15 October 2020
EMA/CHMP/493940/2020
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Dasatinib film-coated tablets 20, 50, 70, 80, 100 & 140 mg and suspension 10 mg/ml product-specific bioequivalence guidance' (EMA/CHMP/675838/2014/Rev.1*)

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

Stakeholder no.	Name of organisation or individual
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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	No explanation is provided on how the presence of low-liers is indicative for a specific formulation characteristic. Moreover, dasatinib is not developed with the purpose of having specific formulation characteristics with regard to the release of dasatinib. The appearance of low-lier profiles in the fasting state is more likely an inherent physiological effect. Especially, considering that the abnormal values occur both in the test and reference product.	Several factors probably contribute to the occurrence of low-liers e.g. pH dependent solubility of dasatinib, physiological effects under fasting conditions but also formulation characteristics. Even though the innovator product is an immediate release formulation without having specific formulation characteristics, based on information on dasatinib from multiple sources the incidence of low-liers appeared to be a formulation dependent effect.
1	The presence of low-lier profiles will result in higher variability and can be taken into account in the sample size calculations, and possibly widened acceptance criteria can be applied in case of replicate cross-over design studies. Dasatinib is not a product having specific formulation characteristics (e.g. microemulsions, solid dispersions) and the fasting state is considered to be most sensitive condition to detect a potential difference between formulations, even in the presence of low-liers. Therefore, when a successful bioequivalence study under fasting conditions has been performed, such a study should be sufficient evidence of bioequivalence. An additional study under fed conditions would not add any new insights to such a conclusion and is therefore unnecessary.	Not agreed. The variability in dasatinib exposure was estimated to be mainly due to inter-occasion variability in bioavailability and, to a lesser extent, due to inter-individual variability in bioavailability and inter-individual variability in clearance. Although the acceptance criteria of Cmax can be widened based on a replicate cross-over design study, this is not acceptable for AUC values (Guideline on the investigation of bioequivalence). Since, after carefully reviewing the available data on dasatinib from multiple sources i.e. public information and information provided to regulatory agencies, the formulation can affect the incidence of low-liers, dasatinib bioequivalence is recommended to be demonstrated under fasted and fed conditions, conforming to the bioequivalence guideline for products with specific formulation characteristics.
2	While it is considered acceptable and even appreciated to fill gaps in the existing general guidelines by product-specific bioequivalence guidances, the general principles set out in the general documents,	Specific comments will be provided below.

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	namely those in the EMA Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr), should still be followed. This applies specifically to the requirement to conduct both fed and fasting studies which should not be enforced due to the abnormal behaviour linked to physiological effects (as this is the case for dasatinib, see comments below).	
2	It seems as if the draft product-specific guidance (PSG) takes into account recent submissions where the generic products contained the anhydrate instead of the originator's monohydrate as API, since low-liers are observed less frequently with the anhydrate. However, from our perspective, a product-specific guidance which does not explicitly refer to a specific situation (e.g. a certain salt form) should be applicable irrespective of the salt or hydrate form and irrespective whether this form is the same as or different from the one in the originator product. This aspect should be considered in the final version of the PSG.	Accepted. Dasatinib anhydrate and dastinib monohydrate are considered the same active substance because they have no significant different properties that result in major differences in pharmacokinetics. Therefore, the product specific guidance is irrespective to the dasatinib form and a change of the product specific guidance is not needed.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Page 3, last paragraph	2	**Comments:** It is not clear why randomly occurring low concentrations of dasatinib when administered in the fasted state are considered as cases of "specific formulation characteristics", especially if they occur in the reference product as well. Therefore, as long as the conditions in the general guidance are met, no additional studies should be required. **Proposed change:** 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.~~ However, if there are no such cases or if the number of such observations is low and the general criteria for exclusion of subjects in the general BE guideline are being followed, a fasting study will suffice.	Not accepted. After carefully reviewing the available data on dasatinib from multiple sources i.e. public information and information provided to regulatory agencies it appeared that the inter-occasion variability / the incidence of low-liers under fasting conditions appeared to be formulation dependent. Therefore, dasatinib bioequivalence is recommended to be demonstrated under fasted and fed conditions, conforming to the bioequivalence guideline for products with specific formulation characteristics.
Page 3, table, Section 'Bioequivalence study design'	2	**Comments:** We consider the proposed single-dose, cross-over study in healthy volunteers as well as the choice of primary pharmacokinetic metrics, study strength, analyte and achiral analytical method adequate for demonstration of bioequivalence for dasatinib. However, we have comments to the proposal to	Not accepted. Since, after carefully reviewing the available data on dasatinib from multiple sources i.e. public information and information provided to regulatory agencies, the formulation can affect the incidence of low-liers, dasatinib bioequivalence is recommended to be demonstrated under fasted and fed conditions, conforming to the bioequivalence guideline for

