



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2020
EMA/516696/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 29(4) of Directive 2001/83/EC

Ibuprofen Kabi 400 mg Infusionslösung and associated names:

INN: ibuprofen

Procedure number: EMEA/H/A-29(4)/1498

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us

Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

An agency of the European Union



Table of contents

1. Information on the procedure	3
2. Scientific discussion	3
2.1. Introduction	3
2.2. Assessment of the issues raised as a potential serious risk to public health during the referral	4
3. Benefit-risk balance	6
4. Grounds for Opinion	6

1. Information on the procedure

An application was submitted under the decentralised procedure for Ibuprofen Kabi 400 mg Infusionslösung and associated names, 400mg/100ml solution for infusion on 30 November 2018.

The legal basis under which the application was submitted is Article 10(3) of Directive 2001/83/EC (hybrid application).

The application was submitted to the reference Member State (RMS): Germany and the concerned Member States (CMSs): Austria, Belgium, Czech Republic, Hungary, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and United Kingdom.

The decentralised procedure (DCP) DE/H/6050/001/DC started on 29 January 2019.

On day 210, major issues on safety, raised by the Netherlands, as set out under section 2.1 below, remained unsolved; hence the procedure was referred to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), under Article 29(1) of Directive 2001/83/EC by Germany on 12 December 2019. The CMDh 60 Day procedure was initiated on 06 January 2020.

Day 60 of the CMDh procedure was on 05 March 2020, and as no agreement could be reached, the procedure was referred to the CHMP according to Article 29(4) of Directive 2001/83/EC.

On 16 March 2020 the RMS Germany therefore triggered a referral under Article 29(4) of Directive 2001/83/EC.

2. Scientific discussion

2.1. Introduction

Ibuprofen is a propionic acid derivative with analgesic, anti-inflammatory and anti-pyretic activity. The drug's therapeutic effects are thought to result from its inhibitory effect on the enzyme cyclooxygenase, which results in a marked reduction in prostaglandin synthesis.

Ibuprofen (intravenous) is indicated in adults

- for the short-term symptomatic treatment of acute moderate pain, and
- for the short-term symptomatic treatment of fever,

when administration by intravenous (IV) route is clinically justified and when other routes of administration are not possible.

Background information on the dossier and the DCP procedure

The procedure concerns a hybrid application for a marketing authorization for Ibuprofen Kabi 400mg/100ml intravenous solution for infusion submitted under Article 10(3) of Directive 2001/83/EC. The reference medicinal product (RefMP) is Espidifen 400 mg granules for oral solution from Zambon, S.A.U, approved in Spain in 03 December 2006, and withdrawn in the meantime on 26 May 2014.

The Article 10(3) application for Ibuprofen Kabi 400 mg/100 ml solution for infusion was submitted to introduce a different pharmaceutical form, route of administration, and therapeutic indications vis-à-vis the EU reference medicinal product.

In this application the applicant made reference to another ibuprofen 400 mg/100 ml solution for infusion, which has also been authorized according to Article 10(3) of Directive 2001/83/EC and had the same RefMP as Ibuprofen Kabi 400 mg/100 mL solution for infusion. For the application related to

the authorized product a bridge was established to the RefMP (Espidifen, granules for oral solution) with a comparative bioequivalence (BE) study.

No comparative bioavailability study comparing Ibuprofen Kabi 400 mg/100 mL solution for infusion with the EU reference medicinal product has been conducted.

In support of the efficacy and safety of Ibuprofen Kabi 400 mg/100 mL solution for infusion, the applicant also submitted extensive published literature for intravenous ibuprofen preparations, in particular with the product Caldolor (IV ibuprofen product approved in the US in 2009).

The proposed SmPC for Ibuprofen Kabi 400mg/100ml solution for infusion is consistent (e.g. indications, duration of infusion) with the SmPCs of other IV Ibuprofen formulations. In the SmPC it was also taken into account the latest published information on safety and efficacy of medicinal products containing ibuprofen.

