September 7, 2016

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

CITIZEN PETITION

Vanda Pharmaceuticals Inc. (Vanda) submits this citizen petition under section 505(q) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) and in accordance with 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs not approve any abbreviated new drug application (ANDA) referencing Fanapt® (iloperidone) until the expiration of the three-year exclusivity that covers changes made to the labeling of Fanapt for which a clinical study relating to maintenance treatment was essential to approval. Vanda holds approved New Drug Application (NDA) 22-192 for Fanapt.

Fanapt is approved for the treatment of schizophrenia in adults. Because schizophrenia is a chronic condition, effective therapy generally is continued beyond six weeks into a period known as the maintenance phase. Information about the safety and effectiveness of a schizophrenia drug for maintenance treatment therefore is very important to prescribers. Accordingly, FDA approved Fanapt subject to a post-marketing commitment to study the product for maintenance treatment. Vanda satisfied that commitment through a long-term study known as REPRIEVE, which demonstrated that Fanapt is more effective than a placebo in preventing or delaying relapse when administered for longer than six weeks. REPRIEVE thus provided valuable new information about the use of Fanapt for treating schizophrenia. FDA recently granted three-year exclusivity to Fanapt for labeling changes resulting from REPRIEVE's findings.

REPRIEVE enabled not only the addition to Fanapt's labeling of information about maintenance treatment, but also the removal of existing language describing the limited information previously available regarding maintenance treatment. Because REPRIEVE was essential to the approval of both types of changes, both are protected by three-year exclusivity. As a result, it is not possible for generic products to bear approvable labeling. Fanapt's exclusivity bars them from either including the new information about maintenance treatment or omitting the prior limitation regarding maintenance treatment. Meanwhile, they cannot include statements about the limited evidence regarding maintenance treatment because that limitation no longer is accurate in light of the REPRIEVE findings. Moreover, generic labeling cannot carve out the new information about maintenance treatment for an additional reason: that would render the generic product less safe or effective for Fanapt's sole approved indication (*i.e.*, the treatment of schizophrenia in adults) given the critical role of maintenance treatment for this indication.

Vanda recognizes that it is rare for three-year exclusivity granted to a reference listed drug (RLD) in connection with a supplemental NDA to prevent the approval of any ANDA that

references that RLD. In this case, however, and for the reasons set forth below, this outcome is compelled by law and is consistent with the importance of maintenance therapy in the treatment of schizophrenia.

A. Actions Requested

Vanda respectfully requests that the Commissioner refrain from approving any ANDA referencing Fanapt before May 26, 2019, the date of expiration of the three-year exclusivity that covers changes made to the labeling of Fanapt for which a clinical study relating to maintenance treatment was essential to approval.

B. Statement of Grounds

I. Background

A. Factual Background

1. Schizophrenia

Schizophrenia is a chronic, debilitating disorder that affects approximately one percent of the U.S. population.[1] Patients may experience hallucinations, delusions, disorganized speech, and other symptoms that affect their thoughts, feelings, and behavior.[2]

The majority of patients with schizophrenia have repeated relapses during which they suffer acute exacerbations of symptoms.[3] Relapse "may have serious implications. For example, there is a risk of patients harming themselves or others [or] of jeopardising personal relationships, education or employment status."[4] The possibility that patients may harm themselves is of particular concern because "[a]pproximately 5%-6% of individuals with schizophrenia die by suicide, about 20% attempt suicide on one or more occasions, and many more have significant suicidal ideation."[5]

Despite the availability of a number of treatments for schizophrenia, none of them is curative, and they provide only symptomatic relief. Thus, the goal of treatment is to control symptoms during an acute exacerbation and maintain this effect over a longer period of time.

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[1] *See generally* National Alliance on Mental Illness, Schizophrenia, https://www.nami.org/Learn-More/Mental-Health-Conditions/Schizophrenia (last accessed September 6, 2016).

[2] *Id.*; *see also* Am. Psychiatric Ass'n, *Diagnostic and Statistical Manual of Mental Disorders* § 295.90 (Schizophrenia) (5th ed. 2013) (DSM-5).

[3] Emsley R et al. 2013. The nature of relapse in schizophrenia. BMC Psychiatry. 13:50.

[4] *Id.*

[5] DSM-5, at 104.

