4 November 2024
EMA/479935/2024
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on `Methylphenidate, prolonged-release tablet 18 mg, 27 mg, 36 mg and 54 mg and modified release capsule 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg and 60 mg product-specific bioequivalence guidance' (EMA/94136/2024)

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

Stakeholder no.	Name of organisation or individual
1	Develco Pharma Schweiz AG
2	Novartis Pharma AG

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

1. General comments – overview

Stakeholder no.	General comment	Outcome
1	**Comment:** In general, we welcome the draft of a product-specific bioequivalence guidance for methylphenidate modified release products and are grateful for the opportunity to comment on it. However, we would like to point out that the methylphenidate clinical reference medicinal products (RMP) covered by this guidance are biphasic modified release (MR) products with a first phase determined by an immediate release (IR) dose fraction and a second phase determined by a prolonged release (PR) dose fraction. Moreover, the methylphenidate clinical RMPs currently available in the EU have different pharmaceutical properties and a different distribution of the active substance between the IR and the PR dose fraction. As cut-off time for the partialAUCs the tmin,between (tmin,between observed at Cmin,between, i.e. between IR Cmax and PR Cmax) after administration of the clinical RMP could be used, which separates the IR and PR parts of the biphasic in vivo plasma concentration time curve. The tmin,between can be derived from published data, pilot studies or determined in the pivotal studies for the clinical RMP in the single dose fasting and the single dose fed study, respectively. This approach has been successfully applied in bioequivalence studies, endorsed by the competent authorities and has led to several marketing authorizations for generic medicinal products of this class throughout the EU in recent years. In line with the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (CPMP/EWP/280/96 Corr1) However, due to the above-mentioned differences in the four clinical RMPs currently available in the EU, the time point for truncating the partialAUC based on the PK profile for the IR and the MR parts is not the same for all four RMPs. The question therefore	Please see responses for the specific comments.

Stakeholder no.	General comment	Outcome
	arises as to how these four different clinical RMPs can be covered in one product-specific bioequivalence guidance with generalised, fixed pharmacokinetic variables, in particular one fixed cut-off point for the partialAUCs to be universally applicable for all four clinical RMPs in this class. We agree that it would not be appropriate to establish separate product-specific bioequivalence guidance for each of the four clinical RMPs in this class. However, to ensure that the product-specific bioequivalence guidance is universally applicable for all products in this class, the cut-off points for partialAUCs should not be defined in the product-specific bioequivalence guidance, but should be justified and pre-specified in the respective study protocol depending on the clinical RMP used.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 4-7	1	**Comment:** The title of the guidance should clearly state that it refers to methylphenidate MR products with biphasic release properties and should be phrased in such a way that it applies to all products in this class. **Proposed change:** Methylphenidate, biphasic modified release products, 5 mg to 60 mg, product-specific bioequivalence guidance	**Not accepted** Although biphasic, the pharmaceutical denomination of these products is either "prolonged-release tablet" or "modified release capsule".
Line 23 Bioequivalence assessment	1	**Comment:** There are currently four methylphenidate biphasic MR clinical RMPs available in the EU which have different pharmaceutical properties and a different distribution of the active substance between the IR and the PR dose fraction. To ensure that the product-specific bioequivalence guidance is universally applicable for all products in this class, the cut-off points for partialAUCs should not be defined in the product-specific bioequivalence guidance, but should be justified and pre-specified in the respective study protocol depending on the clinical RMP used. **Proposed change:** Single dose fasting: AUC0-t, AUC0-inf, C_{max}, partialAUC(IR phase), C_{max}(IR phase), partialAUC(PR phase) and C_{max}(PR phase) Single dose fed: AUC0-t, AUC0-inf, C_{max}, partialAUC(IR	**Not accepted** Although different products, they all have in common an initial burst followed by a prolonged or a delayed releasing phase. Experience in the regulatory assessment has shown that it is possible to define common cut-off times for the partialAUC on both the fasting and fed condition for the different products. Literature also exists showing that these partialAUC are able to discriminate between different reference formulations (e.g., https://doi.org/10.5414/cpp47761).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		phase), C_{max}(IR phase), partialAUC(PR phase) and C_{max}(PR phase)	
Line 23 To be noted	1	**Comment:** There are currently four methylphenidate biphasic MR clinical RMP available in the EU which have different pharmaceutical properties and a different distribution of the active substance between the IR and the PR dose fraction. To ensure that the product-specific bioequivalence guidance is universally applicable for all products in this class, the cut-off points for partialAUCs should not be defined in the product-specific bioequivalence guidance, but should be justified and pre-specified in the respective study protocol depending on the clinical RMP used. **Proposed change:** To be noted: - This product-specific bioequivalence guidance covers methylphenidate biphasic modified release products with a first phase determined by an immediate release dose fraction (IR phase) and a second phase determined by a prolonged release dose fraction (PR phase). The time point for truncating the partialAUCs should be based on the PK profile for the IR and the MR parts respectively and should be justified and pre-specified in the study protocol. - *In vitro* studies of release in alcohol solutions should also be performed. - *In vitro* compatibility with mixing with applesauce should be demonstrated where applicable.	**Not accepted** See previous comment

