31 May 2018
EMA/CHMP/730723/2017
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Ibuprofen 200 – 800 mg oral use, immediate release formulations product-specific bioequivalence guidance' (EMA/CHMP/356876/2017)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	SciencePharma
2	AESGP
3	Cadore INV s.r.o., Czech Republic and Zentiva, k.s., Czech Republic
4	Patheon Softegels B.V.

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
4	The applicant Patheon Softgels B.V. would like to provide his comments even though the deadline for comments has expired. This because the applicant considers his comments to be very useful for the evaluation before the guideline becomes final. Please be informed that we do not agree to publish the assessment report provided as annex, because there is more confidential information which may discredit our clients.	

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2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Bioequivalence assessment, Main PK variables (in the table)	1	Comment: In this section, Tmax for S enantiomer is listed as one of the main PK variables (together with Cmax and AUC(0-t)). Could you please clarify if the intention was to make the Tmax one of the primary endpoints of the study? In our opinion, the inclusion of Tmax in the primary endpoint analysis is not justified for ibuprofen and should be avoided. According to the "*Guideline on the investigation of bioequivalence*", CPMP/EWP/QWP/1401/98 Rev.1/Corr**, the evaluation of Tmax should be performed when the rapid release of the substance is clinically relevant and of importance for the onset of action or is related to adverse events (AE). Rapid onset of action is usually of importance for life-saving products, and ibuprofen is not one of those. Also, there is no data that any AEs could be related to the rapid release of the substance from the formulation. Therefore, for a standard pain-killer like ibuprofen, in immediate release oral formulations, it is recommended to keep the requirements as they are presented in the abovementioned guideline CPMP/EWP/QWP/1401/98 Rev.1/Corr**, that is the statistical evaluation of Tmax should not be required.	Partly accepted T_{max} is not an end point to be included in the statistical analysis but a comparison of the values should be made and any differences discussed in the context of the application (see later).

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		Proposed change (if any): Main pharmacokinetic variables: C_{max}, $AUC_{(0-t)}$	
Bioequivalence assessment, 90% confidence interval (in the table)	1	Comment: In this section, it is proposed that the median and range for Tmax should be “comparable”. On the other hand, as it was stated above, the principle “*Guideline on the investigation of bioequivalence*”, CPMP/EWP/QWP/1401/98 Rev.1/Corr** states that in general, the statistical evaluation of Tmax is not required. Could you please clarify in this section how the applicants should demonstrate the comparability of Tmax, if, at the same time, statistical evaluation of this parameter is not required. Proposed change (if any):	Partly accepted. T_{max} is not an end point to be included in the statistical analysis but a comparison of the values should be made and any differences discussed in the context of the application (see later).
	2	Comment: “While it is true that the pharmacokinetic literature indicates that the ratio of the S- and R-ibuprofen in plasma may vary slightly according to different rates of absorption of the pharmaceutical form, the AUC and Cmax (Garcia-Arieta et al, 2016; Ferrero-Cafiero et al, 2015) or AUC (Jamali et al, 1988) of the active S-enantiomer remain bioequivalent across formulations. Therefore, the requirement to use a chiral assay to demonstrate bioequivalence is not necessary.”	Partly accepted. It has been agreed that an enantioselective analytical method is not required to demonstrate bioequivalence.

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		Proposed change (if any):enantioselective analytical method - NO	
Table Requirements for bioequivalence demonstration (PKWP) / Analyte / Bioequivalence assessment	3	**Comment:** The draft guidance EMA/CHMP/356876/2017 is introducing a requirement of enantioselective analytical method with the justification that the enantiomers have different pharmacodynamics and pharmacokinetics and that the rate of absorption has been shown to affect the ratio of enantiomers. Indeed, it has previously been demonstrated (García-Arieta et al., 2016; Torrado et al., 2010; Jamali et al., 1988) that the pharmacokinetics of individual enantiomers is affected by the rate of absorption nevertheless the clinical relevance of such observation remains highly controversial. We have reviewed the available evidence from published clinical studies comparing "faster" forms of ibuprofen such as ibuprofen arginate, ibuprofen lysinate and sodium ibuprofen dihydrate with "conventional" form of ibuprofen acid (refer to publications of Black et al., 2002; Mehlisch et al., 2002; Desjardins et al., 2002; Seibel et al., 2004; Schleier et al., 2007; Nørholt et al., 2011 and PL 00063/0372-4, 0411-2). It is expected that if these forms were compared using enantioselective analytical method they would have different ratio of enantiomers because of faster absorption rate	Partly accepted. It has been agreed that an enantioselective analytical method is not required to demonstrate bioequivalence.

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		(shown e.g., by Dewland et al., 2009). The above-mentioned clinical studies have demonstrated faster onset of pain relief with ibuprofen "faster" salt formulations than with conventional ibuprofen formulations, however, have substantially varied with regards to statistically significant differences between treatment groups for time to first symptom relief. Despite statistically significant differences in onset of action as consequence of faster onset of plasma concentrations, the peak pain relief was often comparable for both "faster" and "conventional" ibuprofen acid formulations (Black et al., 2002 and Schleier et al., 2007). Therefore, expected different ratio of enantiomers is not affecting the peak response to pain. Even more, very often observed differences for onset of action in the range of several minutes cannot be considered clinically relevant and such a conclusion is supported by previous regulatory decisions (e.g., within the procedure UKPAR PL 00063/0372-4, 0411-2). More importantly, the overall analgesic efficacy of these "faster" forms was not different from the ibuprofen acid, except in the study published by Seibel and colleagues (Seibel et al., 2004) revealing also superior extent of action at dose corresponding to 400 mg of ibuprofen acid. Nevertheless, this effect was observed by using laser somatosensory evoked potentials (LSEPs) obtained	

