30 April 2020
EMA/CHMP/675838/2014/Rev.1*
Committee for Medicinal Products for Human Use (CHMP)

Dasatinib film-coated tablets 20, 50, 70, 80, 100 & 140 mg and suspension 10 mg/ml product-specific bioequivalence guidance

Draft

Draft agreed by Pharmacokinetics Working Party (PKWP)	October 2013
Adopted by CHMP for release for consultation	24 October 2013
Start of public consultation	15 November 2013
End of consultation (deadline for comments)	15 February 2014
Agreed by Pharmacokinetics Working Party	22 October 2014
Adopted by CHMP	20 November 2014
Date for coming into effect	1 June 2015
Draft agreed by Pharmacokinetics Working Party (PKWP)	6 April 2020
Adopted by CHMP for release for consultation	30 April 2020
Start of public consultation	4 May 2020
End of consultation (deadline for comments)	31 August 2020
Agreed by Pharmacokinetics Working Party	
Adopted by CHMP	

*This revision concerns the additional requirement for a fed study and the requirements for a suspension

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Comments should be provided using this template. The completed comments form should be sent to PKWP@ema.europa.eu

Keywords	***Bioequivalence, generics, dasatinib***

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***Disclaimer*:**

This guidance should not be understood as being legally enforceable and is without prejudice to the need to ensure that the data submitted in support of a marketing authorisation application complies with the appropriate scientific, regulatory and legal requirements.

Requirements for bioequivalence demonstration (PKWP)*

BCS Classification	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** dasatinib may be considered a low solubility compound.
Bioequivalence study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☐ **fasting** ☐ **fed** ☒ **both** ☐ **either fasting or fed** **Background:** Some subjects may randomly exhibit low concentrations of dasatanib when taking dasatinib products in the fasted state. Therefore, these products are considered with specific formulation characteristics and, consequently, bioequivalence should be evaluated under fasting and fed conditions.

	Strength: 140 mg for the tablets and 120 mg for the oral suspension. **Background:** Dasatinib film-coated tablets and dasatinib powder for oral suspension are not bioequivalent. For the tablets, the highest strength to be used for a drug with linear pharmacokinetics and low solubility. For the oral suspension, the highest dose for a drug with linear pharmacokinetics and low solubility.
	Number of studies: two
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t} and C_{max}
	90% confidence interval: 80.00–125.00% **Background:** In order to avoid the bias introduced by the randomly occurring low-lier values under fasting conditions, it is considered acceptable that low-lier profiles can be excluded from statistical analysis of the fasted state study if they occur with the same or lower frequency in the test product compared to the reference product. The low-lier profiles are defined as those profiles with dasatinib AUC exposures < 10% of the geometric mean AUC obtained in the rest of the profiles. This should be predefined in the protocol.

* As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to recommend at this stage the use of a replicate design to demonstrate high intra-subject variability and widen the acceptance range of C_{max}. If high intra-individual variability (CV_{intra} > 30 %) is expected, the applicants might follow respective guideline recommendations.