23 February 2017
EMA/CHMP/810545/2016
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on Paliperidone palmitate depot suspension for injection 25 mg, 50 mg, 75 mg, 100 mg and 150 mg product-specific bioequivalence guidance (EMA/CHMP/474825/2016)

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

Stakeholder no.	Name of organisation or individual
1	Alkermes Pharma Ireland Limited (Alkermes)
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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Alkermes Pharma Ireland Limited (Alkermes) respectfully submits these comments in response to the August 2016 release by the European Medicines Agency (EMA) of the draft "Paliperidone palmitate depot suspension for injection 25, 50, 75, 100 and 150 mg product-specific bioequivalence guidance" (EMA/CHMP/474825/2016) (referred to below as the draft guidance) for public consultation. The reference medicinal product that serves as the basis for the draft guidance is Xeplion® paliperidone palmitate prolonged release suspension for intramuscular (IM) injection, indicated for the maintenance treatment of schizophrenia in adult patients stabilized with paliperidone or risperidone. Xeplion – a Janssen-Cilag International NV product – uses modified-release technology developed in partnership with Alkermes to deliver rapid and sustained therapeutic levels of paliperidone through a single injection administered once every month. Maintaining the continuity of treatment and preventing future psychotic episodes are primary goals in the treatment of schizophrenia. Achieving these goals is confounded by the impact of the underlying disease on the cognitive functioning of patients. To address this problem, paliperidone IM depot is designed, formulated, and manufactured to release the active ingredient in a predictable and consistent manner, beginning immediately after the initial injection of the product and sustained throughout the entire dosing interval at steady-state. As a result, the product offers patients the benefit of receiving long-term antipsychotic treatment with only one	

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	injection every month, improving patient compliance and minimizing the serious and potentially life-threatening consequences of relapse. Furthermore, the carefully controlled release of active ingredient from the depot into systemic circulation avoids serious, concentration-dependent adverse events including extrapyramidal symptoms (EPS) and QTc interval prolongation. Two medicinal products are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their rate and extent of bioavailability lie within acceptable predefined limits when administered in the same molar dose. For modified-release medicinal products EMA generally requires that bioequivalence be established through both single-dose and multiple-dose pharmacokinetic (PK) studies. ("Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms" (EMA/CPMP/EWP/280/96 Corr1) (referred to below as the MR guideline).) For single-dose studies, bioequivalence should be demonstrated by showing equivalence after statistical evaluation of the PK parameters $AUC_{(0-t)}$, $AUC_{(0-inf)}$, and C_{max}. For the multiple dose study, equivalence should be established based on statistical evaluation of $AUC_{(0-tau)}$, $C_{max,ss}$, $C_{tau,ss}$. The MR guideline provides that the normally required multiple-dose study may be waived if it is demonstrated that there is low risk of accumulation, i.e., a single-dose study at the highest approved strength has shown that $AUC_{(0-tau)}$ (active substance released in a single dosing-interval) is greater than 90% of $AUC_{(0-inf)}$. When a multiple-dose study is not required, the shape of the single-dose PK curve should be analysed using partial AUC. Furthermore, if a	

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	product is multiphasic, EMA will generally require partial AUC analysis on the single-dose PK profile to evaluate bioequivalence in all phases, regardless of whether multiple-dose studies are also required. As per the EMA's MR guideline, single-dose and multiple-dose studies are generally required for IM depot formulations. However, in situations where it is not possible to perform single-dose studies in healthy volunteers, EMA instructs that multiple-dose studies in patients may be acceptable, and the usual requirement for single-dose studies can be waived. In such cases, the EMA will not have the benefit of comparative PK data from a single-dose study in healthy volunteers, and the MR guideline does not otherwise provide instruction on how to analyse the shape of the single-dose release profile for IM depot dosage forms with both rapid and sustained release properties. Paliperidone palmitate depot suspension has a clinically important single-dose PK profile exhibiting biphasic kinetics with zero-order release during the first two weeks, followed by first-order release. (Samatani, M.N., *et al.*, Population Pharmacokinetics of Intramuscular Paliperidone Palmitate in Patients with Schizophrenia A Novel Once-Monthly, Long-Acting Formulation of an Atypical Antipsychotic, *Clin. Pharmacokinet.* (2009) 48(9):585-600.) The rate and extent of each phase is important for achieving early onset, as well as for establishing and maintaining steady-state in accordance with the authorized dosing regimen. Initial therapeutic plasma levels are facilitated by the first phase of release and are generally attained by 72 hours. ("Assessment Report" (EMA/60983/2011) (p. 59/118).) Likewise, the shape of the single-dose PK profile affects the onset of	

