DEPARTMENT OF HEALTH & HUMAN SERVICES

JUN 1 2 2015

Emily Robin
[redacted]

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

RE: Docket No. FDA-2010-P-0091

Dear Ms. Robin:

This letter responds to your citizen petition received on February 16, 2010 (Petition). You request that the Food and Drug Administration (FDA or the Agency):

- Take action to amend the labeling for benzodiazepine products to:
  - match the recommended short dosing period found on the Ativan label, which states: "benzodiazepines should be prescribed for short periods only (e.g., 2-4 weeks)";
  - include the specific warning from the Ativan labeling stating that possible withdrawal symptoms have been noted "after as little as one week of therapy" and clearly define the symptoms of physical dependence, drug tolerance and withdrawal, and the development of physical dependence;
  - provide "clear instructions" on how to taper off of benzodiazepines after short or long term use;
  - warn of the possibility of "protracted withdrawal;" and
  - clarify the definitions of physical dependency, addiction, and abuse.
- Promptly notify doctors and pharmacists of the modified labeling information requested in the Petition as well as distribute dose equivalencies and half-life tables;
- Require that pharmacists supply patients with leaflets with all benzodiazepine prescriptions that contain the modified labeling information requested in the Petition;
- Require manufacturers' toll-free numbers and websites to be included in labeling for all benzodiazepine products;
- Require that manufacturers disclose the labeling modifications requested in the Petition on their websites; and
- Apply a "Black-Box Warning" to all FDA-approved benzodiazepine products warning against prescribing benzodiazepines for longer than two to four weeks' use and warning against risk of suicide and depression with benzodiazepine use.[1]

We have carefully considered the points raised in your Petition as well as the comments submitted to the docket and other relevant data identified by the Agency. Because FDA believes the current labeling for benzodiazepine products contains the essential scientific information needed for the safe and effective use of the drug, as discussed below in section II of this response, your requests are denied.

[1] Petition at 3 and 38.

I. BACKGROUND

A. Benzodiazepine products

The first benzodiazepine was approved by FDA for marketing in the early 1960s.[2] The precise mechanism of action for benzodiazepines is unknown, but the resulting activity in the brain is related to their anti-anxiety, sedative, hypnotic, and anticonvulsant properties.

The most common use for benzodiazepines products is treatment of anxiety. Whereas other classes of psychotropic drugs can require weeks or months of use to effectively treat the symptoms of anxiety, benzodiazepines have a short onset of action and can provide a degree of immediate relief to patients with anxiety.[3] Benzodiazepines are classified, based on their elimination half-lives, as long-acting, short-acting, or intermediate-acting. They are administered with a wide range of half-lives, dosages, and dosing frequencies, depending on the condition they are intended to treat.

Products in the benzodiazepine drug class are approved for a wide array of indications including, but not limited to, anxiety disorder, seizure disorder, and symptom relief of acute alcohol withdrawal. On average, 100 million prescriptions for benzodiazepines are filled in the United States each year.[4] Because they have been broadly used over a long period of time, there is extensive clinical experience with benzodiazepines.

Table 1 details the approved indications for all benzodiazepine products intended to treat anxiety disorders, which are the subject of your petition.

Table 1 – Benzodiazepines by Indication

Active Ingredient	Proprietary Name	Indication
alprazolam	Xanax XR, Niravam (ODT), Xanax	Alprazolam tablets are indicated for the management of anxiety disorder (a condition corresponding most closely to the APA Diagnostic and Statistical Manual [DSM-III-R] diagnosis of generalized anxiety disorder) or the short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Alprazolam tablets are also indicated for the treatment of panic disorder, with or without agoraphobia.
clonazepam	Klonopin	Klonopin is useful alone or as an adjunct in the treatment of the Lennox-Gastaut syndrome (petit mal variant), akinetic and myoclonic seizures. In patients with absence seizures (petit mal) who have failed to respond to succinimides, Klonopin may be useful. Klonopin is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern