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		from UV-irradiated skin in healthy volunteers, which is to our best knowledge an experimental model of pain not validated to evaluate the efficacy of medicines used for pain relief. Furthermore, ibuprofen is a molecule with pharmacodynamic (PD) response that is not very sensitive to changes in dose and consequently in the pharmacokinetic (PK) profile. E.g., results from clinical trials have shown that ibuprofen doses of 7 and 11.8 mg/kg or 200 and 400 mg were not different from each other when evaluating the antipyretic response (Tróconiz et al., 2000) or the total dental pain relief (McQuay et al., 2006), respectively. Due to this flat dose-response relationship, despite being bioinequivalent in terms of PK, two products with point estimates for the test-to-reference ratios of Cmax and AUC around 70% would still be therapeutically equivalent as shown by means of physiologically based PK models coupled with antipyretic and dental pain relief PD models (Cristofoletti & Dressman, 2014). Therefore, in our opinion the above-mentioned draft guidance is introducing analytical methodology, which is over-discriminative and unnecessary from clinical perspective. In the light of our review of clinical studies comparing "faster" forms of ibuprofen with ibuprofen acid and	

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		unproblematic several decade-long clinical use of generic products approved based on achiral bioanalytical methods, we would like to suggest that the use of ibuprofen racemate as an analytical method should be sufficient. The addition of Tmax comparison (median and range) as already suggested by the respective draft guidance is in our opinion sufficient measure to address the quality attributes of generic products containing ibuprofen. This is fully in line with scientific literature where quantification of racemate is considered adequate if the rate of absorption is similar enough (García-Arieta et al., 2005). **Proposed change:** In the table 'Requirements for bioequivalence demonstration (PKWP)': section Analyte, in the recommendation regarding analytical method modify to: **Enantioselective analytical method:** ☐ yes, ☒ no; and, in the section **Main pharmacokinetic variables:** keep Cmax, AUC(0-t) and Tmax, however, delete requirement for S-enantiomer. Finally, please delete the entire Background/justification section. **References** Black, P., et al. (2002). Clin Ther 24(7): 1072-89 Cristofoletti, R. & Dressman, J.B. (2014). J Pharm Sci	

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		103(10): 3263-75 Desjardins, P., et al. (2002). Eur J Clin Pharmacol 58(6): 387-94 Dewland, P.M., et al. (2009). BMC Clin Pharmacol 9:19 García-Arieta, A., et al. (2005). Chirality 17(8): 470-5 García-Arieta, A., et al. (2016). Chirality 28(5): 429-433 Jamali, F., et al. (1988). Pharm Res 5(1): 40-3 McQuay, H.J., et al. (2006). Pain 66(2-3): 247-51 Mehlisch, D.R., et al. (2002). J Clin Pharmacol 42(8): 904-11 Nørholt, S.E., et al. (2011). Int J Clin Pharmacol Ther 49(12): 722-9 Schleier, P., et al. (2007). Int J Clin Pharmacol Ther 45(2): 89-97 Seibel, K., et al. (2004). Arzneimittelforschung 54(8): 444-51 Torrado, J.J., et al. (2010). Eur J Clin Pharmacol 66 (6): 599-604 Tróconiz, I.F., et al. (2000). Clin Pharmacokinet 38 (6): 505-518 UK PAR for Nurofen Express (PL 00063/0372-4, 0411-2), 2008	
	4	Comment: During one of the procedures for Ibuprofen 200 mg the applicant received an remark	Partly accepted. It has been agreed that an enantioselective analytical

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		from the authorities to show that the bioequivalence must demonstrate the pharmacologically active S-enantiomer. The applicant has argued this by providing the data available from the scientific literature and proving that the bioequivalence study performed is sufficient. Please find enclosed the Assessment report on the Clinical part for procedure NL/H/2232/001-002/DC. The proposed rationale was acceptable by the assessor (reference to response in separate attachment 1). Proposed change (if any): Based on the substantial amount of data available in scientific literature on the pharmacokinetics of the ibuprofen enantiomers the Applicant is of the opinion that a stereoselective analysis of the pharmacologic active S-ibuprofen is not required to assess the bioequivalence of ibuprofen liquid capsule containing a racemic mixture. Therefore, the bioequivalence studies based on the total concentration of the ibuprofen enantiomers, and bioequivalence was proven when comparing the pharmacokinetic performance of the softgel capsules with the liquid capsules used as reference product. Therefore, the applicant would like to change the guideline where the responses given have been taken into account.	method is not required to demonstrate bioequivalence.
	4	Comment: Proprietary data from the company has	Partly accepted.

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		shown that even in cases there is difference in rate of release and absorption, bioequivalence is met and there is no change in the ratio of the enantiomers. This means in general that criteria 3 as outlined in the Guideline on the Investigation of Bioequivalence is not met for various different immediate release formulations : (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. Proposed change (if any): It is suggested that the leading guidance on bioequivalence is based on the Guideline on the investigation of bioequivalence and if no or minimal difference in rate of absorption is expected as shown by tmax there is no need to conduct stereo-selective bioanalysis	It has been agreed that an enantioselective analytical method is not required to demonstrate bioequivalence.