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	steady-state and may impact maintenance therapy upon switching between the reference medicinal product to a proposed generic product with a different PK profile. As a result, a generic paliperidone palmitate depot suspension with delayed or altered single-dose release properties may differ in onset and maintenance properties, and may result in significant disruption to therapeutic levels upon switching at steady-state. EMA's draft guidance for paliperidone palmitate depot suspension does not adequately account for the single-dose PK profile. Instead, it relieves sponsors from conducting single-dose studies because such studies in healthy volunteers are not considered feasible. The draft guidance specifies a multiple-dose study only (to be conducted on any strength), with bioequivalence to be established based on statistical evaluation of $AUC_{(0\text{-}tau)}$, $C_{max.ss}$, $C_{tau.ss}$ (90% confidence interval, 80-125%). Accordingly, Alkermes submits the following three specific comments to enable the EMA to revise the draft guidance so as to help avoid unnecessary risk of relapse or adverse events in patients who may be exposed to a generic medicinal product with a different PK profile.	
2	According to the *Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1)*, Section 6.8.2.1 (Parameters to be evaluated), for multiphasic modified release products, statistical evaluation of single-dose PK parameters (partial AUCs, C_{max}, $AUC_{0\text{-}t}$ and AUC_{inf}) and multiple dose PK parameters ($C_{max.ss}$, $C_{tau.ss}$ and $AUC_{0\text{-}tau.ss}$) have to show bioequivalence. The draft product-specific bioequivalence guideline for paliperidone palmitate (EMA/CHMP/474825/2016) only requires a	Partly accepted. It is acknowledged that single-dose studies in patients stabilized on other antipsychotic drugs are possible to conduct. Differences in the initial release phase may be of importance for efficacy and safety at least for initial treatment and after switching from oral paliperidone. It is uncertain if a multiple-dose bioequivalence study will be able to detect a clinical relevant difference in the absorption rate. As a precautionary measure, it is agreed that waiving

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	multiple dose parallel or cross-over bioequivalence study, evaluating $C_{max.ss}$, $C_{tau.ss}$ and $AUC_{0\text{-}tau.ss.}$ The following argumentation will explain that the suggested multiple dose parallel or cross-over study at steady-state, is insufficient to detect inadequate release of paliperidone during the first phase of the release. It is suggested that a single dose bioequivalence study would be a necessary complement to a multiple dose cross-over switching study in order to enable the detection of significant differences between the reference medicinal product (hereafter referred to as "reference paliperidone palmitate") and the test medicinal product (hereafter referred to as "test paliperidone palmitate"). Paliperidone Palmitate (Xeplion or reference paliperidone palmitate) is characterized by a biphasic release profile: an initial zero-order release phase during the first two weeks, and subsequently a first-order release phase. The selection of paliperidone palmitate 150 mg eq. on Day 1 and 100 mg eq. on Day 8 as the initial doses is based on the demonstrated efficacy and safety of the doses as well as on their ability to rapidly result in plasma concentrations within the potential therapeutic range for pharmacologic effect. The 72-hour time point in administration of Xeplion reflects a turning point between a phase of increasing exposure to paliperidone and a phase of more stable exposure. If the test paliperidone palmitate has a different release profile, this may result in (1) different rate and extent of plasma concentrations upon initiation with the test paliperidone palmitate which could lead to i.e. efficacious systemic exposure being observed 1 or 2 weeks	of a single-dose bioequivalence study is not recommended. The product specific guidance document has been updated. Including additional requirements for demonstration of bioequivalence for partial AUCs is not supported. In the single-dose bioequivalence study evaluation of $AUC_{0\text{-}t}$, AUC_{inf} and C_{max} is recommended as primary parameters. In addition T_{max} (median and range) should be comparable to assure that there is no relevant difference in rate of absorption and lag time. Xeplion exhibits flip-flop kinetics, i.e. the rate of elimination is determined by the absorption rate. A difference in absorption rate between two formulations is expected to be sufficiently detected if bioequivalence is evaluated after both single-dose and multiple-dose administration. If bioequivalence is satisfactorily demonstrated after both single and multiple-dose administration, an additional multiple-dose switching study is not deemed necessary. It is agreed that a crossover design is generally preferred in bioequivalence studies. A parallel group design is however acceptable for substances with long half-life if the demographic characteristics are comparable in both groups. It is usually more difficult to demonstrated bioequivalence in