[2] The first benzodiazepine was Valium (diazepam), approved on November 15, 1963.
[3] Longo LP, Johnson B., Addiction: Part I. Benzodiazepines—side effects, abuse risk and alternative. Am. Fam. Physician, 2000 Apr. 1; 61(7): 2121-8.
[4] See e.g., Cascade E and Kalali AH. Use of benzodiazepines in the treatment of anxiety. *Psychiatry.* 2008;5(9):21-22; data from IMS Health, IMS National Sales Perspective™, SDI Vector One®, SDI Physician Drug and Diagnosis Audit™.

		about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.
clorazepate	Tranxene	TRANXENE is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. TRANXENE tablets are indicated as adjunctive therapy in the management of partial seizures. TRANXENE tablets are indicated for the symptomatic relief of acute alcohol withdrawal.
diazepam	Valium	Valium is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. In acute alcohol withdrawal, Valium may be useful in the symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis. Valium is a useful adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology (such as inflammation of the muscles or joints, or secondary to trauma), spasticity caused by upper motor neuron disorders (such as cerebral palsy and paraplegia), athetosis, and stiff-man syndrome. Oral Valium may be used adjunctively in convulsive disorders, although it has not proved useful as the sole therapy.
lorazepam	Ativan	Ativan (lorazepam) is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.
oxazepam	Serax	Oxazepam is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Anxiety associated with depression is also responsive to Oxazepam therapy. This product has been found particularly useful in the management of anxiety, tension, agitation, and irritability in older patients. Alcoholics with acute tremulousness, inebriation, or with anxiety, associated with alcohol withdrawal are responsive to therapy.
chlordiazepoxide	Librium	Chlordiazepoxide HCl capsules USP are indicated for the management of anxiety disorders or for the short term relief of symptoms of anxiety, withdrawal symptoms of acute alcoholism, and preoperative apprehension and anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

Between 1960 and 1981, the Agency reviewed seven new drug applications (NDAs) for benzodiazepine products to treat anxiety disorders and concluded for each, based on the data provided, that the benefits outweigh the risks.[5] While FDA strives for consistency in the way scientific information is described in drug labeling, each product was approved for different conditions of use based on the data and information submitted by the sponsor. Accordingly, there is some variation among the labeling for approved

[5] Information on each product approval date is available at http://www.fda.gov/Drugs/InformationOnDrugs/.

benzodiazepine products. However, labeling for each benzodiazepine product discusses potential risks, such as physical dependence, abuse, and addiction. As discussed in detail below, the labeling for benzodiazepine products already includes the essential scientific information needed for their use.

B. Warnings in Drug Labeling

Labeling for prescription drug products is generally governed by 21 CFR 201.50, et seq., with specific requirements for content and format set forth in 21 CFR 201.57. Under § 201.57, drug product labeling must describe clinically significant adverse reactions,[6] other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these occur. (§ 201.57(c)(6)(i)). Labeling for prescription drugs must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug. (Id.) The "Drug Interactions" section must contain a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs. (§ 201.57(c)(8)(i).) Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), after the approval of a prescription drug, FDA is authorized to require holders of approved drug applications to make labeling changes based on new safety information that FDA believes should be included in the labeling of the drug. (Section 505(o)(4) of the FD&C Act; 21 U.S.C. 355(o)(4).)[7]

C. Medication Guides

A Medication Guide is FDA-approved patient labeling that conforms to the specifications in 21 CFR part 208 and other applicable regulations. The Agency will require a manufacturer of a prescription drug product to distribute a Medication Guide when it determines that the drug product poses a serious and significant public health concern and that patient labeling is necessary to ensure the safe and effective use of the product (§§ 208.1(a) and (b).) Under § 208.1(c), FDA will require a Medication Guide when it determines that one or more of the following circumstances exist:

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[6] § 201.57(c)(7) defines "adverse reaction" as "an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence." See also FDA Guidance for Industry on Warnings and Precautions. Contraindications. and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products-Content and Format, October 2011, at 3-5. Guidances are available on FDA's Web site at http://www.fda.gov/RegulatoryInformation/Guidances/default.htm.. The Warnings Guidance represents FDA's current thinking on this topic.

