4 November 2024
EMA/479330/2024
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on `Nilotinib hard capsules 50, 150 and 200 mg product-specific bioequivalence guidance' (EMA/CHMP/518671/2023)

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

Stakeholder no.	Name of organisation or individual
1	Novartis Pharma AG
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1. General comments – overview – None received

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 1	1	**Comment:** Available forms of nilotinib hydrochloride Generic nilotinib formulations may be based on nilotinib free base or on different salts, hydrates and/or solvates and/or different crystalline forms of nilotinib hydrochloride compared to "Form B" of the nilotinib hydrochloride monohydrate as contained in Tasigna®. Novartis' studies with this specific Form B of the nilotinib hydrochloride monohydrate as contained in Tasigna found an important, safety-related food effect. Several crystal hydrates and solvates of nilotinib hydrochloride exist, and different crystalline Forms A, B, C and amorphous forms have been characterized as follows: (1-3) • Form A corresponds to a dihydrate form; • Form B and Form C are monohydrate forms which can be obtained after desolvation of different solvates; • The monohydrate Form B, isolated from the synthetic process and used in Tasigna, is believed to be the most stable form. It shows the least hygroscopic behaviour of all the three crystalline Forms A, B, and C. Unlike some polymorphs that may transform into different polymorphic forms during storage, no transformation was observed after storing the three forms of nilotinib at room temperature, even for several months (4). Food effect of nilotinib hydrochloride monohydrate Nilotinib	**Not accepted** Because of a patent in Europe (i.e., EP2501384), SmPC of generics cannot detail how patients who are unable to swallow hard capsules may take the product. To mitigate the risk for patients who are used to dispersing the innovator product in applesauce, doing the same with the generic product, *in vitro* studies showing compatibility of the generic nilotinib formulation with apple sauce should be conducted. If bioequivalence has been demonstrated under fasted conditions with the intact capsules, an additional bioequivalence study with apple sauce under conditions as described for the reference product is not necessary and *in vitro* studies showing that administration with apple sauce does not impact stability of nilotinib of the generic product are sufficient (Q&A 3.6). Additional *in vivo* or *in vitro* dissolution data with apple sauce is not considered necessary. The crystalline form, salt, or hydrate may affect the pH dependent solubility of nilotinib, which as a result may affect the absorption of nilotinib under elevated gastric pH. Therefore, additional information on pH-dependent solubility data is needed when there is a difference in crystalline form, salt, or hydrate between test and

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		hydrochloride monohydrate has been shown to have an important, safety-related food effect: In the authorization of Tasigna in the EU, it was found that nilotinib has an important food effect in that "significant prolongation of the QT interval may occur when nilotinib is inappropriately taken with food" because "the absorption and bioavailability of nilotinib are increased if it is taken with food, resulting in a higher serum concentration…". (5) The Summary of Product Characteristics (SmPC)§ instructs that Tasigna "must not be taken with food" and that "[t]he hard capsules should be swallowed whole with water" and "[n]o food should be consumed for 2 hours before the dose is taken and no food should be consumed for at least one hour after the dose is taken". (6) On that basis, the package leaflet of Tasigna instructs patients as follows: "Do not take Tasigna with food. Food may enhance the absorption of Tasigna and therefore increase the amount of Tasigna in the blood, possibly to a harmful level. Do not drink grapefruit juice or eat grapefruit. It may increase the amount of Tasigna in the blood, possibly to a harmful level." (7) The existence of the food effect is particularly important for patients who are unable to swallow the intact capsules, which includes part of the paediatric population. In compliance with the Paediatric Investigation Plan (PIP) under EU legislation (8), Novartis investigated the administration of Tasigna – i.e. the crystal Form B of the monohydrate of nilotinib monohydrochloride – by dispersing the contents of the capsules	reference product. Depending on differences in pH-dependent solubility between test and reference active substance, an additional bioequivalence study with concomitant treatment of a Proton-Pump Inhibitor (PPI) as an acid reducing agent may be necessary (ICH-M13A). However, the product-specific guideline refers to the salt, polymorphic form and hydration/solvation state of the drug substance used in the formulation of the reference medicinal product. Thus, the potential need for an additional PPI study due to a different form of the active substance will not be reflected in the product-specific guideline.

