Annex II

Scientific conclusions
Scientific conclusions

The procedure concerns an application submitted under Article 10(1) of Directive 2001/83/EC, generic application for Ibuprofen NVT, 400 mg, soft capsules and on the basis of the marketing authorisation granted by Lithuania on 8 June 2022. The reference medicinal product is Nurofen Rapid 400mg.

During the repeat use procedure (RUP), Spain raised major issues on bioequivalence which remained unresolved also during the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh); hence the procedure was further referred to the CHMP. On 17 November 2023, Lithuania triggered this referral under Article 29(4) of Directive 2001/83/EC.

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. 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.

Overall summary of the scientific evaluation by the CHMP

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.

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. 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 post hoc the $T_{\text{max}}$ parameter by another one, $T_{\text{onset}}$, 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_{max}; comparable median (≤ 20% difference, 80.00–125.00%) and range for T_{max}).

**Grounds for the CHMP 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_{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.