[7] As defined in the FD&C Act, "new safety information" is information derived from a clinical trial, an adverse event report, a postapproval study, or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k) of the FD&C Act; or other scientific data deemed appropriate by the Agency about, among other things, a serious or an unexpected serious risk associated with use of the drug that the Agency has become aware of (that may be based on a new analysis of existing information) since the drug was approved. (Section 505-l(b)(3) of the FD&C Act; 21 U.S.C. § 355-l(b)(3).) See also FDA Guidance for Industry on Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act, available on FDA's Web site at http://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

- The drug product is one for which patient labeling could help prevent serious adverse effects;
- The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product; or
- The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

D. Dear Healthcare Provider Letters

Dear Healthcare Provider Letters ("DHCP Letters", also known as Dear Doctor Letters) are correspondence from the manufacturer or distributor of a drug (or, in some cases, from FDA) intended to alert physicians and other health care providers responsible for patient care about important new or updated information regarding a drug product.[8] DHCP Letters can be issued when it is important to communicate information to health care practitioners involved in prescribing or dispensing a drug or in caring for patients who receive a drug.[9]

II. DISCUSSION

A. Requested Changes to Benzodiazepine Labeling

The Petition asserts that a number of risks are associated with use of benzodiazepine products, including the development of physical dependency and protracted withdrawal symptoms. You request that FDA take certain actions to change the labeling of these products and take certain actions to notify consumers and physicians about these risks. The specific requests set forth in the Petition are discussed below.

1. Recommended Duration of Benzodiazepine Use

The Petition requests that all FDA-approved labeling for benzodiazepine products be amended to contain standardized, comprehensive information. Specifically, you request that FDA add the exact language from the Ativan labeling, "In general, benzodiazepines should be prescribed for short periods only (e.g., 2-4 weeks)," to all benzodiazepine labeling to "help prevent the needless suffering that occurs when patients develop physical dependency and withdrawal" from taking benzodiazepines.[10] You request that this information be included as a "strong warning," and note that recommending

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[8] See 21 CFR 200.5; FDA Guidance for Industry and FDA Staff on Dear Health Care Provider Letters: Improving Communication of Important Safety Information, January 2014, at I. Guidances are available on FDA's Web site at http://www.fda.gov/RegulatoryInformation/Guidances/default.htmThe guidance represents FDA's current thinking on this topic.

[9] FDA Draft Guidance on Drug Safety Information-FDA's Communication to the Public, March 2012, at 10. Guidances are available on FDA's Web site at http://www.fda.gov/RegulatoryInformation/Guidances/default.htmThis draft guidance, when finalized, will represent FDA's current thinking on this topic.

[10] Petition at 4.

benzodiazepines for "short term" use is not sufficient because the phrase "short-term" is "vague and undefined."[11]

In support of your requests, you cite the labeling for Ativan as well as articles, statements from practitioners, and international guidelines.[12] You also note that the clinical trials performed to support benzodiazepine marketing applications only lasted "a few months at most," so this class of drug is not meant for long-term use.[13] Finally, you give the results of a survey of 346 users of the Web site Benzodiazepine Withdrawal Support, http://www.benzosupport.org, as well as anecdotal evidence from other posts on the site stating that benzodiazepines are often prescribed and used for longer periods of time.[14]

FDA Response

FDA has reviewed the evidence and information provided in the Petition and we do not agree that it warrants the labeling change you seek, nor does it support your contention that such a labeling change would prevent physical dependency and withdrawal symptoms. The Petition is focused on the use of benzodiazepines to treat anxiety disorders, many of which are chronic in nature. These disorders often have a relapsing course and may need frequent, regular treatment. For example, some benzodiazepines are indicated for the treatment of generalized anxiety disorder (GAD) and panic disorder, both of which are chronic conditions and can be treated for up to 8 months with benzodiazepines.[15] In addition, a review of the literature supports chronic use of many benzodiazepines in the treatment of GAD, panic disorder, and social anxiety disorder.[16] In light of their effective use in controlling the symptoms of these chronic conditions, FDA believes it would be clinically inappropriate and overly restrictive to recommend a maximum duration of use for benzodiazepines of 2 to 4 weeks as the Petition requests.

