Assessment report

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

Ibuprofen NVT 400 mg soft capsules and associated names

INN: Ibuprofen

Procedure number: EMEA/H/A-29(4)/1533

Note: Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.
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1. Information on the procedure

An application was submitted under the repeat use procedure for Ibuprofen NVT, 400 mg, soft capsules on the basis of the marketing authorisation granted by Lithuania on 8 June 2022.

The legal basis under which the application was submitted is: Article 10(1) of Directive 2001/83/EC, generic application.

The application under the current wave was submitted to the concerned Member State (CMS): Spain.

The names and MAH(s) of this medicinal product currently authorised following previous decentralised procedure (DCP) are listed in Annex I of the CHMP opinion, as said marketing authorisations also concerned by the outcome of the present referral.

The repeat use procedure LT/H/0162/002/E/001 started on 6 June 2023.

On day 90, major issues on bioequivalence raised by Spain remained unresolved; hence the procedure was referred to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), under Article 29, paragraph 1, of Directive 2001/83/EC, by Lithuania on 4 September 2023. The CMDh 60 day procedure was initiated on 18 September 2023.

Day 60 of the CMDh procedure was on 16 November 2023, and since there could be no agreement the procedure was referred to the CHMP.

On 17 November 2023 the RMS Lithuania therefore triggered a referral under Article 29(4) of Directive 2001/83/EC. Spain raised objections on the lack of adequate proof to demonstrate bioequivalence between the generic medicinal product and the reference medicinal product that were considered to be a potential serious risk to public health.

2. Scientific discussion

2.1. Introduction

Ibuprofen NVT and associated names is a soft capsule containing 400 mg of ibuprofen. It is a non-steroidal anti-inflammatory drug (NSAID) which acts by preventing the synthesis of prostaglandins, through competitive and reversible inhibition of the various cyclooxygenase (COX) isoforms, both at a peripheral level and in the central nervous system.

The proposed indication of Ibuprofen NVT is: “symptomatic relief of mild to moderate pain such as headache, dental pain, period pain/dysmenorrhea, muscular pain (contractures) or backache, febrile states. This medicinal product is indicated for adults and children over than 12 years of age.”

The referral was triggered because of different views on the acceptable difference for median $T_{\text{max}}$ between the product applied for and the reference medicinal product, Nurofen rapid 400 mg soft capsules, for them to be considered bioequivalent. At the time of application of both the decentralised and repeat use procedures, and the start of the present referral, the ibuprofen product-specific bioequivalence guidance (EMA/CHMP/356876/2017) in force already identified $T_{\text{max}}$ as an important pharmacokinetic (PK) parameter to consider in the bioequivalence assessment of oral use immediate release formulations containing 200 mg to 800 mg of ibuprofen; in particular, said product specific guidance required that the $T_{\text{max}}$ between the test and reference product have a comparable median and range. The CMS Spain considered the difference for median $T_{\text{max}}$ between the generic medicinal product and the reference medicinal product not acceptable and therefore that the bioequivalence could not be considered proven.
Furthermore, the guideline on the definition of a potential serious risk to public health in the context of Article 29(1) and (2) of Directive 2001/83/EC states: "Therefore, a potential serious risk to public health in relation to a particular medicinal product can mainly be considered to exist under the following circumstances:

— Efficacy: the data submitted to support therapeutic efficacy in the proposed indication(s), target population(s), and proposed dosing regimen (as defined by the proposed labelling), do not provide sound scientific justification for the claims for efficacy; **adequate proof for bioequivalence demonstrated by generic medicinal products to the reference medicinal product is lacking**."

Therefore, for a generic medicinal product the lack of proof of bioequivalence to the reference medicinal product is considered a potential serious risk to public health.

In this case, Spain was of the view that adequate proof for bioequivalence demonstrated by the generic medicinal product to the reference medicinal product was lacking and, consequently, there was a potential serious risk to public health preventing the authorisation of the medicinal product.

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

The major issue of divergency in the repeat use procedure was whether the generic medicinal product and the reference medicinal products could be considered bioequivalent due to the notably different median $T_{\text{max}}$ values (1.27 h vs 0.67 h, i.e. 87.5% difference) in the bioequivalence (BE) study, although the other main BE criteria, $C_{\text{max}}$ and AUC were met.