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	later than for reference paliperidone palmitate and (2) when switching patients between reference paliperidone palmitate and a test paliperidone palmitate with i.e. a lag period of 1 or 2 weeks, different systemic drug concentrations (C_{trough}, C_{max} and AUC_{tau}) in the first few dosing cycles directly after switching may occur. These consequences would unnecessarily place patients at risk for adverse events or lack of efficacy (relapses) from improper release of paliperidone palmitate from the test paliperidone palmitate. In response to the draft bioequivalence guideline for paliperidone palmitate one-month injectable, which was first released by the US FDA in 2011, Janssen drafted a Citizen Petition (https://www.regulations.gov/document?D=FDA-2013-P-0608-0001). For this Citizen Petition, Janssen simulated different switching scenarios to determine if a product with different release properties but the same C_{max} and AUC after single dose could, upon switching, have different C_{trough}, C_{max} and AUC_{tau} during the next dosing cycles. The simulations were performed using the validated population PK model for Xeplion that was also used to support dosing recommendations in the SmPC. Evaluation of steady-state PK parameters from a multiple dose parallel study design will not permit detection of different release profiles among test and reference paliperidone palmitate. Since absorption is subject-specific, a parallel design does not allow the within-subject (intra-subject) determination of equivalence of the release profiles of test and reference paliperidone palmitate. A difference in release profiles among test and reference paliperidone palmitate could potentially become problematic upon switching between these two products or upon initiation of the test paliperidone	a parallel group than in a crossover study. Thus, this is not considered to be an advantage in the evaluation of bioequivalence.

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	palmitate. Patients may be exposed to an excessive amount of paliperidone that, in turn, could lead to significant adverse events. Alternatively, such switching may cause patients to undergo periods with inadequate release of paliperidone that could result in decreased efficacy and clinically significant relapses. A switching study, such as a steady-state two-period cross-over study may enable such detection, provided that transient C_{min}, C_{max} and AUC_{tau} are thoroughly evaluated by extensive PK sampling during the first dosing intervals after switching. A parallel design does not provide the opportunity to measure the potential impact of differences in release profiles among test and reference paliperidone palmitate on C_{min}, C_{max} and AUC_{tau} upon switching between these two products or upon initiation of the test paliperidone palmitate .Additionally, a single dose bioequivalence study would be a necessary complement to this multiple dose cross-over switching study evaluating $pAUC_{0-72h}$ and $pAUC_{0-28d}$, in addition to the traditional bioequivalence metrics of C_{max}, AUC_{0-t} and AUC_{inf}. Such a single-dose bioequivalence study would provide greater assurance that differences that are potentially clinically significant between test and reference paliperidone palmitate will be detected. Like all antipsychotics, paliperidone products are tolerated less well by healthy volunteers compared to patients with schizophrenia and a single-dose bioequivalence study in healthy volunteers is not favourable. However, it is feasible to perform single-dose bioequivalence studies in patients with schizophrenia of both the one-month injectable of paliperidone palmitate (Cleton *et al.* J Clin Pharmacol. 2014;54(9):1048-1057) and the 3-month injectable of	