We also disagree with your characterization of the current language in benzodiazepine labeling regarding duration of use as "vague and undefined." The labeling for all benzodiazepine products contains language noting that the product has not been studied for long-term use and that physicians should periodically reevaluate the long-term utility

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[11] Id.
[12] Petition at 4 and 8.
[13] Petition at 7.
[14] Petition at 13.
[15] See Table 1 above.
[16] See, e.g., Kaplan E, DuPont R. Benzodiazepines and anxiety disorders: a review for the practicing physician. Current Medical Research and Opinions. 2005; 21 (6): 941-950; Potts N, Krishnan K. Long-Term Use of Benzodiazepines Implications and guidelines. Canadian Family Physician. January 1992; 38:149-153; Rynn M , Brawman-Mintzer O. Generalized Anxiety Disorder: Acute and Chronic Treatment. CNS Spectr. 2004; 9(10): 716-723; Davidson, JR. First-line pharmacotherapy approaches for generalized anxiety disorder. J Clin Psychiatry 2009; 70 (Suppl 2):25-31; Talley, Joseph H. But what if a patient gets hooked? Fallacies about long-term use of benzodiazepines. Postgraduate Medicine. 1990; 87 (1): 187-204; Gliatto, Michael. Generalized Anxiety Disorder. American Family Physician 2000;62: 1591-600, 1602; and Shader R, Greenblatt D. Use of Benzodiazepines in Anxiety Disorders. NEJM May 13, 1993; Vol 328 (19): 1398-1405.

of the drug for each individual patient.[17] FDA believes that these statements in the labeling are sufficient to alert physicians to be vigilant in monitoring their patients who take benzodiazepines for extended periods of time. After consideration of the information provided in your Petition, the Agency continues to believe that the current labeling for each benzodiazepine product contains the essential scientific information needed for the safe and effective use of that drug to help prevent physical dependency and withdrawal symptoms and, as such, the addition of the information you request to be added to the labeling is not warranted to address these particular issues. In addition, the Petition provides no evidence that "2 to 4 weeks" is the appropriate duration of use to prevent physical dependency and withdrawal symptoms for all benzodiazepine products.

The Petition also cites international guidelines as evidence that benzodiazepines should be prescribed for less than four weeks of use.[18] There are several sets of international guidelines regarding the use of benzodiazepines in anxiety disorders. FDA does not agree that these guidelines all recommend that all benzodiazepine use be restricted to four weeks or less. While we acknowledge that guidelines from various bodies in the United Kingdom recommend only short courses (2-4 weeks),[19] the American Psychiatric

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[17] The labeling for Niravam ODT (alprazolam) states, "In general, benzodiazepines should be prescribed for short periods. Reevaluate the need for continued therapy before extending the treatment period."
- The labeling for Klonopin (clonazepam) states that, "There is no body of evidence available to answer the question of how long the patient treated with clonazepam should remain on it. Therefore, the physician who elects to use Klonopin for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient."
- The labeling for Tranxene (clorazepate) states, "The effectiveness of TRANXENE tablets in long-term management of anxiety, that is, more than 4 months, has not been assessed by systematic clinical studies. Long-term studies in epileptic patients, however, have shown continued therapeutic activity. The physician should reassess periodically the usefulness of the drug for the individual patient."
- The labeling for Valium (diazepam) states, "The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient."
- The labeling for Xanax (alprazolam) states, "Demonstrations of the effectiveness of XANAX by systematic clinical study are limited to 4 months duration for anxiety disorder and 4 to 10 weeks duration for panic disorder; however, patients with panic disorder have been treated on an open basis for up to 8 months without apparent loss of benefit. The physician should periodically reassess the usefulness of the drug for the individual patient."
- The labeling for Ativan (lorazepam) states, "The effectiveness of Ativan (lorazepam) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient. In general, benzodiazepines should be prescribed for short periods only (e.g. 2- 4 weeks). Extension of the treatment period should not take place without reevaluation of the need for continued therapy. Continuous long-term use of product is not recommended."
- The labeling for Serax (oxazepam) states, "The effectiveness of Serax in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient."
- The labeling for Librium (chlordiazepoxide) states, "The effectiveness of Librium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient."

[18] Petition at 10.

