20 May 2021
EMA/CHMP/209314/2021
Committee for Medicinal products for Human use (CHMP)

Overview of comments received on 'Deferasirox, dispersible tablets (125 mg, 250 mg and 500 mg), film-coated tablets (90 mg, 180 mg, and 360 mg), and granules (90 mg, 180 mg and 360 mg) product-specific bioequivalence guidance' (EMA/CHMP/472383/2020)

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

Stakeholder no.	Name of organisation or individual
1	Billev farmacija vzhod d.o.o.
2	ANSM (France)

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	N/A	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Page 2, Section "Bioequivalence study design"	1	**Comments:** The request for fasting and fed bioequivalence studies for film-coated tablets and granules should be revised to include only fasting study. <u>Introduction</u> The guidance deals with three different Deferasirox formulations: dispersible tablets (DT), film-coated tablets (FCT), and granules. The requirements for film-coated tablets and granules state that both fasting and fed studies must be performed. The reasoning behind this request is that since the specific formulation (excipients) is known to be critical to the performance in fed conditions both fasted and fed state comparisons of test to reference formulations are required. The requirement for dispersible tablets is set to only fasting study, as deferasirox dispersible tablets should be taken without food according to the SmPC, therefore, one study under fasting conditions is sufficient. <u>Composition of formulations</u> The aim of developing FCT was to improve patient compliance. The dispersible tablets contain lactose and sodium lauryl sulphate which are thought to cause gastro-intestinal side effects. Excipients for FCT were chosen to optimize the dissolution profile and stability whilst minimizing adverse effects. In contrast to the existing DT, the FCT do not contain	Not accepted. The reference product is considered to have specific formulation characteristics and, therefore, it cannot be assumed that the impact of food will be the same regardless of formulation. The products (film-coated tablets and granules) can be taken with or without a light meal. Thus, both fasted and fed state comparisons of test to reference formulations are required. A waiver for this fed study may be applicable if excipients that might affect bioavailability are qualitatively the same and quantitatively similar between test and reference product.

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		lactose which will ensure better acceptance in lactose-intolerant patients. The FCT require less disintegrant as they are intended to be swallowed rather than dispersed. As a result, the percentage of active substance in the formulation increased resulting in smaller tablets which are easier to swallow. Sodium lauryl sulphate was replaced by poloxamer 188 to further reduce gastric irritation. Microcrystalline cellulose was added in order to improve flow properties and a wet granulation step introduced in order to increase bulk density [1]. The composition of the granules is identical to the uncoated tablet cores of Exjade film-coated tablets, approved as a line extension in 2016 [2]. <u>Bioavailability of formulations</u> Exjade FCT and Exjade granules demonstrate higher bioavailability compared to the Exjade DT formulation. After adjustment of the strength, the FCT (360 mg strength) was equivalent to Exjade DT (500 mg strength) with respect to the mean area under the plasma concentration time curve (AUC) under fasting conditions. The Cmax was increased by 30% (90% CI: 20.3% - 40.0%); however, a clinical exposure/response analysis revealed no evidence of clinically relevant effects of such an increase [3]. After adjustment of the strength, the granules formulation (4 x 90 mg strength) was equivalent to Exjade DT (500 mg strength) with respect to the mean area under the plasma concentration time curve (AUC) under fasting conditions. The Cmax was increased by 34% (90% CI: 27.9% - 40.3%); however, a	

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		clinical exposure/response analysis revealed no evidence of clinically relevant effects of such an increase [4]. <u>Food effect on formulations</u> For DT, the total exposure (AUC) was approximately doubled when taken along with a high-fat breakfast (fat content >50% of calories) and by about 50% when taken along with a standard breakfast. The bioavailability (AUC) of deferasirox was moderately (approx. 13–25%) elevated when taken 30 minutes before meals with normal or high fat content. Hence, the Exjade DT must be taken on an empty stomach at least 30 minutes before food [5]. For FCT, A food-effect study involving administration of the FCT to healthy volunteers under fasting conditions and with a low-fat (fat content <10% of calories) or high-fat (fat content >50% of calories) meal indicated that the AUC and Cmax were slightly decreased after a low-fat meal (by 11% and 16%, respectively). After a high-fat meal, AUC and Cmax were increased (by 18% and 29%, respectively). Hence it is recommended that the FCT should be taken either on an empty stomach or with a light meal [3]. For granules, a food-effect study involving administration of the granules to healthy volunteers under fasting conditions and with a low-fat (fat content = approximately 30% of calories) or high-fat (fat content >50% of calories) meal indicated that the AUC and Cmax were slightly decreased after a low-fat meal (by 10%	

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		and 11%, respectively). After a high-fat meal, only AUC was mildly increased (by 18%). When the granules were administered with apple sauce or yogurt, a food effect was absent. The granules should hence be administered by sprinkling the full dose onto soft food, e.g. yogurt or apple sauce (pureed apple) and taken with or without a light meal [4]. It is thus clear, that greater bioavailability of deferasirox is expected when administering all three formulations after high fat meal. What is unclear though, is a reason for this food effect (i.e. greater deferasirox bioavailability when administered with a high fat meal). Deferasirox draft guidance states that the specific formulation (excipients) is known to be critical to the performance in fed conditions but does not specify one. More plausible explanation for this food effect would be the intrinsic property of deferasirox molecule. As it is BCS class II molecule (practically insoluble in water, good permeability [2]), it would generally be expected that the food would enhance its absorption [6,7]. Especially high fat meals would influence the absorption in the greatest amount, as deferasirox is subjected to enterohepatic recirculation. The administration of cholestyramine (which binds bile in the gastrointestinal tract to prevent its reabsorption) after a single dose of deferasirox resulted in a 45% decrease in deferasirox exposure [3-5]. Bile is discharged into the duodenum after high fat meals in order to aid the digestion of lipids in the small intestine. This reasoning is supported by clinical data from FCT and granule formulations after high fat and low-fat meals. High fat meals increase	