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	paliperidone palmitate (Ravenstijn *et al.* J Clin Pharmacol. 2016;56(3):330-339). In these studies, patients diagnosed with schizophrenia were included that were on treatment with antipsychotics other than paliperidone- or risperidone-based products. All allowed medications, including antipsychotics that had been started before screening, were continued during the course of the study. Medications that could potentially affect or interfere with the measurement of the PK of paliperidone were prohibited. Antipsychotics not allowed during the open-label phase were risperidone, paliperidone, clozapine, ziprasidone, thioridazine, and all long-acting injectable antipsychotics (Ravenstijn *et al.* J Clin Pharmacol. 2016;56(3):330-339). In summary, to ensure bioequivalence of test and reference paliperidone palmitate, it is strongly recommended to perform a single dose bioequivalence study evaluating $pAUC_{0-72h}$, $pAUC_{0-28d}$, C_{max}, AUC_{0-t} and AUC_{inf} as well as a multiple dose, steady-state two-period cross-over study evaluating transient C_{min}, C_{max} and AUC_{tau} during the first dosing intervals after switching and $C_{max,ss}$, $C_{tau,ss}$ and $AUC_{0-tau,ss}$. A parallel study design is not recommended as it will not permit detection of different release profiles among test and reference paliperidone palmitate.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 18	1	Comment: EMA is taking the position that an otherwise required single-dose study in healthy volunteers is not feasible in this case. Because the single-dose PK profile is both clinically important and is not reflected in the currently specified steady-state equivalence metrics, Alkermes believes the EMA should require a single-dose bioequivalence study in patients. Generally single-dose studies are recommended for immediate and modified-release products because they are the most direct way of evaluating systemic bioavailability, and are more sensitive in determining PK differences between test and reference medicinal products. In this case, in order to ensure bioequivalence in the onset and run-in period, as well as sustained release, the study should specify partial AUCs (AUC_{0-72h} and AUC_{0-28d}) in addition to the usual requirement to analyse $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max}. With regard to onset, the initiation regimen was designed to rapidly attain therapeutic paliperidone concentrations when initiating therapy without the use of oral supplementation. In Study PSY-3006, for example, mean paliperidone plasma concentrations exceeded a previously established antipsychotic efficacy threshold of 7.5 ng/mL from the first sampling	See response to General comments from Stakeholder No 2 above.

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		point after dosing (Day 4, i.e., 72 hours after dosing). As observed by the EMA, "the majority of subjects receiving the recommended initiation regimen achieved a therapeutic concentration of paliperidone (>7.5 ng/mL) by Day 4." (EMA Assessment Report for Xeplion (EMA/60983/2011) (p. 59/118).) Similarly, the inability of EMA's current proposal for paliperidone palmitate IM depot to capture potential differences in the PK profiles of proposed generic products could become problematic when switching treatment between reference medicinal product and generic products with different release properties. Patients may be exposed to an excessive amount of paliperidone, leading to significant adverse events, or may undergo periods with inadequate exposure leading to decreased efficacy and relapse. Accordingly, Alkermes respectfully submits that EMA should revise the draft guidance to include a single-dose study in patients, and evaluate bioequivalence using $pAUC_{(0\text{-}72h)}$ and $pAUC_{(0\text{-}28d)}$ in addition to the traditional bioequivalence metrics C_{max}, $AUC_{(0\text{-}t)}$ and $AUC_{(0\text{-}inf)}$. The 72 hour time point is the first time-point for which an association with clinical effect has been shown. Therefore, $pAUC_{(0\text{-}72h)}$ will help ensure equivalence in initial onset, and $pAUC_{(0\text{-}28d)}$ will help ensure bioequivalence of release over the course of a single dosing interval and will help avoid disrupted	