[19] See, e.g., UK Government Bulletin to Prescribing Doctors January 1988; Benzodiazepine Warning. A communication to all doctors from the UK Chief Medical Officer (January 2004); Clinical Guidelines for

Association, the Canadian Psychiatric Association, the Royal Australian College of General Practitioners, and the World Federation of Societies of Biological Psychiatry all support chronic use of benzodiazepines as second-line treatment in the treatment of GAD, panic disorder, and social anxiety disorder where Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) have failed, and also as adjunctive therapy.[20]

FDA continues to believe that long-term use of benzodiazepines may be appropriate for some patients who suffer from chronic conditions for which these drugs are indicated. We disagree with your contention that, generally, benzodiazepines "[are] not meant for use for more than two to four weeks" or else patients will become physically dependent and experience withdrawal. For the reasons discussed above, your request is denied.

2. *Benzodiazepine Physical Dependency and Withdrawal Symptoms*

The Petition requests that the symptoms of tolerance, physical dependency and withdrawal be better defined in benzodiazepine labeling. Specifically, you request that warnings for all benzodiazepines should be made to match Ativan's warning that physical dependence and withdrawal symptoms have been noted to "appear following cessation of the recommended dose after as little as one week of therapy,"[21] and that many physicians "are unaware that this drug [benzodiazepines] is not meant for use for more than two to four weeks." In support of this request, you cite articles, practice guidelines, and medical opinions. You also note that the symptoms of tolerance and withdrawal are often

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the Management of Anxiety Dec 2004; funded by Royal College of General Practitioners on behalf of the National Institute for Clinical Excellence (NICE).

[20] See, e.g., APA Guidelines for Panic Disorder. Practice Guideline (January 2009) (In general, benzodiazepines seem to be well tolerated by patients with panic disorder, with very few serious side effects. Existing studies support continuing benzodiazepine treatment to prevent recurrence. Clinical experience also suggests that many patients can be maintained with stable doses of benzodiazepines for many years with no recurrence of symptoms.); Bandelow, Borwin et al.World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders-First Revision. The World Journal of Biological Psychiatry. 2008; 9 (4): 248-312. (recommending SSRIs/SNRIs as first-line therapy in GAD and social anxiety disorder. They rate benzodiazepines as A2 drugs. The "A" rating refers to the highest level of evidence for efficacy and the "2" rating refers to their use as second-line due to their abuse potential. These guidelines also recommend at least 12 months of treatment with these agents. Therefore, these guidelines would support the use of benzodiazepines for more than four weeks if SSRIs/SNRIs fail.); Clinical Practice Guidelines: Management of Anxiety Disorders. Can J Psychiatry. 2006; 51 (Supplement 2): 29S, 54S. (noting that some patients with GAD will require long-term adjunctive treatment with benzodiazepines to stay well. The guidelines also recommend that therapy for panic disorder continue for 8 to 12 months and that many patients require long-term therapy to achieve full benefits and to prevent relapse.); The Royal Australian College of General Practitioners: Benzodiazepine Guidelines 3/8/2010 (allows for chronic use of benzodiazepines but recommends the lowest dose for the shortest course): and UN Guidelines March 2001 (agree that short courses at minimal doses might be the optimal use for benzodiazepines but recognizes the extreme usefulness of this class of drugs and leaves decisions about chronicity of use to the provider.)

[21] Petition at 14.

misdiagnosed by practitioners as other mood disorders, which is why better definitions are needed.[22]

You also request that FDA add a statement to all benzodiazepine labeling clarifying the difference between the terms "physical dependency" and "addiction."[23] You cite the difficulties patients experience in managing withdrawal symptoms, which, you contend, should be differentiated from issues associated with addiction. You also cite two opinions regarding physical dependency on benzodiazepines.[24]

FDA Response

Physical dependence and withdrawal symptoms[25] can occur with benzodiazepine use, even after a relatively short period of time. The statement in the Ativan labeling that withdrawal symptoms "appear following cessation of the recommended dose after as little as one week of therapy" was supported by data submitted as part of the NDA for Ativan.