About the objecting Member State's grounds for refusing the application for marketing authorisation

The objecting Member State (MS), the Netherlands (NL), was of the opinion that a positive benefit-risk balance had not been established for the product applied for due to missing bridging data between Ibuprofen Kabi 400 mg/100 mL solution for infusion and the RefMP, and as such there was no reassurance regarding being able to rely on the relevant data in the dossier of the reference product. Accordingly, the pre-clinical and clinical data related to the active substance ibuprofen, as provided in the dossier of this applicant, should be considered insufficient. NL requested a referral to the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). As no agreement could be reached during the CMDh procedure, the unresolved issue, which was considered to be a potential serious risk to public health (PSRPH) by the Netherlands, was referred to the CHMP.

2.2. Assessment of the issues raised as a potential serious risk to public health during the referral

Summary of the applicant's position

The applicant was requested during the decentralised procedure and in the context of the present referral procedure to justify how the data and/or scientific rationale submitted enabled the bridging with the reference medicinal product as required for an hybrid application according to Article 10(3) of Directive 2001/83/EC and allowed to establish a positive benefit-risk balance for Ibuprofen Kabi 400 mg/100 ml solution for infusion.

The applicant justified the absence of a comparative study with the RefMP by referring to the Q&A – Generic Applications (CMDh/272/2009/Rev.4) which states that an application for marketing authorization based on an abridged dossier can refer to the complete dossier of a reference product (i.e. Espidifen, in this case) and in addition to clinical studies contained in a hybrid dossier. However, during the decentralized procedure, it was clarified to the applicant that in the context of this Q&A the clinical studies of the hybrid dossier that may be referred to should be those that resulted in new clinical data justifying differences of clinical particulars *versus* the reference medicinal product (e.g. new indication, strength, route of administration, pharmaceutical form).

The applicant reiterated their initial approach of referring to a BE study performed against the reference product Espidifen, as a valid approach to establish the bridging between Ibuprofen Kabi and Espidifen. The applicant is of the opinion that, even if reference to BE in the hybrid dossier is not possible, still sufficient data have been submitted for the bridging to the reference product and to draw a conclusion on the positive benefit-risk balance of the applied product.

The applicant recognised that in the course of a hybrid application the applicant relies on all or some of the results of pre-clinical tests and clinical trials generated for a reference product and thus has to justify or demonstrate the applicability of said data to its own product, if necessary by generating own clinical data.

The applicant is of the opinion that the requirement of the Notice to Applicants to provide appropriate data to bridge to the reference product can in this case be fulfilled by studies referenced in the literature, due to the vast experience gained so far with various ibuprofen formulations including also IV formulations.

Reference was also made to BE studies already performed for other intravenous ibuprofen formulations which, according to the applicant, provided more information on the efficacy and safety profile of IV ibuprofen than a new BE study conducted with the RefMP.

The applicant also presented a publication describing results of four single-dose comparative bioavailability studies in which a solution for intravenous administration was compared with Espidifen 400mg granules for oral solution. Additionally, the applicant provided literature data that investigated the efficacy and safety of IV ibuprofen, mainly with the medicinal product Caldolor but also with other IV ibuprofen products. Literature data comparing IV and other oral formulations was submitted as well.

Assessment of the issues raised

The active substance of Ibuprofen Kabi 400 mg/100 ml solution for infusion is ibuprofen, a well-known substance which has been in clinical use in the EU for oral administration for more than 50 years and available as an over-the-counter (OTC) product for more than 30 years in a large number of countries for the treatment of a number of self-limiting conditions including the symptomatic relief of mild to moderate pain and fever. Ibuprofen has a wide therapeutic range between 10 and 50 µg/mL, the toxic serum concentration being >100 µg/mL.

The use of ibuprofen in the inpatient or post-operative setting has previously been limited by the lack of a commercially available parenteral formulation. Meanwhile, several ibuprofen-containing solutions for infusion are available in the EU.

The Article 10(3) application for Ibuprofen Kabi 400 mg/100 ml solution for infusion was submitted to introduce a different pharmaceutical form, route of administration and indications compared to the EU reference medicinal product. A bridge to the reference medicinal product is needed to be able to rely on the appropriate results of pre-clinical tests and clinical trials generated with said RefMP. However, due to the different route of administration (the intravenous vs. the oral route), comparative bioavailability studies provide limited evidence on safety and efficacy and, consequently, have to be supported by additional data.

