Janssen Research & Development, LLC
Global Regulatory Affairs
Neuroscience Therapeutic Area

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2014 APR 11 A 9:42

janssen

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

April 10, 2014

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061, HFA-305
Rockville, MD 20852

Re: Submission to Supplement to Docket No. FDA-2013-P-0608/CP

Dear Sir or Madam:

The above-referenced Citizen Petition was filed in May 2013 by Janssen Research and Development, L.L.C. (JRD) on behalf of Janssen Pharmaceuticals, Inc. (JPI) requesting that FDA require that any ANDA referencing INVEGA® SUSTENNA® (paliperidone palmitate) extended-release injectable suspension meet certain conditions, including conditions related to demonstrating bioequivalence. While FDA has not yet responded to the petition, it has released a revised "Draft Guidance on Paliperidone Palmitate" in December 2013 (Dockert No. FDA-2007-D-0369; Formely Docket No. 2007D-0168). This Revised Draft Guidance addressed some of the same concerns raised in the petition, but did not address all of them. On February 11, 2014, JRD submitted comments to the Revised Draft Guidance docket.

JRD hereby requests that the comments submitted to the Revised Draft Guidance docket, which are attached hereto, be considered a supplement to the Citizen Petition. JRD believes that the PK suggestions in the original petition are preferable to the requirements set forth in the December 2013 Revised Draft Guidance, but is submitting this supplement for consideration by FDA in the event FDA does not accept those suggestions.

The undersigned makes the following verification for this submission, as required by 21 USC 355(q)(1)(I):

I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about December 5, 2013. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: __N/A_____ I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

In addition, the undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that includes representative data and information known to the petitions which are unfavorable to the petition.

Sincerely,

Donald L. Heald

Donald L. Heald, Ph.D.
Clinical Pharmacology Therapeutic Area Head for Neurosciences

Docket No. FDA-2007-D-0369

Janssen Research & Development, LLC
Global Regulatory Affairs
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February 11, 2014

Division of Dockets Management (HFA-305)
Docket No. FDA-2007-D-0369
(formerly Docket No. 2007D-0168)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RLD Application Number: NDA 22-264

Re: Docket No. FDA-2007-D-0369 (Formerly Docket No. 2007D-0168) "Draft Guidance for Industry on Bioequivalence Recommendations for Paliperidone Palmitate Extended-Release Injectable Suspension" revised December 2013; Requests for Comments

Dear Sir/Madam:

On behalf of Janssen Research & Development, L.L.C.[1] ("Company"), a company of Johnson & Johnson, we are providing the following comments and recommendations in response to the U.S. Food and Drug Administration ("FDA") revised guidance entitled "Draft Guidance on Paliperidone Palmitate," revised in December 2013 ("Revised Draft Guidance"), for paliperidone palmitate intramuscular injection.

In response to the FDA's release of the initial Draft Guidance issued August 2011, ("Draft Guidance"), the Company (formerly Johnson & Johnson Pharmaceutical Research & Development, L.L.C. ["J&JPRD"]) submitted comments on 28 February 2012.

In May 2013, the Company submitted "A Citizen Petition Concerning Bioequivalence of Proposed Generic Versions of INVEGA® SUSTENNA®" ("Citizen Petition") to the FDA. In light of potentially significant safety and efficacy issues during *de novo* treatment with a generic or follow-on product or in a switching scenario, the Company requested that FDA not approve a generic or follow-on product unless the agency has assured bioequivalence by requiring

[1] The Company is the authorized regulatory agent for Janssen Pharmaceuticals, Inc. ("JPI"). JPI is the holder of the New Drug Application for INVEGA® SUSTENNA® (paliperidone palmitate). The former holder of the NDA, Ortho-McNeil-Janssen Pharmaceuticals, Inc. was renamed JPI.

applicants to measure the following PK parameters: $pAUC_{0\text{-}72h}$, and $pAUC_{0\text{-}28d}$, in addition to the traditional bioequivalence metrics of C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$.

The Company evaluated the new bioequivalence study design in the Revised Draft Guidance. The comments below address areas in which the new proposal does not fully address the safety and efficacy concerns raised earlier, or are unclear. The Company is planning to submit a supplement to the Citizen Petition to address these concerns, in addition to submitting these comments.

1. BACKGROUND

INVEGA® SUSTENNA® 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.

As described in more detail in the initial Citizen Petition filed May 9, 2013 (Docket No. FDA-2013-P-0608),[2] the Company believes that potentially significant safety and efficacy issues may arise if FDA accepts bioequivalence determinations for proposed generic products based solely on the traditional PK metrics of C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$, since reliance solely on these metrics may not detect potentially significant and clinically meaningful differences stemming from different PK profiles of INVEGA® SUSTENNA® and proposed test products. That would be especially problematic if INVEGA® SUSTENNA® and generic products with different release properties are switched, resulting in patients undergoing periods with inadequate paliperidone release, as shown in Figures 2 through 5 of the Citizen Petition, that could result in decreased efficacy and clinically significant relapses or in increased risks for adverse events.