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		therapy upon switching. Proposed change (if any): *A single dose study in patients should be included. Such a study should specify partial AUCs (AUC_{0-72h} and AUC_{0-28d}) in addition to the usual requirement to analyse $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max}*	
Line 18	1	Comment: Given the importance of the PK profile to the overall efficacy of the medicinal product during the dosing interval, and the risk of disruptions to therapy upon switching and potentially serious adverse events, Alkermes believes the guidance must be amended to specify a multiple-dose cross-over study design capable of evaluating the effect of switching. Specifically, in order to help ensure there is no disruption in therapeutic levels, Alkermes believes that EMA should clarify in the draft guidance that a 2-sequence, 2-way cross-over multiple-dose study is required, with evaluation of transient changes in C_{min}, C_{max}, and $AUC_{(0-tau)}$ after patients are switched from reference to test and vice-versa, in addition to overall $AUC_{(0-tau),ss}$, $C_{max,ss}$, $C_{tau,ss}$.	See response to General comments from Stakeholder No 2 above.

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		Proposed change (if any): *The draft guidance should be revised to include additional detail regarding the multiple-dose study design. Specifically, the recommended study should comprise a 2-sequence, 2-way cross-over switching multiple-dose study with evaluation of transient C_{min}, C_{max}, and AUC_{tau} upon switching.*	
Line 18	1	Comment: In light of the clinical impacts that may result from inadequate or excessive treatment with paliperidone, it is critical to ensure that any proposed generic medicinal product maintains an equivalent release profile. The release of paliperidone palmitate is characterized by a biphasic release profile: an initial zero-order release phase (i.e., the same amount of active substance is released per day) during the first two weeks, and subsequently a first-order release phase (i.e., the amount released per day diminishes, proportionally to the amount left at the injection site). The release profile is controlled by the particle size and distribution of paliperidone palmitate within the particle, which are functions of the manufacturing technology. As a result, even products having similar quantitative and qualitative composition can have significantly different PK profiles while having equivalent	Not applicable as the EMA suggests to amend the draft guidance (see response to General comments from Stakeholder No 2 above).

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		C_{max} and AUC after a single-dose administration. Accordingly, Alkermes suggests that EMA amend the draft guidance to include a single-dose study in patients, with partial AUC analysis consistent with Alkermes Specific Comment 1. Alternatively, if it is determined that a single-dose study cannot reasonably be conducted, a comparative *in vitro* study should be included in place of the single-dose *in vivo* study, with statistical analysis of the release profile to determine that there are no significant differences in release rates between test and reference products. To be clear, the *in vivo* single-dose study would be considered a stronger, more sensitive model and, thus, should be preferred over an *in vitro* study. However, an *in vitro* study could be designed to take the place of the single-dose *in vivo* study if it is determined that the *in vivo* study cannot be conducted. For such an *in vitro* study, we suggest the f2 test be used to show similarity in dissolution profile between test and reference samples. According to EMA, comparative dissolution testing must be used to "demonstrate in certain cases similarity between different formulations of an active substance and the reference medicinal product." ("Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), Appendix 1.) In such cases, the similarity factor, f2, statistical	

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		test is used to analyse release profile similarity. Thus, if a single-dose *in vivo* study with partial AUC analysis is not included in the revised guidance then Alkermes recommends that, at minimum, an *in vitro* study with f2 analysis be required; with adequate sampling of early time points to help ensure bioequivalence with respect to the early release phase. Proposed change (if any): *An in vitro study (biorelevant comparative dissolution assay) should be included as a requirement of bioequivalence, with equivalence based on f2 analysis; with adequate sampling of early time points to help ensure bioequivalence with respect to the early release phase.*	