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		conduct studies both under fasting and fed conditions. As per reference drug SmPC, dasatinib tablets may be taken with or without food (Sprycel, EMEA/H/C/000709). Data from healthy subjects administered a single, 100 mg dose of dasatinib 30 minutes following a high-fat meal indicated a 14% increase in the mean AUC of dasatinib. The observed food effect does not represent clinically relevant change in dasatinib exposure (Sprycel, EMEA/H/C/000709, EPAR Scientific Discussion). In line with the EMA Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr), for products where the SmPC recommends intake of the reference medicinal product irrespective of food intake, the bioequivalence study should be conducted under fasting conditions as this is considered to be the most sensitive condition to detect potential difference between formulations. Compared to fasting study, fed conditions are not expected to reveal additional insights in biopharmaceutics quality of developed generic formulations. Indeed, fasting conditions are most discriminative for dasatinib since factors like increased stomach pH (Koziolek et al., 2015), partitioning into fat, increased bile salts solubilisation and delayed gastric emptying under fed conditions will not interfere with the absorption process. Notably, to increase the sensitivity to detect formulation differences between products, a fasting study is preferred over a fed one for another drug from the group of tyrosine kinase inhibitors, namely for imatinib	products with specific formulation characteristics.

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		(Glivec, EMEA/H/C/000406), even if the drug should be administered only with meal (Imatinib hard capsules 50 and 100 mg, film-coated tablets 100 and 400 mg product-specific bioequivalence guidance, EMA/CHMP/315242/2014). Moreover, applications with reference to Article 10(1) of Directive 2001/83/EC, as amended, were recently approved for dasatinib based on data from pivotal bioequivalence study conducted in fasting conditions only (e.g., procedure DE/H/5897/001-006/DC, finalized on 28.10.2019). In conclusion, dasatinib bioequivalence study should be performed only under fasting conditions since it is expected to adequately assess the formulation performance. **Proposed change:** In the table 'Requirements for bioequivalence demonstration (PKWP)', modify appropriate sections. The section Bioequivalence study design, in the recommendation regarding posology modify to: ☒ fasting, ☐ fed, ☐ either fasting or fed. In this section, delete the entire Background information. In addition, in the section Number of studies, modify to: 'one single-dose study'. **References** Koziolek et al., 2015, J Control Release. 2015;220(Pt A):71-78	
Page 3 and 4, table,	2	**Comments:** Dasatinib is weakly basic in nature and exhibits a pH-	Not accepted.

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Sections 'Bioequivalence study design' and 'Bioequivalence assessment'		dependent solubility with highest solubility obtained at acidic pH and sharp decrease with increasing pH. Acid modifying drugs (e.g., H2-receptor antagonists and proton pump inhibitors) increase the intragastric pH, which decreases the solubility and consequently significantly reduces the absorption of dasatinib (Yago et al., 2014). Thus, the low absorption of the reference product is not a special formulation characteristics but is likely linked to diminished gastric acid secretion. Hypochlorhydria or achlorhydria is present in some study volunteers as the condition is asymptomatic, with frequency expected between 1% and 5% in healthy population (Christiansen, 1968). Interestingly, the reference listed drug (Sprycel) has demonstrated low pharmacokinetic exposure in similar extent, approximately 5.22% of healthy subjects had anomalously low plasma concentration and AUC values, relative to the population mean (i.e., less than 10% of the population mean) (Chandani, et al., 2017). However, the number of low-liers in pharmacokinetic studies in healthy volunteers is variable, occurs randomly and thus it shall be allowed to exclude subjects from the BE evaluation even if they occur more frequently in the test product. In the light of previously available data, the low-lier profiles defined as those profiles with dasatinib AUC exposures < 10% of the geometric mean AUC obtained in the rest of the profiles is concurred. **Proposed change:**	Indeed, dasatinib exhibits a pH-dependent solubility with highest solubility obtained at acidic pH and sharp decrease with increasing pH and co-medication with drugs that increase the gastric pH reduces the absorption of dasatinib significantly. Hypochlorhydria or achlorhydria present in some study volunteers may result in lower absorption of dasatinib or low-liers. For the innovator product it has been demonstrated based on many studies that the variability in dasatinib exposure was estimated to be mainly due to inter-occasion variability and, to a lesser extent, due to inter-individual variability in bioavailability and inter-individual variability in clearance. For a generic application, there is only data from one study, hence, it cannot be concluded if a higher incidence of low-liers in the test product is a formulation effect or a chance finding. Therefore, the incidence of low-liers should not be higher for the test product compared to the innovator product.

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		The Bioequivalence assessment, section Background should be modified to: 'Some subjects may randomly exhibit low concentrations of dasatanib when taking dasatinib products in the fasted state. 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.' **References** Chandani, et al., 2017, presented at AAPS Annual Meeting, San Diego (M6107) Christiansen, 1968, Scand J Gastroenterol. 3(5): 497-508 Yago et al., 2014, AAPS J 16(6): 1358-1365	