The primary PK parameters are defined in the ibuprofen product-specific bioequivalence guidance (EMA/CHMP/356876/2017) as $C_{\text{max}}$, AUC, and $T_{\text{max}}$, the latter being assessed on the basis of the difference between its medians and ranges. Despite the lack of definition for ‘comparable $T_{\text{max}}$’ in the version of the ibuprofen product specific guidance (EMA/CHMP/356876/2017) effective at the time of the initial marketing authorisation and of the present referral, in the results of the BE study submitted, the median $T_{\text{max}}$ of the test medicinal product differs largely compared to the median $T_{\text{max}}$ of the reference medicinal product (1.27 h vs. 0.67 h, i.e. 87.5% difference) and cannot be concluded to be comparable when one median (1.27h) is almost twice the other (0.67h). Moreover, $T_{\text{max}}$ is indicative of the rate of absorption with more sensitivity than $C_{\text{max}}$. The CHMP also noted that the rate of absorption determines the onset of action, therefore a longer $T_{\text{max}}$ may induce a delayed onset of action, which is clinically relevant.

In addition, in the submitted BE study, there are two sampling times between the observed $T_{\text{max}}$ values for the reference medicinal product and for the test product. $T_{\text{max}}$ occurred during the 6th sampling time for the reference medicinal product, meanwhile $T_{\text{max}}$ of the test product occurred only during the 9th sampling time. If the distributions were similar, the median would be located in the same or an adjacent sampling time, not with two sampling times in between. This result shows that the difference in median $T_{\text{max}}$ is not due to infrequent sampling times, but to an actual difference between products.

The argument that the differences in medians are caused by the higher variability observed in the $T_{\text{max}}$ of the reference product (range of $T_{\text{max}}$ of test product: 0.5 to 3 hours and range of $T_{\text{max}}$ of reference: 0.33 to 4 hours) was also not accepted. Indeed, in spite of the variability, the Wilcoxon test was able to detect statistically significant differences ($p=0.0243$) (Figure 1).
The applicant also claimed that $T_{\text{max}}$ was not indicative of the efficacy of immediate release formulations and therefore that the difference between median $T_{\text{max}}$ of the generic medicinal product and reference medicinal product could not be considered as a potential serious risk to public health.

Following an existing pharmacokinetic-pharmacodynamic (PK-PD) model available in the literature (Troconiz et al. 2000), the applicant claimed that $T_{\text{onset}}$, the time at which the plasma concentration for the onset of its therapeutic effects is reached, should be taken into account as a primary PK parameter instead of $T_{\text{max}}$. In this study the maximum antipyretic effect was similar and occurred at the same time for two formulations of ibuprofen with a 1-hour difference in $T_{\text{max}}$ (i.e., a 50% difference). However, CHMP considered that the study did not constitute evidence supporting this claim due to the lack of early measurement of the clinical response. The first measurement was performed after 30 minutes and it is not possible to determine if the onset of action has not happened prior to this measurement following the results of other studies:

- Black et al. 2002 compared the onset of action with measurements at 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 300 and 360 minutes. Any relief was reached after 10 minutes, some relief at 15 minutes, pain half gone at 20 minutes and meaningful relief at 28-29 minutes. By 30 minutes the relief had already been achieved.

- Melhisch et al 2002 detected differences in onset of action by measuring at 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 300, and 360 minutes.

- Melhisch et al. 2003 also detected differences by measuring at 10, 20, 30, 40, 50, 60 and 90 minutes and 2, 3, 4, 5 and 6 hours after administration.

- Seibel at al. 2004 also detected differences by measuring at 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 240 and 300 minutes after administration. These authors detected that during the first 30 minutes after dosing, Ibuprofen Lysine was more effective than plain ibuprofen.