Ibuprofen Kabi 400mg/100ml solution was designed to be chemically, therapeutically and functionally equivalent to the other ibuprofen-containing solutions for infusion already approved in the EU. It has been shown that Ibuprofen Kabi 400 mg/ 100 ml solution for infusion and excipients are not expected to influence the delivery of ibuprofen and these products are administered over the same time period (30 minute infusion). In view of the similar composition of the different intravenous solutions and taking into account the Guideline on investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**) where it is stipulated that a BE study in general is not required in this case, no further studies are considered to be necessary for the application referred here.

The applicant provided published data showing that with infusion time adjusted to 30 minutes the 90% CIs of C_{max} and AUC are well within the limits of the acceptance range (80-125%) when comparing a solution for intravenous administration *versus* the reference medicinal product (i.a. Espidifen 400mg granules for oral solution, Zambon). The IV formulation used is comparable to the applied product

based on the comparison of the main quality characteristics. Based on this, the CHMP considered that a bridge between the applied product and the reference medicinal product is established, allowing to rely on non-clinical and clinical data of the latter.

In addition, the CHMP took note of several randomised, controlled clinical trials where were assessed the efficacy of IV Ibuprofen in different clinical settings where pain was the predominant symptom or fever as accompanying sign (Southworth et al [2009], Singla et al [2010], Kroll et al [2011], Bernard et al [1997], Morris et al [2010], Krudsood et al [2010], Promes et al [2011]. These studies have included over 1500 patients, out of which over 700 patients were treated with IV Ibuprofen solution (e.g., Caldolor).

Overall, sufficient data have been provided to support the differences *versus* the reference medicinal product (new route of administration, pharmaceutical form and indication), as well as to establish the reliance on pre-clinical and clinical data of the reference medicinal product.

The CHMP considered therefore that the efficacy and safety of the applied product in the proposed indication have been established.

3. Benefit-risk balance

The CHMP considered that sufficient data has been submitted to justify referring to data generated with the RefMP and additionally to published clinical trials for substantiating the safety and efficacy due to the differences with the RefMP.

The applicant provided published data showing that with infusion time adjusted to 30 minutes the 90% CIs of C_{max} and AUC are well within the limits of the acceptance range (80-125%) when comparing a solution for intravenous administration *versus* the reference medicinal product (i.a. Espidifen 400mg granules for oral solution, Zambon). The IV formulations used in the published data is comparable to the applied product based on the comparison of the main quality characteristics. Based on this, the CHMP considered that a bridge between the applied product and the Reference medicinal product is established, allowing to rely on non-clinical and clinical data of the latter.

In addition, CHMP considers that sufficient literature data have been provided to justify the differences versus the reference medicinal product (i.e. additional efficacy and safety data related to the pharmaceutical form, route of administration and indication of the product applied for and which are not covered by the dossier of the RefMP).

Overall, sufficient data are available to support the efficacy and safety of Ibuprofen Kabi 400 mg/ 100 ml solution for infusion in the claimed indication.

4. Grounds for Opinion

Whereas

- The Committee considered the referral under Article 29(4) of Directive 2001/83/EC.
- The Committee considered the totality of the data submitted by the applicant, both in writing and during an Oral Explanation, in relation to the objections raised as potential serious risk to public health as reflected in the notification of this referral.
- The Committee considered that sufficient data has been submitted to allow to establish the bridge between the hybrid product Ibuprofen Kabi 400mg / 100ml solution for infusion against the EU reference medicinal product in order to rely on the relevant data in the dossier of the latter.

- The Committee also considered that sufficient data has been submitted to support the efficacy and safety of the new pharmaceutical form, route of administration and therapeutic indication for Ibuprofen Kabi.
- Therefore, the efficacy and safety of Ibuprofen Kabi 400mg/ 100ml solution for infusion are considered to be established.

The Committee, as a consequence, considers that the benefit-risk balance of Ibuprofen Kabi and associated names is favourable and therefore recommends the granting of the marketing authorisation(s) for the medicinal products referred to in Annex I of the CHMP opinion. The product information remains as per the final version achieved during the Coordination group procedure as mentioned in Annex III of the CHMP opinion.