Moreover, FDA reviewed the labeling for each benzodiazepine product and determined that the labeling for each product addresses the risk of physical dependence and withdrawal symptoms, often in multiple sections.[26] Based on this review, FDA believes

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[22] Petition at 14–24.

[23] Petition at 29.

[24] Petition at 29, citing two statements by Professor Malcom H. Lader, as reported in various media sources and a statement by Caroline Adams, who is identified as a British government official.

[25] Withdrawal symptoms can include heightened sensory perception, impaired concentration, dysosmia (altered sense of smell), clouded sensorium (inability to think clearly or concentrate), paresthesias (tingling, burning, pricking, or numbness of the skin), muscle cramps, muscle twitch, diarrhea, blurred vision, appetite decrease, and weight loss. Seizures may also occur.

[26] The labeling for Niravam ODT (alprazolam) states, "The [withdrawal] symptoms can range from mild dysphoria and insomnia to a major syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors and convulsions. Psychological dependence is a risk with all benzodiazepines, including NIRAVAM. Even after relatively short-term use at the recommended doses, there is some risk of dependence and withdrawal symptoms."

- The labeling for Klonopin (clonazepam) states, "Generally milder withdrawal symptoms (eg, dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months."
- The labeling for Tranxene (clorazepate) states, "Withdrawal symptoms associated with the abrupt discontinuation of benzodiazepines have included convulsions, delirium, tremor, abdominal and muscle cramps, vomiting, sweating, nervousness, insomnia, irritability, diarrhea, and memory impairment. Evidence of drug dependence has been observed in dogs and rabbits which was characterized by convulsive seizures when the drug was abruptly withdrawn or the dose was reduced."
- The labeling for Valium (diazepam) states, "These withdrawal symptoms may consist of tremor, abdominal and muscle cramps, vomiting, sweating, headache, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases, the following symptoms may occur: derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures."
- The labeling for Xanax (alprazolam) states, "The [withdrawal] symptoms can range from mild dysphoria and insomnia to a major syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors and convulsions. Even after relatively short-term use at the doses recommended for the treatment of transient anxiety and anxiety disorder (ie, 0.75 to 4.0 mg per day), there is some risk of dependence."

that the language provided in the labeling is sufficient to warn physicians of the possibility of physical dependence and withdrawal symptoms for patients using these products and to inform physicians of the symptoms of physical dependence and withdrawal.

In addition, adding specific definitions for physical dependence and addiction to the benzodiazepine labeling is unnecessary. The purpose of drug labeling is to provide "a summary of the essential scientific information needed for the safe and effective use of the drug" by practicing physicians.[27] Although the concepts of physical dependence and addiction are important to consider when using benzodiazepines, the definitions of those terms are not unique or specific to benzodiazepines. Rather, they are common medical terms with definitions that are generally known to medical professionals or are available from other authoritative medical resources. For these reasons, your request is denied.

3. *Protracted Withdrawal after Benzodiazepine Use*

You request that FDA add a statement to the labeling of all benzodiazepine products regarding the risk of "protracted" withdrawal syndrome.[28] In support of this request, you cite articles noting the symptoms and occurrence of "protracted" withdrawal.[29] You also cite the results of a survey of 346 users of the Web site Benzodiazepine Withdrawal Support, http://benzosupport.org, noting that, on average, patients needed 12 months to recover after stopping benzodiazepine use.[30]

FDA Response

In response to the claims in the Petition regarding protracted withdrawal, FDA conducted an independent literature review. According to our research, the literature does not support the existence of a "protracted" benzodiazepine withdrawal syndrome. One study

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- The labeling for Ativan (lorazepam) states, "[Withdrawal] Symptoms reported following discontinuation of benzodiazepines include headache, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating, rebound phenomena, dysphoria, dizziness, derealization, depersonalization, hyperacusis, numbness/tingling of extremities, hypersensitivity to light, noise, and physical contact/perceptual changes, involuntary movements, nausea, vomiting, diarrhea, loss of appetite, hallucinations/delirium, convulsions/seizures, tremor, abdominal cramps, myalgia, agitation, palpitations, tachycardia, panic attacks, vertigo, hyperreflexia, short-term memory loss, and hyperthermia. Withdrawal symptoms (e.g. rebound insomnia) can appear following cessation of recommended doses after as little as one week of therapy."
- The labeling for Serax (oxazepam) states, "Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting, and sweating), have occurred following abrupt discontinuation of oxazepam."
- The labeling for Librium (chlordiazepoxide) states, "Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating), have occurred following abrupt discontinuance of chlordiazepoxide."