The applicant referred also another study, Cristofoletti and Dressman 2014, which showed that a 2.2-hour delay in $T_{\text{max}}$ translates into a 30-minute delay in the onset of dental pain relief with no difference in maximum efficacy. In the applicant’s opinion, this supports the claim that differences in $T_{\text{max}}$ are noticed in onset of action. In the analysis of $T_{\text{onset}}$ in the bioequivalence study submitted, no difference was observed between the test product and the reference product for the time to reach an ibuprofen plasma concentration for the onset of its therapeutic effects. In CHMP opinion, it is not acceptable to ignore the differences in $T_{\text{max}}$ based on this study results. As described above in the study by Seibel at al., it was shown that the arginine and lysine ibuprofen tablets with shorter $T_{\text{max}}$ are superior clinically to ibuprofen tablets, for which $T_{\text{max}}$ differences are similar to those observed in the submitted study. In addition, it is not known how the observed $T_{\text{max}}$ difference of 40 minutes translates into onset of action for the generic medicinal product and the reference medicinal product. Although the pharmacodynamic
parameter $T_{\text{onset}}$ is less discriminative than the pharmacokinetic $T_{\text{max}}$, this finding does not support the applicant’s claim that there is no scientifically demonstrated association between ibuprofen $T_{\text{max}}$ and the onset of pain relief. On the contrary, the relationship between $T_{\text{max}}$ and time of pain relief has been shown in the referenced study by Cristofoletti and Dressman.

Furthermore, in any case, the CHMP is of the view that it is not acceptable to change post hoc the $T_{\text{max}}$ primary variable to $T_{\text{onset}}$.

3. Benefit-risk balance

The issue raised in this CHMP referral procedure under Article 29(4) is on whether the generic medicinal product could be considered bioequivalent to the reference medicinal product and more specifically, whether the difference in median $T_{\text{max}}$ between the generic medicinal product and the reference medicinal product, Nurofen rapid 400 mg soft capsules, is acceptable.

After reviewing the data submitted by the applicant, the CHMP concluded that bioequivalence between the generic medicinal product and the reference medicinal product has not been proven. As indicated in the product specific bioequivalence guidance (EMA/CHMP/356876/2017) in force at time of initial marketing authorisation and of the start of the present referral, $T_{\text{max}}$ is a primary PK parameters along with $C_{\text{max}}$ and AUC. $T_{\text{max}}$ is assessed on the comparability of its median and range. In the submitted study, bioequivalence with the reference medicinal product was shown for $C_{\text{max}}$ and AUC but the median $T_{\text{max}}$ was not comparable (one median (1.27h) is almost twice the other (0.67h), translating in a 87.5% difference). The CHMP also noted that $T_{\text{max}}$ is indicative of the rate of absorption with more sensitivity than $C_{\text{max}}$, whereas the rate of absorption determines the onset of action and is therefore clinically relevant. Replacing the $T_{\text{max}}$ parameter by another one, $T_{\text{onset}}$, post hoc can also not be accepted by CHMP, for methodological reasons.

In light of the overall available data, the CHMP is of the opinion that bioequivalence between the generic medicinal product and the reference medicinal product is not demonstrated and, consequently, considers that the benefit-risk balance of the generic medicinal product is negative. Therefore, the CHMP recommends, as applicable, the refusal of the marketing authorisation application concerned by the repeat use procedure, and the suspension of the already granted marketing authorisations. For the lifting of the suspension bioequivalence between the generic medicinal product and the reference medicinal product shall be demonstrated for all criteria (90% confidence interval: 80.00 – 125.00% for $AUC_{0-t}$ and $C_{\text{max}}$; comparable median (≤ 20% difference, 80.00–125.00%) and range for $T_{\text{max}}$).

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 in relation to the objection raised as potential serious risk to public health.
- The Committee was of the view that the median $T_{\text{max}}$ of the generic medicinal product and of the reference medicinal product were not comparable.
- The Committee concluded that the data available did not establish the bioequivalence of Ibuprofen NVT 400mg soft capsule to the reference medicinal product.
The Committee, as a consequence, considers that the benefit-risk balance of Ibuprofen NVT 400mg soft capsules is not favourable.

Therefore, the Committee recommends the refusal of the marketing authorisation application and the suspension of the existing marketing authorisations.

The condition for lifting the suspension of the marketing authorisation(s) is set out in Annex III of the CHMP opinion.
References