Treatment guidelines therefore recommend that "[p]eople with treatment-responsive, multi-episode schizophrenia who experience acute and sustained symptom relief with an antipsychotic medication should be offered continued antipsychotic treatment in order to maintain symptom relief and to reduce the risk of relapse or worsening of positive symptoms."[6] Accordingly, maintenance treatment has been described as "the gold standard treatment paradigm for schizophrenia."[7]

Because maintenance therapy is an essential part of the treatment of schizophrenia, safety and efficacy data for both acute and maintenance treatment are important when prescribers choose a treatment for their patients. The long-term goal of treatment is to identify a drug product that controls symptoms in the acute phase, is tolerated well, and delays relapse for those patients stabilized during the acute phase.

Many drug products approved by FDA for the treatment of schizophrenia initially were approved based upon evidence of efficacy during the acute phase, and subsequently were studied for effectiveness in the maintenance phase.[8] That approach appears to reflect a recognition by FDA of the importance of having sponsors of schizophrenia treatments study the safety and effectiveness of their products in both the acute and maintenance phases.

2. Initial Approval of Fanapt

FDA approved NDA 22-192 for Fanapt tablets on May 6, 2009.[9] Fanapt is an atypical antipsychotic indicated for "the treatment of schizophrenia in adults."[10] FDA's initial approval of Fanapt was based in part on data from two short-term (4- and 6-week) trials.[11] In light of the importance of the maintenance phase in treating schizophrenia, FDA required Vanda to conduct

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[6] Buchanan RW et al. 2010. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophrenia Bulletin. 36(1): 71, 76.

[7] Emsley R et al. 2016. How long should antipsychotic treatment be continued after a single episode of schizophrenia? Current Opinion Psychiatry. 29(3):224, 225.

[8] This pattern was followed for drug products including, among others, Abilify® (aripiprazole), Invega® (paliperidone), Risperdal® (risperidone), Saphris® (asenapine), and Zyprexa® (olanzapine). *See, e.g.*, Approval Letters and Approved Labeling for NDA 21-436 (Abilify) (Nov. 15, 2002) & NDA 21-436 S-001 (Aug. 28, 2003); Approved Labeling for NDA 21-999 (Invega) (Dec. 19, 2006) & NDA 21-999 S-001, S-002 (Dec. 21, 2007); Approval Letters for NDA 20-272 (Risperdal) (Dec. 29, 1993) & NDA 20-272 S-008 (Mar. 3, 2002); Approval Letters and Approved Labeling for NDA 22-117 (Saphris) (Aug. 13, 2009) & NDA 22-117 S-003 (Sept. 3, 2010); Approval Letter and Approved Labeling for NDA 20-952 S-011 (Zyprexa) (Nov. 9, 2000).

[9] *See* FDA Approval Letter for NDA 22-192 (May 6, 2009).

[10] Fanapt Package Insert (May 26, 2016) § 1 (Indications and Usage).

[11] *See* FDA Summary Review for NDA 22-192 (Mar. 27, 2009), at 10-11.

"a randomized withdrawal clinical trial to address longer-term efficacy for [the] drug at appropriate doses" as a post-marketing commitment.[12]

Because no long-term data were available when Fanapt was first approved, FDA required the following limitation in the final paragraph of the Indications and Usage section of Fanapt's labeling:

> The effectiveness of FANAPT in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use FANAPT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient *[See Dosage and Administration (2.3)]*.[13]

Similarly, FDA required the following statement in section 2.3 of the Dosage and Administration section, entitled "Maintenance Treatment," when Fanapt was first approved:

> Although there is no body of evidence available to answer the question of how long the patient treated with FANAPT should be maintained, it is generally recommended that responding patients be continued beyond the acute response. Patients should be periodically reassessed to determine the need for maintenance treatment.[14]

3. Long-Term Maintenance Trial: REPRIEVE Study

Vanda satisfied its postmarketing commitment to study long-term efficacy through the Relapse Prevention Study in Patients With Schizophrenia (REPRIEVE) study, which demonstrated the safety and effectiveness of Fanapt for long-term maintenance treatment of schizophrenia of up to 26 weeks.[15] Patients with schizophrenia who remained clinically stable following at least 12 weeks of open-label treatment with flexible doses of Fanapt (8 mg/day - 24

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[12] *See* FDA Approval Letter for NDA 22-192 (May 6, 2009), at 4-5. *See also* Office Director's Memo to File for NDA 22-192 (May 6, 2009), at 4-5 ("The sponsor has committed to the conduct of a long-term effectiveness (maintenance) study (placebo-controlled randomized withdrawal study) . . . .").