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 23-24	2	**Comment:** The labelling of certain multiple unit formulations recommends that the product can be opened, and the beads can e.g. be sprinkled on soft foods. For the generics to indicate this additional type of administration, demonstrating bioequivalence is recommended, with the contents of the test and reference formulations opened and sprinkled on soft food. This is particularly important for modified release products as the disruption of the structure or coating of the modified release beads may lead to efficacy and safety concerns. Hence, we propose for an additional bioequivalence study under fasting condition, with the contents of the capsules sprinkled on soft food. **Proposed change:** For Multiple Unit Formulations Single dose fasting: All strengths or bracketing approach, healthy volunteers. Single dose fed: All strengths or bracketing approach, healthy volunteers. Single dose fasting: Highest strength, with capsule contents sprinkled on soft-food, healthy volunteers with successful demonstration of bioequivalence on the highest strength, bioequivalence studies on lower strengths can be waived, if the compositions of the strengths are proportional, the formulations contain identical beads produced by the same manufacturing process, and the dissolution profiles are similar. Background: Single dose fasting and fed studies are required for prolonged-release formulations without accumulation. Bioequivalence study with	**Not accepted** The capsules used on these products are not responsible for the release mechanism itself, that is simply coming from the proportion of IR and ER beads included in them. As such, it is considered that being shown BE in fasting and fed conditions (the extreme conditions) the additional mode of administration (e.g. capsules opened, and beads sprinkled on soft foods) can be waived based on appropriate *in vitro* studies.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the capsule contents sprinkled on soft-food is required for products to indicate such additional type of administration. Bioequivalence studies are required on all the strengths (or bracketing approach) if the strengths are not proportionally formulated.	
Line 23-24	2	**Comment:** Bioequivalence studies on the highest strength can be considered sufficient when the formulations are proportional in nature. In case of multi-unit formulations, if the beads are produced in bulk and filled in capsule by weight to match the appropriate dose, BE studies at the highest strength can be considered adequate. However, if the beads for different strengths are manufactured separately and filled in capsule, to demonstrate formulation proportionality across different strengths, additional BE studies on other strengths are recommended. **Proposed change:** For Multiple Unit Formulations Single dose fasting: All strengths or bracketing approach, healthy volunteers. Single dose fed: All strengths or bracketing approach, healthy volunteers. Single dose fasting: Highest strength, with capsule contents sprinkled on soft-food, healthy volunteers with successful demonstration of bioequivalence on the highest strength, bioequivalence studies on lower strengths can be waived, if the compositions of the strengths are proportional, the formulations contain identical beads produced by the same manufacturing process, and the	**Not agreed** The requirement of the different strengths being produced by the same manufacturing process and with proportional composition (identical beads or pellets) is already a regulatory condition for strength biowaiver existing in the relevant guidelines and there is no need to repeat this in the context of a product-specific bioequivalence guidance.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		dissolution profiles are similar. Background: Single dose fasting and fed studies are required for prolonged-release formulations without accumulation. Bioequivalence study with the capsule contents sprinkled on soft-food is required for products to indicate such additional type of administration. Bioequivalence studies are required on all the strengths (or bracketing approach) if the strengths are not proportionally formulated.	
Line 23-24	2	**Comment:** Certain long-acting methylphenidate exhibit bi-modal absorption profile with two peaks within 10 hours and the concentrations of Methylphenidate are expected to be below threshold of efficacy approximately 10 hours post dose. The efficacious plasma levels within the active hours of children are important to ensure quality of life. Hence the criteria to meet equivalence of AUC0-3h and AUC3-10h is important to ensure the required plasma levels before 10 hours and minimal contribution of AUC after 10 hours considering the efficacy and safety. We recommend splitting the AUC3-24h to AUC3-10h and AUC10-24h for fasting condition and AUC4-24h to AUC4-10h and AUC10-24h for fed condition. **Proposed change:** Main pharmacokinetic variables: Single dose fasting and Single dose fasting with soft food: AUC0-t, AUC0-inf, Cmax, AUC0–3h, Cmax0-3h, AUC3–10h, AUC10–24h and Cmax3-	**Not accepted** The inclusion of a partialAUC from 10h to 24h, as the stakeholder proposes, where the methylphenidate concentrations are expected to be below threshold would probably result in a highly variable parameter without any expected major gain in comparing formulations, especially taking in consideration the remaining large number of primary parameters already required.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		10h Single dose fed: AUC0-t, AUC0-inf, Cmax, AUC0–4h, Cmax0-4h, AUC3–10h, AUC10–24h and Cmax4-10h.	