The Company requested that FDA not approve a generic or follow-on product unless the agency has assured bioequivalence by requiring applicants to measure the following PK parameters: $pAUC_{0\text{-}72h}$, and $pAUC_{0\text{-}28d}$, in addition to the traditional bioequivalence metrics of C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$.

The Company believes that the study design requested in the Citizen Petition provides greater assurance that differences that are potentially clinically significant will be detected and therefore continues to request adoption of that study design. However, in the event that FDA proceeds with the study design set forth in the Revised Draft Guidance, the Company believes the study may be appropriate but the end points are not adequate to detect potentially clinically significant differences in the release characteristics to allow patients to safely start de novo on the generic or follow-on product. The Company is therefore providing the recommendations set forth in the remainder of these comments.

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[2] A color copy of the citizen petition was re-filed on May 10, 2013.

2. RECOMMENDATIONS FOR THE REVISED DRAFT GUIDANCE

In the event that FDA does not adopt the recommendations set forth in the initial Citizen Petition dated May 2013, the Company is concerned that the study design proposed in the Revised Draft Guidance is not sufficiently sensitive to detect differences in the release characteristics of paliperidone from a generic or follow-on product.

The Company believes that generic and follow-on products with different PK profiles will unnecessarily place patients at risk for adverse events or lack of efficacy from improper release of paliperidone palmitate. Those adverse effects may arise both from inadequate treatment of schizophrenia, as well as from excessive or insufficient release of paliperidone. Evaluating the potential for both of these effects is considered critically important.

As described in the Citizen Petition, two different switching scenarios were simulated to investigate whether products with different release properties but the same C_{max} and AUC after single dosing could, upon switching, have a different trough concentration, C_{max}, and AUC_{tau} during the next dosing cycles. In the first scenario, the consequences of switching between INVEGA® SUSTENNA® and a generic or follow-on product with delayed release properties (start of release is delayed by a lag period of 1-5 weeks) but no other changes in the release characteristics were simulated. In the second scenario, the consequences of switching between INVEGA® SUSTENNA® and a generic or follow-on product with altered release properties were simulated. Both simulations demonstrated that such switching can result in significant changes in the systemic drug concentrations for a significant time afterwards. Similarly, these simulations reveal that, when switching patients between INVEGA® SUSTENNA® and a generic or follow-on product with a lag period of 1 or 2 weeks, the transient C_{min} or C_{max} upon switching would be within the 80-125% BE criteria (see page 15 of the Citizen Petition). However, such delay in release by 1 or 2 weeks is clinically important when treating patients *de novo* with the generic or follow-on product, given that efficacious systemic exposure may be observed 1 or 2 weeks later than observed for INVEGA® SUSTENNA® (i.e., after 72 hours). These simulations show that a switching study at steady-state only is inadequate to detect inadequate release of paliperidone during the first phase of the release and confirm that the newly proposed study design does not provide an adequate alternative to the Company's proposal (Citizen Petition dated May 2013) to control for the early release by implementing partial AUC measures. Based upon these simulations, it is possible that a single dose BE study would be a necessary complement to the switching study in order to enable the detection of significantly different generic or follow-on products.

2.1 Comments on the Recommended Multiple Dose Study

2.1.1 Study Design

The study design described in the Revised Draft Guidance requires completion of a steady-state 2-period cross-over study. From this description, it is not clear whether FDA intends a cross-over bioequivalence study, simply comparing steady-state PK parameters $AUC_{tau,ss}$, $C_{max,ss}$ and $C_{min,ss}$

for reference and follow-on drug product, or a cross-over switching study (with a direct switch between drug products), evaluating also the changes in exposure upon switching. The first scenario, ie, cross-over multiple dose bioequivalence study evaluating solely steady-state PK parameters, will not enable detection of inadequate paliperidone intramuscular drug products with a different release profile (see simulations in Citizen Petition, Figures 2 through 5), whereas the switching 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.

The Revised Draft Guidance provides that "in period 2 (when patients are switched from reference to test or vice versa)....", which suggests that FDA indeed intends a switching study, such that patients stabilized on the reference drug before enrollment in the study will be randomized to one of the two sequences (reference/follow-on or follow-on/reference) in a randomized, two-way, 2-sequence cross-over switching study. The Company agrees that a 2-sequence, 2-way cross-over switching study, evaluating transient C_{min}, C_{max} and AUC_{tau} in all dosing intervals upon switching is appropriate. Given the critical importance of detecting inadequate paliperidone intramuscular drug products, it is recommended that the expected study design be clarified in more detail to avoid potential misinterpretation.

2.1.2 PK Parameters to be Assessed

The Revised Draft Guidance specifies that the 90% confidence interval for the ratio of geometric means of AUC and C_{max} should be within 80-125%. No criteria were specified for C_{min}. Although the Revised Draft Guidance states that individual and average $C_{min,SS}$ should be submitted for review, the Revised Draft Guidance does not state that the 90% confidence interval for the ratio of geometric means of $C_{min,SS}$ should be within 80-125%.