[13] *See* Fanapt Package Insert (May 2009) § 1 (Indications and Usage) (emphasis added).

[14] *Id.* § 2.3 (Maintenance Treatment) (emphasis added).

[15] The protocol for the REPRIEVE study was submitted in 2010 and the study was initiated in March 2011, with an original goal of completion by May 2013. FDA later granted an extension to complete the study by April 2015 due primarily to drug supply and recruitment issues. The study was completed in 2015. The following information about the REPRIEVE study appears in a recent publication. *See* Weiden PJ et al. 2016. A randomized trial of iloperidone for prevention of relapse in schizophrenia: the REPRIEVE study. CNS Drugs. 30(8): 735.

mg/day) were randomized to placebo or Fanapt during a double-blind relapse prevention phase. Subjects randomized to Fanapt during the relapse prevention phase initially received their current dose of Fanapt, and subsequently were treated with flexible doses of Fanapt of 8 mg/day - 24 mg/day. Follow-up was conducted for up to 26 weeks and subjects were withdrawn upon showing signs of relapse or impending relapse. The primary endpoint was time to relapse or impending relapse.

The double-blind relapse prevention phase included 195 subjects, with 99 receiving Fanapt and 96 receiving placebo. A planned interim analysis conducted by an independent unblinded biostatistics team was conducted after 68 relapse or impending relapse events were observed. The results of the interim analysis demonstrated that patients who received Fanapt experienced a statistically significant longer time to relapse than patients who received placebo. Based on the results of the interim analysis, an independent data monitoring committee decided that the study should be discontinued due to evidence of efficacy. The results of the interim analysis were supported by the results of a final analysis conducted after 104 relapse or impending relapse events. In addition, the study did not identify any new safety concerns with respect to the long-term use of Fanapt. The REPRIEVE study demonstrated that Fanapt is both safe and effective in preventing relapse or impending relapse in adult patients with schizophrenia.

4. Approval of Changes to Fanapt Labeling Based on REPRIEVE Data

In July 2015, Vanda submitted the REPRIEVE results to FDA in supplemental NDA 22-192 S-015 (Supplement 15). FDA approved Supplement 15 on May 26, 2016. Based on the REPRIEVE results, FDA approved the following significant changes to Fanapt's labeling:

> 1. In Indications and Usage (1), the deletion of the following limitation: "The effectiveness of FANAPT in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use FANAPT for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient [see Dosage and Administration (2.3)]."
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> 2. In Maintenance Treatment (2.3), the deletion of the following language: "Although there is no body of evidence available to answer the question of how long the patient treated with FANAPT should be maintained, it is generally recommended that responding patients be continued beyond the acute response."
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> 3. In Maintenance Treatment (2.3), the addition of the following language: "In a longer-term study, FANAPT was effective in delaying time to relapse in patients with schizophrenia who were stabilized on FANAPT up to 24 mg/day [*see Clinical Studies (14)*]."

4. In Clinical Studies (14), the addition of information about the REPRIEVE study and its results.

Upon the approval of Supplement 15, FDA granted Fanapt three years of "new clinical investigation" exclusivity.[16] Vanda had requested exclusivity for both the addition of information to Fanapt's labeling about the product's efficacy for maintenance treatment and the deletion of statements that were based upon the prior lack of efficacy evidence for such use.[17] FDA assigned Fanapt the exclusivity code M-180, for "information added to the labeling regarding the addition of maintenance treatment in patients with schizophrenia."[18]

B. Legal Background

1. Three-Year Exclusivity

Changes made in a supplement to an approved NDA are entitled to three years of marketing exclusivity if the supplement "contains reports of new clinical investigations (other than bioavailability studies) essential to approval of the supplement and conducted or sponsored by the person submitting the supplement."[19] During that three-year period, FDA will not grant final approval to an ANDA or an NDA submitted under FDCA section 505(b)(2) for the change approved in the supplement.[20] FDA has explained that "[t]he statute sets up a

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[16] FDCA § 505(c)(3)(E)(iv) & (j)(5)(F)(iv); *see* Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) (exclusivity data for Fanapt).

[17] *See* Exclusivity Request, NDA 22192/S-015.

[18] Orange Book (exclusivity data for Fanapt).

