved in 240 ml water.

Each subject received a total of 9 doses of both products during each study period.

Doses were separated by an interval of 6 hours. At the time of administration, the subjects should be sitting semi-recumbent (i.e. upright) in bed.

Based on the multiple dose regimen administered and the elimination half-live (approx. 2 hours) it is considered that the steady state was reached.

A total of 20 (12 male + 8 female) subjects were considered sufficient for achieving the objectives of the study. No subject was discontinued from the trial prematurely. All enrolled subjects completed the study for two periods and were analyzed and included in the statistical analysis.

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

The plasma pharmacokinetics of S-Ibuprofen and R-Ibuprofen were profiled for up to 6 hours after multiple doses of 400 mg Ibuprofen administered by infusion (treatment T) or by oral intake (treatment R).

The table below shows a list of the pharmacokinetic parameters assessed in this study and their definitions. The time courses of the plasma concentrations were analyzed by non-compartmental methods.

Primary PK parameters: Bioavailability will be tested based on the primary evaluable PK parameters	
Primary evaluable PK parameter	
$AUC_{(0\text{-}T,SS)}$:	Area under the plasma ibuprofen concentrations during a dosage interval at steady state
Primary PK parameter	
$C_{max,ss}$	Observed maximum plasma concentration at steady state
Secondary PK parameters	
$T_{max,ss}$	Time until $C_{max,ss}$ is reached
$C_{min,ss}$	Observed minimum steady-state plasma concentration (trough)
$T_{min,ss}$	Time of $C_{min,ss}$
C_{avg}	Average plasma concentration
%fluctuation	$100*(C_{max,ss} - C_{min,ss}/C_{avg})$

The selected pharmacokinetic variables ($AUC_{0\text{-}\tau ss}$ and $C_{max,ss}$) are appropriate for a multiple dose bioequivalence study of an IR formulation, but taking into account that this is a new route of administration the other PK parameters are also very relevant.

Statistical analysis

Log transformed $AUC_{0\text{-}\tau ss}$ and $C_{max,ss}$ was subject to an analysis of variance.

Differences between treatments with respect to $AUC_{0\text{-}\tau ss}$ and $C_{max,ss}$ was assessed using mixed random effects ANOVA model (WinNonlin version 6.2). The terms used in the ANOVA model was sequence, treatment and period as fixed effect whereas subject within sequence was considered as a random factor.

The acceptance range was 80 ï 125%, for the primary evaluable parameter $AUC_{0\text{-}\tau ss}$ and $C_{max,ss}$ (log transformed).

Bioequivalence between the two products would be shown if for $AUC_{0-\tau ss}$ and $C_{max,ss}$ the 90% confidence interval for the ratio of population geometric means based on log-transformed data, was included in the range of 80% to 125%.

The statistical software and method is considered acceptable.

Using mixed random effects of WinNonlin version 6.2 is acceptable as only subjects with observations in both treatment were used (there were no missing data)

ANOVA analysis has been performed correctly (sequence, period and treatment as fixed factor and subject [nested within sequence] as random factor).

Results

The evaluation of the bioequivalence $AUC_{0-\tau ss}$ and $C_{max,ss}$ for S- and R-Ibuprofen is presented below:

	S-Ibuprofen			R-Ibuprofen		
	Ratio	**Lower bound CI 90%**	**Upper bound CI 90%**	**Ratio**	**Lower bound CI 90%**	**Upper bound CI 90%**
Ln($AUC_{0-T,SS}$)	91.99	88.53	95.58	107.79	99.65	116.61
Ln($C_{max,ss}$)	90.86	86.59	95.34	101.27	95.09	107.84
Ln(Tmax,ss)	NC	NC	NC	NC	NC	NC
Ln(Cmin,ss)	99.69	93.92	105.82	88.93	80.32	98.47
Ln(tmin,ss)	NC	NC	NC	NC	NC	NC
Ln(Cavg)	108.71	104.62	112.95	101.27	95.09	107.84
Ln(%fluctuation)	103.11	98.33	108.13	109.40	101.81	117.55

NC: Not calculated

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 S- and R-Ibuprofen the 90% confidence intervals for not only the ln-transformed $AUC_{0-\tau ss}$ and $C_{max,ss}$, but also for $C_{min,ss}$ and fluctuation 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 March 2017.