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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 agreed by Pharmacokinetics Working Party (PKWP)	October 2013
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*This revision concerns the additional requirement for a fed study and the requirements for a suspension

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. The incidence of these low-liers has been observed to depend on the formulation. 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.