[27] 21 CFR 201.56(1).
[28] Petition at 25.
[29] Petition at 25–28.
[30] Petition at 28.

by Kaplan states that withdrawal symptoms usually disappear over a few weeks.[31] Another study by Shader says that the withdrawal syndrome is generally mild and always self-limited and that, after withdrawal is complete, patients recover completely without residual sequelae. Shader concludes that, "there is no reliable evidence to support the existence of post withdrawal syndrome. Experimental neuropharmacologic studies document that all the side-effects of benzodiazepines, whether behavioral or neurochemical, disappear within several days or weeks after the drug is eliminated. The weight of evidence indicates that any new symptoms that persist for more than two months after the last dose of a benzodiazepine either are part of the premorbid condition or have appeared by coincidence or as a consequence of the natural history of the underlying illness."[32] Yet another study by Mattilla-Evenden et al. found that the symptoms reported as evidence of benzodiazepine-induced psychiatric morbidity seemed in most cases to have been a feature of pre-existing psychopathology that became more manifest after discontinuation of benzodiazepine treatment.[33]

Based on our review of the literature, FDA cannot conclude that a "protracted" withdrawal syndrome results from use of benzodiazepine products. Therefore, adding a warning regarding a "protracted" withdrawal syndrome to the labeling for each benzodiazepine would not be appropriate and your request is denied.

4. *Instructions for Tapering*

You also request that FDA add a statement to the labeling of benzodiazepine products instructing physicians on the best method to taper patients off the product.[34] In support of this request, you cite statements in current benzodiazepine labeling that you believe are confusing and unclear.[35] You assert that the terms "slowly" and "gradually" should not be used when discussing use stoppage, and FDA should instead provide specific instructions for how to taper off these medications. You also cite the results of a survey of 346 users of the Web site Benzodiazepine Withdrawal Support, http://www.benzosupport.org, which, you claim, show that a large percentage of respondents had been improperly or too-rapidly tapered off benzodiazepines.[36] You also discuss a method of tapering advanced by Professor C. Heather Ashton.[37]

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[31] Kaplan E and DuPont R. Benzodiazepines and anxiety disorders: a review for the practicing physician. *Current Medical Research and Opinions*. 2005;21 (6):941-950.
[32] Shader R and Greenblatt D. Use of Benzodiazepines in Anxiety Disorders. *NEJM* May 13, 1993; Vol 328 (19):1398-1405.
[33] Mattila-Evenden, Marja et al. A study of benzodiazepine users claiming drug-induced psychiatric morbidity. *Nord J Psychiatry* 2001;55:271-278.
[34] Petition at 33.
[35] Petition at 33.
[36] Petition at 34.
[37] Petition at 35, citing Ashton, C. Heather, "Benzodiazepines: How they Work and How to Withdraw," available at http://www.benzo.org.uk/manual/contents.htm (2002).

FDA Response

The labeling for each benzodiazepine product intended to treat anxiety disorders recommends a gradual dosage tapering schedule, and the labeling for Xanax, Niravam, and Klonopin provide more specific instructions.[38] A relatively gradual dose reduction schedule, rather than rapid or abrupt discontinuation, can reduce the risk of developing a withdrawal syndrome. However, that schedule needs to be tailored to each individual patient and cannot be generalized in a tapering schedule such as that provided in the Petition. Furthermore, existing data do not support a precise dose reduction and discontinuation regimen for any of the benzodiazepine products; therefore, the Agency does not believe that the tapering instructions provided in your Petition are scientifically supportable. For these reasons, your request is denied.