[19] FDCA § 505(j)(5)(F)(iv); *see also* FDCA § 505(c)(3)(E)(iv). FDA's regulations define "new clinical investigation" as:

> an investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.

21 C.F.R. § 314.108(a). "Essential to approval" means "that there are no other data available that could support approval of the application." *Id*.

[20] 21 C.F.R. § 314.108(b)(5)(ii). In addition, during the exclusivity period, FDA will not approve an ANDA submitted pursuant to an approved suitability petition "that relies on the information supporting a change approved in" the supplement. *Id*.; *see Veloxis Pharms., Inc. v. FDA*, 109 F. Supp. 3d 104, 118 (D.D.C. 2015) ("The element of "reliance" is relevant only where 'an [ANDA is] submitted pursuant to an approved petition under section 505(j)(2)(C) of the [FDCA]....'" (quoting analogous language in 21 C.F.R. § 314.108(b)(4)(iv)).

relationship between the 'new clinical investigations' that are 'essential to the approval of the supplement,' and the scope of exclusivity."[21]

2. "Same Labeling" Requirement

An ANDA must contain the same labeling as the RLD, except for differences due to a suitability petition or the fact that the drugs "are produced or distributed by different manufacturers."[22] FDA's regulations provide that permissible labeling differences between a generic drug and its RLD may include, among other things, "omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the act."[23] The omission of the RLD's protected information from ANDA labeling is allowed only where it does "not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."[24]

II. Discussion

A. Three-Year Exclusivity Protects Both the Addition and Removal of Labeling Information.

FDA granted Vanda's request for three-year exclusivity for the changes to Fanapt's labeling regarding maintenance treatment that stem from the REPRIEVE results. In particular, REPRIEVE enabled both the addition of information regarding Fanapt's safety and efficacy for maintenance treatment and the omission of statements about the absence of such evidence before REPRIEVE was completed. Under the exclusivity provisions of the FDCA, both types of changes are within the scope of three-year exclusivity because the REPRIEVE results were "essential to [their] approval."[25] As discussed below, this conclusion is consistent with the central role that maintenance therapy plays in the treatment of schizophrenia.

A labeling change is covered by three-year exclusivity where, as here, there is a "substantive relationship between new clinical studies and changes in the supplement."[26] Before

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[21] Letter from Keith O. Webber, Ph.D., Deputy Dir., Office of Pharm. Sci., CDER, to Kevin McKenna, Ph.D., regarding Seroquel® (quetiapine fumarate) (Mar. 27, 2012), at 7 ("Seroquel Decision Letter"), quoted in *AstraZeneca Pharms. LP v. FDA*, 872 F. Supp. 2d 60, 80 (D.D.C. 2012), *aff'd*, 713 F.3d 1134 (D.C. Cir. 2013), and available at *AstraZeneca Pharms. LP v. FDA*, No. 12-00472 (BAH), ECF No. 14-1, Administrative Record 293-306 (filed Apr. 2, 2012).

[22] FDCA §§ 505(j)(2)(A)(v) & (4)(G); *see also* 21 C.F.R. § 314.94(a)(8)(iv).

[23] 21 C.F.R. § 314.94(a)(8)(iv).

[24] 21 C.F.R. § 314.127(a)(7). *See also* Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,968 (Apr. 28, 1992) ("FDA cautions that it will not approve an ANDA with different labeling if the labeling differences affect product safety or efficacy.").

[25] FDCA § 505(j)(5)(F)(iv); *see also* FDCA § 505(c)(3)(E)(iv).

[26] *AstraZeneca*, 872 F. Supp. 2d at 83.

FDA approved Supplement 15, Fanapt's labeling was required to include the following statements informing prescribers that efficacy for maintenance treatment had not been demonstrated:

- "The effectiveness of FANAPT in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials," and
- "[T]here is no body of evidence available to answer the question of how long the patient treated with FANAPT should be maintained."[27]

Those statements were necessary because there was no reliable clinical evidence of Fanapt's efficacy for maintenance treatment. The REPRIEVE study supplied that evidence: it demonstrated that maintenance treatment using Fanapt is safe and effective in preventing relapse or impending relapse in adult patients with schizophrenia.[28] As a direct result of the REPRIEVE results, the statements advising prescribers that such efficacy had not been demonstrated were removed from Fanapt's labeling, and statements describing the REPRIEVE results were added to the labeling.[29]

