13 November 2020

Tiffany Farchione, MD, FAPA
Director (Acting)
Division of Psychiatry
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 022192 - Sequence Number 0182
FANAPT® (iloperidone) tablets
RESPONSE TO PREA NON-COMPLIANCE LETTER
DEFERRAL EXTENSION REQUESTED
Cross-Reference INDs 036827 (b) (4)

Dear Dr. Farchione:

This letter is Vanda Pharmaceuticals Inc.'s (Vanda's) written response to the U.S. Food and Drug Administration's (FDA's) Notification of Non-Compliance with PREA dated October 1, 2020. FDA's letter relates to post-marketing requirement (PMR) 4-2 for FANAPT® (iloperidone) tablets, NDA 022192.

The approval letter for NDA 022192 describes PMR 4-2 as follows:

> A deferred pediatric study under PREA for the treatment of schizophrenia in pediatric patients aged 13 to 17. A study of the efficacy and safety of iloperidone tablets in the relevant pediatric population.

By letter dated November 4, 2013, FDA granted a deferral extension and extended the Final Report Submission date for PMR 4-2 to September 25, 2020.

Vanda did not meet the September 25, 2020 date specified in PMR 4-2 because of a number of challenges, including the time transitioning the clinical program to Vanda from the company that previously owned the product and the need to revise FANAPT®'s pediatric development program in light of FDA's General Advice letter dated January 15, 2020.

The ownership of NDA 022192 has been transferred two times since the original approval on May 6, 2009. Vanda took back ownership of this NDA on January 1, 2015. This disruption led to delays in understanding the historical interactions and background with FDA as well as the pediatric information collected thus far, (b) (4) . While ownership of NDA 022192 was transferred back to Vanda on January 1, 2015, (b) (4)

(b) (4) Once the data was transferred to Vanda, we began to review and understand the data and conducted a preliminary analysis comparing the adolescent PK data with the adult PK data.

We are in the process of revising the pediatric development program for FANAPT® to reflect the advice that FDA communicated in its General Advice letter dated January 15, 2020. In that letter, FDA informed Vanda that:

> [T]he Division of Psychiatry has determined that it is acceptable to extrapolate the effectiveness of atypical antipsychotic drugs approved for the treatment of schizophrenia in adults to pediatric patients 13 years of age and older (b) (4)

Accordingly, FDA advised Vanda that for drugs like FANAPT® "that share a similar mechanism of action (D_2-receptor antagonism or partial agonism, 5-HT_{1A} partial agonism, and/or 5-HT_{2A} antagonism) to currently FDA approved antipsychotics for the treatment of schizophrenia (b) (4) it would be acceptable to extrapolate effectiveness for the treatment of schizophrenia to pediatric patients 13 years of age and older rather than conduct an efficacy study. FDA explained that "the following will be required to support" such an indication "that relies on extrapolation":

- An approved indication in adults
- A pharmacokinetic analysis to determine a dosing regimen that provides similar drug exposures (at levels demonstrated to be effective in adults) in pediatric and adult patients. This analysis will require pharmacokinetic data from both the adult and pediatric populations
- A long-term open label safety study(ies) in pediatric patients

The General Advice letter appears to reflect FDA's determination that the study described in PMR 4-2 no longer is necessary from a scientific perspective, as long as the above prerequisites for extrapolation are met. In the General Advice letter, FDA invited Vanda to amend "an initial Pediatric Study Plan (iPSP), a Pediatric Study Plan (PSP), or a Proposed Pediatric Study Request (PPSR) . . . to reflect the acceptability of extrapolation."

Consistent with the General Advice letter, Vanda—by letter dated September 24, 2020—requested that FDA revise the Pediatric Written Request (PWR) for iloperidone to remove the pediatric efficacy and safety study. However, in a further General Advice letter dated October 2, 2020, FDA informed Vanda that the PWR had expired as of December 31, 2014, and "[i]f you wish to seek pediatric exclusivity, a new Proposed Pediatric Study Request (PPSR) should be submitted."

Vanda remains committed to the development of FANAPT® for pediatric use and appreciates the guidance that FDA provided in both General Advice letters. As a first step toward aligning the

pediatric development program for FANAPT® with the extrapolation approach described in FDA's January 15, 2020 General Advice letter, Vanda is also submitting a new PPSR. Once FDA issues a PWR, Vanda intends to amend the PSP for FANAPT® to reflect the terms of the PWR and the extrapolation approach. Vanda also intends to request that FDA rescind PMR 4-2 because the efficacy study described in PMR 4-2 is unnecessary under the extrapolation approach.

To allow time for Vanda and FDA to implement these changes to FANAPT®'s pediatric development program, Vanda requests that FDA grant a further deferral extension of the Final Report Submission date for PMR 4-2 to August 31, 2021, given that PMR 4-2 will remain in place until FDA rescinds it.

Vanda regrets that it did not make the submissions needed for these changes to FANAPT®'s pediatric development program early enough to allow PMR 4-2 to be rescinded before the September 25, 2020 date for Final Report Submission. We apologize for the delay and look forward to working with FDA to revise the FANAPT® pediatric development program to reflect the Agency's current scientific advice.

Vanda requests that FDA post this letter on the Agency's web site with redactions for trade secrets and confidential commercial information, in accordance with section 505B(d)(1) of the Federal Food, Drug, and Cosmetic Act. Attached to this letter as Appendix 1 is a version of this letter from which trade secrets and confidential commercial information have been redacted. Vanda designates the information that is redacted from Appendix 1 as trade secrets and/or confidential commercial information pursuant to Exemption 4 of the Freedom of Information Act and 21 C.F.R. § 20.61(d).

If you have any questions or require additional information, please do not hesitate to contact me at (202) 734-3416 or at Gunther.Birznieks@vandapharma.com.

Sincerely,

Gunther Birznieks
Research and Development Committee Member
Vanda Pharmaceuticals Inc.

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Electronic Submission Specifications

This submission is compliant with FDA's Guidelines for Industry and current eCTD specifications.

All files were checked and verified to be free of viruses prior to transmission through the electronic submission gateway.

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Program Version	14.2.4814.1101
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