Janssen Research & Development, LLC.
Global Regulatory Affairs
Neuroscience

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PHARMACEUTICAL COMPANIES OF Johnson & Johnson

29 February 2016

Division of Dockets Management (HFA 305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Second Supplement to Citizen Petition, Docket No. FDA-2013-P-0608/CP with cross-submission to FDA "Draft Bioequivalence Guidance on Paliperidone Palmitate", Docket No. FDA-2007-D-0369 (29 December 2015)

Dear Sir or Madam:

The purpose of this letter is to inform you that the attached Second Supplement to Citizen Petition, Docket No. FDA-2013-P-0608/CP is hereby also being submitted to the FDA "Draft Bioequivalence Guidance on Paliperidone Palmitate", Docket No. FDA-2007-D-0369 (29 December 2015).

Sincerely,

Beth Geter-Douglass, Ph.D.
Associate Director, Regulatory Affairs

Cc: Ann Sohn, Pharm.D., LT USPHS, Regulatory Project Manager, DPP

Janssen Research & Development, LLC.
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Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Second Supplement to Citizen Petition, Docket No. FDA-2013-P-0608/CP

Dear Sir or Madam:

As background, FDA issued a draft bioequivalence guidance on paliperidone palmitate extended release injectable suspension in August 2011 and Janssen Research and Development, L.L.C (JRD; the Company), formerly Johnson & Johnson Pharmaceutical Research & Development, L.L.C. ("J&JPRD"), submitted comments to the docket in February 2012 (the "February 2012 Comments"). Thereafter, in May 2013, the Company submitted a Citizen Petition 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 (the "Citizen Petition"). In December 2013, without responding to the Citizen Petition, FDA issued a revised version of a draft bioequivalence guidance concerning paliperidone palmitate (the "2013 Draft Bioequivalence Guidance"). The 2013 Draft Bioequivalence Guidance addressed some, but not all, of the concerns the Company had raised in the Citizen Petition and in the February 2012 comments. Thus, in response to the 2013 Draft Bioequivalence Guidance, the Company submitted additional comments to the docket in February 2014 (the "February 2014 Comments") and subsequently cross-filed those comments in a supplement to the Citizen Petition in April 2014 (the "April 2014 Supplement"). On 29 December 2015, FDA issued a further revised version of the guidance, the 2015 Draft Bioequivalence Guidance.

JRD hereby requests that the comments submitted to the Revised Draft Guidance docket (shown below) be considered a supplement to the Citizen's Petition. JRD believes that the pharmacokinetic suggestions in the petition are preferable to the requirements set forth in the 29 December 2015 Revised Draft Guidance, but is submitting this supplement for consideration by the FDA in the event the FDA does not accept those suggestions.

JRD Comments to the 2015 Draft Bioequivalence Guidance for Paliperidone Palmitate

I. Background

INVEGA SUSTENNA® (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. As described in detail in the Citizen Petition, potentially significant safety and efficacy issues may arise if FDA accepts bioequivalence determinations for proposed generic paliperidone palmitate extended release injectable suspensions based solely on the traditional metrics of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. Indeed, reliance solely on these metrics may not detect potentially significant and clinically meaningful differences stemming from different pharmacokinetic ("PK") profiles of INVEGA SUSTENNA® and proposed generic products.

II. Comments on the 2015 Draft Bioequivalence Guidance

Because of these concerns and as explained in more detail in the Citizen Petition, the Company requested that FDA not approve a generic or follow-on paliperidone palmitate extended release injectable suspension unless bioequivalence is assured in a single-dose bioequivalence study evaluating $pAUC_{0-72h}$ and $pAUC_{0-28d}$, in addition to the traditional bioequivalence metrics of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. The Company continues to believe that such a single-dose bioequivalence study would provide greater assurance that differences that are potentially clinically significant between test and reference product will be detected, and so continues to recommend adoption of such design.

If FDA proceeds with the study design set forth in the 2015 Draft Bioequivalence Guidance, however, the Company provides the following recommendations.

A. Recommended Study Design

The study design described in the 2015 Draft Bioequivalence Guidance requires completion of either a steady-state parallel group or steady-state two-period cross-over study. The addition of the option of a parallel group, steady state design is an option that was not contemplated in the 2013 Draft Bioequivalence Guidance. Such a study design is even less likely to ensure bioequivalence of two extended release injectable suspension formulations of paliperidone palmitate than the steady-state two-period cross-over study proposed in the 2013 Draft Bioequivalence Guidance, especially when such design does not incorporate the changes recommended by Janssen in the February 2014 Comments. Indeed, evaluation of steady-state PK parameters from a parallel study design will not permit detection of different release profiles among test and reference paliperidone palmitate intramuscular drug products. 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 intramuscular drug products. A difference in release profiles among test and reference paliperidone palmitate intramuscular products could potentially become problematic upon switching between these two products (see simulations in Citizen Petition, Figures 2 through 5). 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 the steady-state two-period cross-over study also recommended by the 2015 Draft Bioequivalence Guidance, 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 intramuscular products on C_{min}, C_{max} and AUC_{tau} upon switching between these two products.

Given the critical importance of detecting inadequate paliperidone intramuscular drug products, the Company recommends that the proposed study design in the Revised Draft Guidance 2015 be limited to a 2-sequence, 2-way cross-over switching study, and require evaluation of transient C_{min}, C_{max} and AUC_{tau} in all dosing intervals upon switching.

B. PK Parameters to be Assessed

The 2015 Draft Bioequivalence Guidance, like the 2013 Draft Bioequivalence Guidance, specifies that the 90% confidence interval for the ratio of geometric means of AUC and C_{max} should be within 80-125%. As in the 2013 Draft Bioequivalence Guidance, the 2015 Draft Bioequivalence Guidance also continues to be silent with respect to criteria for comparing test and reference $C_{min,SS}$. Although the Revised Draft Guidance 2015 states that individual and average $C_{min,SS}$ should be submitted for review, the Revised Draft Guidance does not, but should, 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), therapeutic equivalence in terms of efficacy requires sustained exposure during the entire dosing interval, and it is essential to ensure bioequivalence in terms of $C_{min,SS}$. In addition, 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, Figures 2 through 5), the Company continues to recommend that a 2-sequence, 2-way cross-over switching study be performed and 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.

C. Dissolution Specifications

The 2015 Draft Bioequivalence Guidance, like the 2013 Draft Bioequivalence 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 sufficiently sensitive to control for inadequate release from a generic or follow-on product during the initial release phase. Taking into consideration the potential clinical consequences of inadequate early release

(e.g. lack of efficacy), 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.

III. Conclusion

The Company believes that the 2015 Draft Bioequivalence Guidance does not fully address the safety and efficacy issues raised in the previously submitted Citizen Petition. Nevertheless, if FDA proceeds with multiple-dose, steady state design set forth in the 2015 Draft Bioequivalence Guidance, the Company recommends that the recommendations be modified as set forth in the February 2014 Comments.

VIII. Certification Statement

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 October 9, 2015, the date I became aware of the October Press Release. 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 it includes representative data and information which are known to the petitioner and unfavorable to the petition.

Sincerely,

Joseph Massarella, PhD
Quantitative Sciences,Clinical Pharmacology & Pharmacometrics Group Leader
Established Products and Medical Affairs

cc: Mitchell V. Mathis, MD, CAPT., USPHS, Director, FDA Division of Psychiatry Products, Office of Drug Evaluation I, Office of New Drugs, CDER