The removal of the limitation on maintenance treatment satisfies the applicable legal standards for eligibility for three-year exclusivity to the same extent as the addition of information about Fanapt's efficacy for maintenance treatment. Both types of changes "derive[] from" the REPRIEVE study and that study "relate[s] to" those changes because REPRIEVE is the sole source of reliable clinical evidence supporting the efficacy of iloperidone for maintenance treatment.[30] Without the REPRIEVE results, there would be no basis for statements describing the efficacy of iloperidone for maintenance treatment, nor would there be support for deleting statements describing the lack of such efficacy data. Because "there are no other data available that could support approval of" these labeling changes made in Supplement 15, REPRIEVE is "essential to approval" of the changes.[31] The direct and logical link between REPRIEVE and the labeling changes is the kind of "substantive relationship between new clinical studies and changes in the supplement" that is required for both types of changes to be covered by three-year exclusivity.[32]

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[27] *See* Fanapt Package Insert (Jan. 2016) §§ 1 & 2.3.

[28] *See* Fanapt Package Insert (May 26, 2016) § 14.

[29] *Compare* Fanapt Package Insert (Jan. 26, 2016) §§ 1 & 2.3, *with* Fanapt Package Insert (May 26, 2016) §§ 1 & 2.3.

[30] *AstraZeneca*, 872 F. Supp. 2d 60, 80 (D.D.C. 2012)

[31] 21 C.F.R. § 314.108(a).

[32] *AstraZeneca*, 872 F. Supp. 2d at 83.

Moreover, the labeling changes made in Supplement 15 are precisely the type of "significant innovations" that three-year exclusivity was intended to reward.[33] Information about the safety and efficacy of a schizophrenia drug in the maintenance phase is essential for prescribers as they choose a therapy for their patients, given the critical role of maintenance treatment in preventing relapse. As discussed above, the goal in treating schizophrenia is to identify a drug product that both controls the patient's symptoms during the acute phase and reduces the occurrence of relapses. Accordingly, treatment guidelines recommend that "[p]eople with treatment-responsive, multi-episode schizophrenia who experience acute and sustained symptom relief with an antipsychotic medication should be offered continued antipsychotic treatment in order to maintain symptom relief and to reduce the risk of relapse or worsening of positive symptoms."[34] The importance of information about the safety and efficacy of a schizophrenia drug for maintenance treatment is underscored by the fact that FDA asked Vanda to conduct REPRIEVE as a postmarketing commitment. Such data were particularly important because Fanapt's labeling recommended "generally . . . that responding patients be continued beyond the acute response," and REPRIEVE was intended to explore the efficacy of that recommended use.[35]

Until the approval of Supplement 15 in May 2016, no reliable information was available about the safety and efficacy of Fanapt for maintenance treatment. That lack of data may have led prescribers to choose other therapies, even if Fanapt otherwise was a better choice for their patients. REPRIEVE demonstrated safety and efficacy for the recommended maintenance treatment, and thus enabled two significant innovations to the Fanapt labeling: both the addition of information about the clinical evidence demonstrating such safety and efficacy, and the omission of statements describing the lack of such evidence. The resulting labeling provides important updated information for health care professionals who now may be more inclined to prescribe Fanapt.[36]

In this way, REPRIEVE generated essential new information for prescribers. It therefore is the very type of clinical research that three-year exclusivity was intended to encourage and reward. Because REPRIEVE enabled both the addition of information regarding safety and

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[33] Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,896 (proposed July 10, 1989) (citing Cong. Rec. H9114, 9124 (daily ed. Sept. 6, 1984) (statement of Rep. Waxman) & Cong. Rec. S10505 (daily ed. Aug. 10, 1984) (statement of Sen. Hatch)).

[34] Buchanan RW et al. 2010, *supra* note 6, at 76.

[35] *See* Fanapt Package Insert (Jan. 2016) § 2.3.

[36] Before Fanapt's labeling included information about the product's safety and efficacy for maintenance treatment, the delay in control of symptoms caused by the titration schedule may have led prescribers to select other therapies, particularly if rapid response to treatment was needed. *See* Fanapt Package Insert (May 2016) § 2.1 ("[C]ontrol of symptoms may be delayed during the first 1 to 2 weeks of treatment compared to some other antipsychotic drugs that do not require similar titration."). Now that Fanapt's labeling includes information about maintenance treatment, prescribers may be more willing to consider prescribing Fanapt despite the initial delay in treatment response, given that schizophrenia is a chronic condition.

efficacy for maintenance treatment and the omission of statements about the absence of such evidence, Fanapt's three-year exclusivity protects both types of changes.