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		in two different soft foods: non-fat plain yogurt and apple sauce. In a bioavailability study comparing the intact to the dispersed capsules, the intact and dispersed capsules were found to be bioequivalent when used with apple sauce but not with yogurt. • With apple sauce, the geometric mean ratios (90% confidence intervals) for nilotinib C(max), AUC(0-tlast), and AUC(0-inf) were 0.95 (0.88-1.02), 0.99 (0.94-1.04), and 0.97 (0.90-1.03), respectively. • With yogurt, bioavailability increased: The geometric mean ratios (90% confidence intervals) for nilotinib C(max), AUC(0-tlast), and AUC(0-inf) were 1.31 (1.22-1.41), 1.11 (1.05-1.16), and 1.08 (1.02-1.15), respectively (9). These study results demonstrated that crystal Form B of the monohydrate of nilotinib monohydrochloride salt could be administered to paediatric patients by dispersing the content of capsules in one teaspoon of apple sauce (puréed apple) immediately before administration. On this basis the label was updated with Commission Decision of 20 December 2010 (C(2010)9644) to include the following instruction: "For patients who are unable to swallow hard capsules, the content of each hard capsule may be dispersed in one teaspoon of apple sauce (puréed apple) and should be taken immediately. Not more than one teaspoon of apple sauce and no food other than apple sauce must be used (see sections 4.4 and 5.2)." (10) The strict limitation to a single teaspoon of apple sauce reflects the pronounced food effect observed for Tasigna – i.e. the crystal Form B of the monohydrate of nilotinib monohydrochloride – and the risk of	

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		cardiotoxicity in the form of QT prolongation associated with improper use of this drug product. No awareness of data of other forms of nilotinib hydrochloride or nilotinib free base when dispersed in apple sauce. These studies conducted by Novartis were limited to the crystal Form B of the monohydrate of nilotinib monohydrochloride salt contained in Tasigna. Further, Novartis is not aware of any similar studies comparing the bioavailability of any other salt, hydrate, solvate or any other crystalline form of nilotinib hydrochloride or nilotinib free base when dispersed in apple sauce. Suitability of in vitro studies to show compatibility of generic nilotinib formulations with apple sauce Novartis is of the view that requiring "in vitro studies showing compatibility of the generic nilotinib formulation with apple sauce" is not a n sufficiently reliable way to exclude a possible food effect of different nilotinib formulations with apple sauce. The feasibility of dispersing nilotinib in apple sauce was initially supported by an in vitro compatibility study (9). This in vitro compatibility study found that nilotinib was stable at room temperature for at least 15 minutes after the capsule contents were dispersed in either yogurt or apple sauce. It showed that the delivery method was accurate, that there was no increase in degradation products, and that there was no content decrease when immediately administered. This in vitro compatibility study concluded that the method of administration of nilotinib	

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		hard gelatin capsules using apple sauce and yoghurt is suitable for a dose range between 50 and 250 mg. Yet, the subsequent clinical study (9) assessing bioavailability when given together with yogurt or apple sauce demonstrated that there was a food effect with yogurt, but not with apple sauce. Although the initial in vitro compatibility study supported use of nilotinib with either yogurt or apple sauce, this was not confirmed in the corresponding clinical bioavailability study. Novartis is therefore concerned that in vitro studies showing compatibility of generic nilotinib formulations with apple sauce may not be reliably predicting presence or absence of a possible food effect with different formulations of nilotinib. In vitro compatibility and/or stability studies could be used to disqualify potential food vehicles, for example if the drug was shown to rapidly degrade in its presence. However, such studies would not be sufficient to demonstrate bioequivalence. Any in-vitro study assessing the impact of apple sauce should specifically aim at establishing bioequivalence. These studies could be in vitro dissolution tests with apple sauce being present. The addition of apple sauce into such media could potentially alter release and delivery of drug substance from the drug product, and dissolution release testing of drug substance from the dosage form mixed with the proposed vehicle should therefore be carried out according to established methods. Dissolution testing should be conducted in media	

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		typically used for testing solid oral dosage forms. These in vitro dissolution tests should enable the assessment of drug dissolution/release patterns for generic nilotinib formulations when mixed with apple sauce and should demonstrate consistency with Tasigna. Implications Since the Tasigna label was updated in December 2010, it may have become established practice that patients who are unable to swallow intact capsules disperse the contents of a nilotinib capsule in one teaspoon of apple sauce. Indeed, many people experience difficulties with swallowing whole tablets or capsules. The cause ranges from difficulties overriding the human instinct to chew food before swallowing, to more complex disorders affecting the ability to swallow and manage food and fluid intake. Also, older people can experience swallowing difficulties because of comorbidities, natural age-related physiological changes, and use of multiple medications. Reports indicate that between 10% and 40% of adults have difficulties swallowing solid oral medications (11). In hospitals and aged care facilities, as many as 50–60% of older people may experience impaired swallowing function (dysphagia) (11-14). While it is unknown which percentage of patients sprinkle Tasigna capsules onto apple sauce, literature suggests that a substantial part of the population (not only	