As outlined in Citizen Petition (see Section B.1), even small and temporary reductions in exposure to paliperidone could lead to significant risks of clinical relapse. While not all patients will relapse due to short interruptions in treatment - even if these interruptions recur due to INVEGA® SUSTENNA® and follow-on product being used interchangeably - for those patients who are susceptible and who are being prescribed INVEGA® SUSTENNA® because non-adherence has been demonstrated and linked to repeated relapse, the consequences of further relapse(s) may be severe. In the clinical setting, relapse is closely linked to adherence with medication, and therefore even small changes in the plasma exposure might trigger a relapse.[3] Therefore, therapeutic equivalence in terms of efficacy requires sustained exposure during the entire dosing interval, and it is accordingly essential to ensure bioequivalence in terms of $C_{min,SS}$.

In addition, it is unclear how to estimate $C_{max,SS}$ and $C_{min,SS}$. Given that $C_{min,SS}$ and $C_{max,SS}$ may be different in the first three to four cycles after switching (see simulations in Citizen Petition,

[3] Morken G et al. BMC Psychiatry 2008, 8:32 doi:10.1186/1471-244X-8-32.

Figures 2 through 5), it is recommended that transient C_{min}, C_{max} and AUC be estimated in each dosing interval upon switching. It is also recommended that estimation of $C_{min,ss}$ and $C_{max,ss}$ be defined based on transient minimum and maximum exposure values estimated in each dosing interval Given the importance to patient safety of ensuring that peak exposure does not change significantly upon switching - and given the importance to efficacy in ensuring that minimal exposure does not change - it is important to characterize these parameters adequately. Therefore, the Company recommends that FDA define how to estimate $C_{min,ss}$ and $C_{max,ss.}$, i.e. by evaluating transient minimum and peak exposure upon switching.

2.2 Dissolution Specifications to Control for Early Release

The Revised Draft Guidance recommends comparative dissolution testing of all strengths of the test and reference products, with the dissolution specifications to be determined upon review of the application.

As described in the initial Citizen Petition dated May 2013 (see Figures 2, 3 and 10), evaluation of bioequivalence in a multiple dose bioequivalence switching study is not sensitive to detect potentially clinically relevant delays in the initial release. The possibility of such delays is especially critical when treating patients de novo with a generic or follow-on product. For example, when switching from INVEGA® SUSTENNA® to a generic or follow-on product with a lag period of 1 or 2 weeks, the transient C_{min} or C_{max} upon switching would be within the 80-125% BE criteria (see page 15 of Citizen Petition). However, such delay in release by 1 or 2 weeks is clinically important when treating patients *de novo* with the generic or follow-on product, given that efficacious systemic exposure is observed for INVEGA® SUSTENNA® after 72 hours and patients switching to a new antipsychotic are at increased risk of relapse compared with those remaining on their previous antipsychotic medications.[4] Given that the Revised Draft Guidance only includes a switching study at steady-state, which is not sufficiently sensitive to control for inadequate release from a generic or follow-on product during the initial release phase, and taking into consideration the potential clinical consequences of inadequate early release, it is recommended that the applicants use the same dissolution specifications as those defined for the original drug product, including at the early time points to ensure adequate control for the early release phase.

3. SUMMARY AND CONCLUSION

The Company believes that the Revised Draft Guidance would not fully address the safety and efficacy issues raised in the Citizen Petition; however, with the addition of additional endpoints, the methodology proposed in the Revised Draft Guidance may be adequate to detect such differences.

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[4] Essock SM, Covell NH, Davis SM, Stroup TS, Rosenheck RA, Lieberman JA,. Effectiveness of Switching Antipsychotic Medications Am J Psychiatry 2006;163:2090-2095. doi:10.1176/appi.ajp.163.12.2090

Accordingly, the Company recommends that FDA modify the Revised Draft Guidance to:

- Clarify that a randomized, 2-sequence (reference/follow-on and follow-on/reference sequences) cross-over switching study, evaluating transient C_{min}, C_{max} and AUC_{tau} in all dosing intervals upon switching, is required;
- Indicate the minimum number of cycles in period 1 and period 2: patients stabilized on INVEGA® SUSTENNA® will need to be stabilized for multiple cycles in period 1, given that half of the patients will be randomized to the follow-on/reference sequence;
- Specify that the bioequivalence limit of 80-125% must be met for $C_{min,SS;}$
- Specify how to estimate $C_{min,ss}$ and $C_{max,ss}$ given that C_{min} and C_{max} may transiently change during the different cycles after switching;
- Require a single-dose BE study and evaluate the drug release during the early release phase (at 72 hours) and
- Use the same dissolution specifications as those defined for the original drug product.

Thank you for the opportunity to review and comment on the Revised Draft Guidance. Should you have any questions or comments, please contact me directly at 609-730-4409.

Sincerely,

Beth Geter-Douglass, Ph.D.
Associate Director, Regulatory Affairs
Janssen Research and Development, L.L.C.

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