B. ANDA Labeling May Neither Omit Nor Include Statements That Effectiveness for Maintenance Therapy Has Not Been Evaluated.

Because Fanapt's three-year exclusivity covers both the addition and omission of labeling information relating to maintenance treatment, no ANDA referencing Fanapt may be approved before the expiration of three-year exclusivity because no generic iloperidone product can bear approvable labeling. Fanapt's three-year exclusivity precludes ANDA labeling from omitting statements describing the lack of evidence of safety and efficacy for maintenance treatment. At the same time, however, ANDA labeling may not include those statements because they are now inaccurate, and because their inclusion would violate the "same labeling" requirement.

As discussed above, Fanapt's three-year exclusivity encompasses the omission of statements regarding the absence of evidence regarding maintenance use. The REPRIEVE results enabled the removal of those statements from Fanapt's labeling. Accordingly, any corresponding omission of those statements from ANDA labeling would reflect the ANDA applicant's reliance upon the REPRIEVE results in violation of Fanapt's three-year exclusivity.

Meanwhile, ANDA labeling may not include the statements that were removed from Fanapt's labeling because they are false now that the REPRIEVE study has been completed and has demonstrated the safety and efficacy of iloperidone for maintenance treatment.[37] Given the REPRIEVE results, it would be untrue for ANDA labeling to state, consistent with Fanapt's prior labeling, that "[t]he effectiveness of [iloperidone] in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials," or that "there is no body of evidence available to answer the question of how long the patient treated with [iloperidone] should be maintained."[38]

ANDA labeling may not include statements that no longer appear in the Fanapt labeling for a second reason: the labeling of the RLD and generic products must be the same, subject to limited exceptions.[39] The inclusion of limitations on maintenance treatment in ANDA labeling– limitations that have been removed from Fanapt's labeling—cannot fairly be characterized as a difference that is permissible because the products are made by "different manufacturers," as FDA has construed that term in its regulations.[40] At the same time, we note that the "same

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[37] A drug is deemed to be misbranded "[i]f its labeling is false or misleading in any particular." FDCA § 502(a). FDA's regulations require that labeling "must be informative and accurate and [not] false or misleading in any particular." 21 C.F.R. § 201.56(a)(2).

[38] *See* Fanapt Package Insert (Jan. 2016) §§ 1, 2.3.

[39] FDCA §§ 505(j)(2)(A)(v) & (4)(G); 21 C.F.R. § 314.94(a)(8)(iv).

[40] *See* 21 C.F.R. § 314.94(a)(8)(iv) ("Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with (continued…)

labeling" requirement cannot independently justify the approval of ANDA labeling that omits the limitations on maintenance treatment. That approach would infringe upon Fanapt's three-year exclusivity no less than ANDA labeling that incorporates the new information added to Fanapt's labeling about maintenance treatment.

C. Generic Labeling May Not Carve Out References to Maintenance Treatment.

An ANDA applicant cannot overcome these hurdles by "carving out" references to maintenance treatment from its labeling. By omitting statements about the absence of clinical safety or efficacy evidence for maintenance treatment, this type of carve-out would violate Fanapt's three-year exclusivity, as discussed above. Moreover, the omission of information about maintenance treatment, including the REPRIEVE results, would be impermissible under FDA's regulations.

The agency's regulations allow generic labeling to "carve out" a protected condition of use as long as the omission does not cause the generic product to be "less safe or effective than [Fanapt] for all remaining, non-protected conditions of use."[41] FDA has allowed labeling carve-outs in the following situations, among others:

- FDA concluded that Altace® (ramipril) had separate indications for the treatment of hypertension and the reduction of risk of certain cardiovascular outcomes, so information relating to the protected risk-reduction indication could be carved out.[42]

- FDA concluded that information about combination therapy approved for Camptosar® (irinotecan HCl) could be carved out to allow ANDA products to be approved solely for monotherapy.[43]

- FDA allowed the carve-out of certain patent-protected indications for Lyrica® (pregabalin) upon concluding that certain safety information could remain in ANDA labeling without disclosing the protected indications.[44]

- FDA allowed the carve-out of a patent-protected indication for Precedex™ (dexmedetomidine hydrochloride) relating to use of the product in an intensive care

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current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the act.").