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		children) may encounter swallowing difficulties and may therefore resort to taking Tasigna with apple sauce. Novartis is concerned that these patients who are used to taking Tasigna with apple sauce will continue doing so out of habit, irrespective of the nilotinib formulation that they use. This underscores the importance of understanding the bioavailability in humans of the different formulations that are available. In-vitro studies should therefore specifically aim at demonstrating bioequivalence with Tasigna when given with apple sauce, rather than only demonstrating compatibility with apple sauce. **Proposed change:** In vitro evaluation: Additionally, in vitro studies showing bioequivalence of the generic nilotinib formulation with applesauce should be conducted. **Reference:** (1) European Public Assessment Report Tasigna, page 2, available at https://www.ema.europa.eu/en/documents/scientific-discussion/tasigna-epar-scientificdiscussion_en.pdf (2) Rao SR, Sreenivas R, Reddy VR et al (2020)	

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		Polymorphic Stress Studies of Nilotinib Hydrochloride Hydrates and Its Characterization, 20 International J. Pharmacy & Pharmaceutical Research 155 Available at: https://ijppr.humanjournals.com/wp-content/uploads /2021/01/12.Cheddi-Srinivasa-Rao-R.-SreenivasVangala-Ranga-Reddy-Durga-Prasad-Gopal- Vaidyanathan.pdf (3) Co-crystals – A Rising horizon for formulating poorly soluble drugs, J Pharm Adv Res, 2018; 1(6): 292-305. Available at: https://www.jparonline.com/review/JPAR-1806-RVA-00045-Dr.%20Parag.pdf (4) European Public Assessment Report Tasigna, https://www.ema.europa.eu/en/documents/scientificdiscussion /tasigna-epar-scientific-discussion_en.pdf, page 2. (5) Tasigna Summary of Product Characteristics, Section 4.4 under "QT prolongation" (page 7) and Section 4.5 under "Food interactions" (page 12). https://www.ema.europa.eu/en/documents/productinformation /tasigna-epar-product-information_en.pdf (6) Tasigna Summary of Product Characteristics, Section 4.2 under "Method of administration'" (page 6). https://www.ema.europa.eu/en/documents/productinformation /tasigna-epar-product-information_en.pdf (7) Tasigna Package Leaflet, Section 2 under "Tasigna with food and drinks" (page	

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		65). https://www.ema. europa.eu/en/documents/product-information/tasignaepar-product-information_en.pdf (8) https://www.ema.europa.eu/en/medicines/human /paediatric-investigation-plans/emea-000290-pip01-08m04. (9) Yin O, Rudoltz M, Galetic I (2011) Effects of yogurt and applesauce on the oral bioavailability of nilotinib in healthy volunteers. J Clin Pharmacol 2011 Nov;51(11): 1580-6 (10) Tasigna Summary of Product Characteristics, Section 4.2 "Method of administration'" (page 6) https://www.ema.europa.eu/en/documents/product-information/tasigna-epar-product-information_en.pdf (11) Lau ETL, Steadman KJ, Cichero JAY et al (2018). Dosage form modification and oral drug delivery in older people. Adv Drug Deliv Rev. 2018 Oct;135:75-84. (12) Cabre M, Serra-Prat E, Palomera J et al (2010) Prevalence and prognostic implications of dysphagia in elderly patients with pneumonia, Age Ageing 39 39–45. (13) Cichero JAY and Altman KW (2012) Definition, prevalence and burden of oropharyngeal dysphagia: a serious problem among older adults worldwide and the impact on prognosis and hospital resources, in: J.A.Y. Cichero, P. Clave (Eds.), Stepping Stones to Living Well with Dysphagia, Karger AG, Switzerland, pp. 1–11.	

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		(14) Wirth R, Dziewas AM, Beck P et al (2016) Oropharyngeal dysphagia in older persons - from pathophysiology to adequate intervention: a review and summary of an international expert meeting, Clin. Interv. Aging 11 189–208.	