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		bioavailability of deferasirox for approx. 20%, while bioavailability after low fat meals is slightly decreased. <u>Generic deferasirox FCT formulations in EU</u> Additionally, generic FCT deferasirox registrations in EU were reviewed whether they performed fasting and/or fed studies. Public Assessment Reports were found for the following procedures: • EMEA/H/C/005014/0000 (Centralised procedure) Mylan performed fasting and fasting study with crushed tablet on apple sauce. • EMEA/H/C/005156/0000 (Centralised procedure) Accord performed only fasting study. • NL/H/4316/001-003/DC (DCP) Vivanta performed only fasting study. • NL/H/4317/001-003/DC(DCP) Vivanta performed only fasting study. • IS/H/0390/001-003/DC (DCP) Alvogen performed fasting and fasting study with crushed tablet on apple sauce. • NL/H/4516/001-003/DC (DCP) Synthon performed fasting and fasting study with crushed tablet on apple sauce. • NL/H/4517/001-003/DC (DCP) Synthon performed fasting and fasting study with crushed tablet on apple sauce.	

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		• NL/H/4518/001-003/DC (DCP) Sidiplast performed fasting and fasting study with crushed tablet on apple sauce. • NL/H/4519/001-003/DC(DCP) Exferana performed fasting and fasting study with crushed tablet on apple sauce. • NL/H/4520/001-003/DC(DCP) Synthon Hispania performed fasting and fasting study with crushed tablet on apple sauce. • NL/H/4521/001-003/DC(DCP) BioOrganics performed fasting and fasting study with crushed tablet on apple sauce. In the applications above, fasting study with crushed tablet on apple sauce was always performed due to a pre-March 2019 PKWP Q&A position. This has now been updated so that additional bioequivalence study with administration of crushed tablets is no longer required if the SmPC of the reference product allows for this possibility. None of the generic formulations present on the market in EU has performed a fed bioequivalence study. <u>Conclusions</u> As argued above, the possibility that the food effect is a result of the intrinsic properties of deferasirox molecule, is more plausible than due to specific excipient. Hence an additional bioequivalence study would be unnecessary, as fasting bioequivalence is considered to be the most sensitive condition	

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		to detect a potential difference between formulations [8]. As described in both deferasirox SmPCs [3,4], administration of FCT and granules with a light meal does not influence bioavailability and clinical efficacy and safety. Additionally, the nature of treatment with deferasirox requires regular monitoring of treatment effects and dose adjustments, so that even in the unlikely case of treatment with non-bioequivalent formulation, the treatment would be adjusted based on clinical efficacy and safety. Hence the risk to the patients would not be present even in the unlikely event of treatment with non-bioequivalent formulation. The requirements for fed study were also never imposed on submissions of marketing authorization holders for deferasirox FCT formulations currently present in EU. Various agencies approved submission based on fasting and/or fasting with apple sauce bioequivalence studies. We are therefore of the opinion, that the results of the fed study would not present additional valuable data and are hence not necessary to support successful demonstration of therapeutic equivalence of generic deferasirox FCT and granule formulations. **Proposed change:** Remove a request for fed bioequivalence study for film coated tablets and granules containing deferasirox.	

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		References: 1. Assessment report EXJADE, Procedure No. EMEA/H/C/000670/X/0043, EMA/CHMP/107225/2016, 28.1.2016, available on https://www.ema.europa.eu/en/documents/variation-report/exjade-h-c-670-x-0043-epar-assessment-report-extension_en.pdf 2. Assessment report EXJADE, Procedure No. EMEA/H/C/000670/X/0054, EMA/639290/2017, 14.9.2017, available on https://www.ema.europa.eu/en/documents/variation-report/exjade-h-c-670-x-0054-epar-assessment-report-extension_en.pdf 3. Summary of product information, Exjade film coated tablets, EMA, available on https://www.ema.europa.eu/en/documents/product-information/exjade-epar-product-information_en.pdf 4. Summary of product information, Exjade granules, EMA, available on https://www.ema.europa.eu/en/documents/product-information/exjade-epar-product-information_en.pdf 5. Summary of product information, Exjade dispersible tablets, EMA, available on https://www.ema.europa.eu/en/documents/product-information/exjade-epar-product-information_en.pdf	

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		6. Cheng L, Wong H. Food Effects on Oral Drug Absorption: Application of Physiologically-Based Pharmacokinetic Modeling as a Predictive Tool. Pharmaceutics. 2020 Jul; 12(7): 672. 7. Lenz K. Current Methods for Predicting Human Food Effect. AAPS J. 2008 Jun; 10(2): 282–288. 8. Guideline on the investigation of bioequivalence, : CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, EMA, available on https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf	
Low fat, light meal study conditions (approximately 250 to 300 kcal, meal fat content <10% of calories) according to the SmPC of the originator product.	2	**Comments:** In the guideline on investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), section 4.1.4 Study conduct – fasting or fed conditions – page 10, composition of an high-fat and high-calorie meal is clearly described : "the meal should be a high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 kcal) meal. This test meal should derive approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively. The composition of the meal should be described with regard to protein, carbohydrate and fat content (specified in grams, calories and relative caloric content (%)).”	The comment has been acknowledged; however, a general recommendation for the composition of a low fat and light meal is currently not foreseen. The recommended composition of the test meal for both formulations of deferasirox is according to the SmPC of the film coated tablets originator product as per the Guideline on investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

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		For a low fat and light meal, could you also detail the recommended kcal for protein, carbohydrate and fat, respectively?	