[41] 21 C.F.R. § 314.127(a)(7); *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1499-1501 (D.C. Cir. 1996).

[42] Letter from FDA to King Pharmaceuticals, Inc. re: Docket No. FDA-2008-P-0304 (June 18, 2008).

[43] Letter from FDA to Watson Labs., Inc. re: Docket No. FDA-2008-P-0069 (July 28, 2008).

[44] Letter from FDA to Sandoz, Inc. re: Docket No. FDA-2010-P-0087 (Aug. 3, 2010).

setting even though the remaining broad, general indication might overlap with the protected indication.[45]

- FDA allowed the carve-out of a protected once-daily dosing regimen for Pulmicort Respules® (budesonide inhalation suspension).[46]

- FDA allowed the carve-out of protected information on the use of Rebetol® (ribavirin) in combination with PEG-Intron, so that an ANDA product could be approved solely for use in combination with Intron A.[47]

- FDA allowed the carve-out of protected information about osteoporosis indications for Reclast® (zoledronic acid) upon concluding that the product was not less safe or effective for the remaining indication for the treatment of Paget's disease.[48]

- FDA allowed the carve-out of a protected titration schedule for the use of Ultram® (tramadol) in one patient population upon concluding that the omission of that schedule would not make an ANDA product less safe or effective for the remaining general patient population.[49]

Unlike those drug products, Fanapt is approved for a single indication—the treatment of adults with schizophrenia—and a carve-out would not omit a distinct dosing regimen or other discrete condition of use. As discussed above, maintenance treatment is an essential part of the general indication for treatment of patients with schizophrenia. Consistent with practice guidelines, Fanapt's labeling "generally recommended that responding patients be continued beyond the acute response," even before long-term safety and efficacy evidence was available.[50] Maintenance treatment thus is not a distinct condition of use, but instead reflects the continuation of treatment for the same condition, in the same population, with the same dosing regimen, for those patients who respond initially to Fanapt.

Because health care professionals treating patients with schizophrenia seek to find a drug product that is effective during the acute phase and continue it for maintenance treatment, any patient who starts iloperidone may respond to initial treatment and thus require continued treatment beyond six weeks. Information about maintenance treatment therefore is essential for the safe and effective treatment of all adult schizophrenic patients taking iloperidone.

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[45] Letter from FDA to Dexmedetomidine Hydrochloride Injection NDA Holder/ANDA Applicant re: Docket No. FDA-2014-N-0087 (Aug. 18, 2014).

[46] Letter from FDA to Ropes & Gray, LLP re: Docket No. FDA-2006-P-0073 (Nov. 18, 2008).

[47] Letter from FDA to Hogan & Hartson, L.L.P. re: Docket No. 2003P-0321/CP1 (Apr. 6, 2004).

[48] Letter from FDA to Novartis Pharms. Corp. re: Docket No. FDA-2013-P-0247 (Aug. 1, 2013).

[49] Letter from FDA to Apotex Corp. et al. re: Docket Nos. 01P-0495/CP1, 02P-0191/CP1, & 02P-0252/CP1 (June 11, 2002).

[50] Fanapt Package Insert (Jan. 2016) § 2.3.

Indeed, by approving Fanapt's labeling with a recommendation for maintenance treatment, even in the absence of long-term safety and efficacy evidence, FDA appears to have recognized that prescribers would need information about the use of the drug after the initial six-week period because the treatment of all responding patients would be expected to continue.

Carving out information about maintenance treatment from the labeling for a generic iloperidone product would leave the product less safe or effective than Fanapt for the remaining, non-protected condition of use: namely, the treatment of adult patients with schizophrenia. A carve-out would leave prescribers with no information about the safety and efficacy of continued treatment for those patients who respond initially to iloperidone—contrary to the requirement that labeling "contain a summary of the essential scientific information needed for the safe and effective use of the drug."[51] A labeling carve-out should be denied where, as here, the protected information "is necessary to enable physicians to adequately assess the risks and benefits of" the drug product for "the general population" of patients for whom the drug product is indicated.[52]

FDA denied a labeling carve-out on analogous facts for generic versions of Rapamune® (sirolimus).[53] Rapamune was indicated for the prophylaxis of organ rejection in patients receiving renal transplants and originally was approved only for use in a regimen with cyclosporine and corticosteroids.[54] But the combination of Rapamune and cyclosporine later was found to be associated with increased renal function impairment. Rapamune's sponsor conducted a clinical study in patients with low-to-moderate risk of immune system reactions that showed the safety benefits of a cyclosporine withdrawal regimen, and received three-year exclusivity for labeling regarding cyclosporine withdrawal in low-to-moderate risk patients. In granting the sponsor's citizen petition, FDA concluded that the protected information about cyclosporine withdrawal could not be carved out to allow approval of an ANDA limited to use in high-risk patients, because "the protected labeling in question contains extensive, critical prescribing information pertaining to cyclosporine withdrawal that any physician should receive to appropriately determine treatment for all indications for sirolimus."[55] FDA explained that the cyclosporine withdrawal information was essential for the safe use of the product in the non-protected condition of use—the high-risk population—because a high-risk patient could be reclassified as a low-to-moderate risk patient, and thus could benefit from cyclosporine withdrawal.[56] FDA found that ANDA labeling that omitted the withdrawal information would be

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[51] 21 C.F.R. § 201.56(a)(1).

[52] Letter from FDA to Covington & Burling re: Docket No. 2003P-0518/CP1 (Sept. 20, 2004), at 4 (denying a carve-out for sirolimus ANDAs).

[53] *Id*. at 3.

[54] *Id*. at 1.

[55] *Id*. at 3 (emphasis added).

[56] *Id*. at 4.

"potentially unsafe and confusing," and would render the product less safe than Rapamune for the remaining, non-protected conditions of use.[57]

Similarly, FDA determined that the labeling of any generic colchicine product referencing Colcrys® and seeking approval for prophylaxis of gout flares could not carve out the RLD's protected lower-dose regimen for the treatment of acute gout flares.[58] FDA reasoned that information about the adequacy of the lower-dose regimen was important to minimize the risk of cumulative toxicity in a patient who had been receiving colchicine for prophylaxis.[59] FDA concluded that it therefore could not approve an ANDA that relied on Colcrys as its RLD until expiration of Colcrys's three-year exclusivity. [60]

Like the cyclosporine withdrawal information for Rapamune or the lower-dose regimen for Colcrys, information on the safety and efficacy of iloperidone for maintenance treatment is essential for the safe use of all patients for whom the product is prescribed. Just as any high-risk patient receiving sirolimus could be reassigned to a lower risk category, or any patient receiving colchicine for acute gout flares may have been taking it for prophylaxis, so too could any patient receiving iloperidone require maintenance treatment upon responding to initial treatment. In light of the general recommendation that responding patients continue taking iloperidone for longer than six weeks, prescribers need to know whether the product is safe and effective for maintenance treatment before they initiate treatment at all. That information is essential as they select which atypical antipsychotic to prescribe.

For these reasons, generic labeling that omits the protected information about maintenance treatment would render a generic iloperidone product less safe or effective than Fanapt for all remaining, non-protected conditions of use, and therefore may not be approved.[61]

III. Conclusion

For the reasons stated above, Vanda respectfully requests that FDA not approve any ANDA referencing Fanapt until the expiration of the three-year exclusivity period on May 26, 2019.

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[57] *Id*.

[58] *See* Letter from FDA to Sidley Austin LLP re: Docket No. FDA-2010-P-0614 (May 25, 2011), at 24, 27.

[59] *Id*. at 24.

[60] *Id*. at 24, 27.

[61] We further note that ANDA labeling may not omit the maintenance treatment information but include a statement that such information is approved for Fanapt. The addition of such a statement is permitted only with respect to information about pediatric or geriatric use. *See* FDCA § 505A(o) & 21 C.F.R. § 201.80(f)(10)(vi) (authorizing the addition of such statements to generic labeling that omits pediatric and geriatric use information, respectively).

C. Environmental Impact

The actions requested herein are subject to categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31.

D. Economic Impact

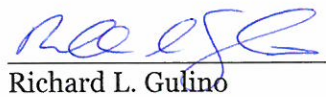
Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted only upon the request of the Commissioner.

E. Certification

Pursuant to 21 C.F.R. § 10.30(b), 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 known to the petitioner which are unfavorable to the petition.

Pursuant to 21 U.S.C. § 355(q)(1)(H), I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: May 26, 2016. 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: I am making these representations on behalf of Vanda Pharmaceuticals Inc. as part of my responsibilities as an employee of Vanda; I am not being separately compensated for submitting this petition. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,



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