5. *Boxed Warning*

You request that FDA add a boxed warning to the labeling of benzodiazepine products to prevent physical dependency or protracted withdrawal with more than two to four weeks' use of these drugs.[39] You cite anecdotal evidence derived from the personal experiences of users of your Web site Benzodiazepine Withdrawal Support, http://www.benzosupport.org, as well as statements from approved labeling and health care provider opinions to support the addition of such a warning.[40]

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[38] The labeling for Niravam ODT (alprazolam) states, "The dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage. Although there are no systematically collected data to support a specific discontinuation schedule, it is suggested that the daily dosage be decreased by no more than 0.5 mg every 3 days. Some patients may require an even slower dosage reduction."

- The labeling for Klonopin (clonazepam) states, "Treatment should be discontinued gradually, with a decrease of 0.125 mg bid every 3 days, until the drug is completely withdrawn."
- The labeling for Tranxene (clorazepate) states, "After extended therapy, abrupt discontinuation of clorazepate should generally be avoided and a gradual dosage tapering schedule followed."
- The labeling for Valium (diazepam) states, "Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed."
- The labeling for Xanax (alprazolam) states, "In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage. Although there are no systematically collected data to support a specific discontinuation schedule, it is suggested that the daily dosage be decreased by no more than 0.5 mg every three days. Some patients may require an even slower dosage reduction."
- The labeling for Ativan (lorazepam) states, "Abrupt discontinuation of product should be avoided and a gradual dosage-tapering schedule followed after extended therapy."
- The labeling for Serax (oxazepam) states, "Abrupt discontinuation should generally be avoided and a gradual dosage-tapering schedule followed."
- The labeling for Librium (chlordiazepoxide) states, "Abrupt discontinuation should generally be avoided and a gradual dosage-tapering schedule followed."

[39] Petition at 38.

[40] Petition at 38–39.

FDA Response

FDA has carefully reviewed the studies and other information cited in the Petition, and we do not believe that a boxed warning regarding risks of physical dependence and withdrawal is warranted at this time. Boxed warnings are intended to encompass "certain contraindications or serious warnings, particularly those that may lead to death or serious injury."[41] FDA bases its determination regarding whether to require a boxed warning and, if so, what types of information to include on clinical data.[42] A boxed warning is ordinarily used when there is an adverse reaction so serious in proportion to the potential benefit of the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug, or when there is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug.[43] As acknowledged in other sections of the Petition, FDA agrees that benzodiazepine use carries a risk of physical dependence and withdrawal. However, we have closely examined current labeling and we believe that these risks are sufficiently described throughout the labeling for benzodiazepine products to alert health care practitioners to their possibility. In addition, we have examined the evidence provided in the Petition and we do not believe that it supports the addition of a boxed warning regarding the risks of physical dependence and withdrawal. For these reasons, your request is denied.

B. Notice of Changes to Benzodiazepine Labeling

1. Notice to Physicians and Pharmacists

You request that FDA contact all pharmacists and medical providers to inform them of the labeling changes requested in your Petition and give them a copy of all benzodiazepine equivalencies. You request that FDA distribute equivalence tables because you believe physicians are confused by the low dosage of benzodiazepines and they erroneously believe they are "weaker" and "safer."[44]

FDA Response

FDA makes the current and updated labeling for benzodiazepine products readily available to the public on the Agency's Web site.[45] In addition, the labeling for benzodiazepine products is available from DailyMed[46] and is distributed in hard copy with the drug product. FDA does not, as a matter of course, send letters to pharmacists and physicians informing them directly of updates to labeling. Manufacturers

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[41] See § 201.57(c)(1).
[42] Id.
[43] *See* Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format, available at: http://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[44] Petition at 32.
[45] See, e.g., http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ and http://labels.fda.gov/.
[46] http://www.dailymed.nlm.nih.gov/dailymed/about.cfm.

occasionally inform medical professionals of important information in a mailing from the manufacturer that is colloquially referred to as a "Dear Health Care Provider Letter" or a "Dear Doctor Letter."[47] Dear Health Care Provider Letters can be issued when it is important to communicate information to health care practitioners involved in prescribing or dispensing a drug or in caring for patients who receive a drug. As explained above and discussed previously, FDA does not intend to make your requested changes to the benzodiazepine labeling, so we do not believe that the communication you requested is necessary or appropriate.

Furthermore, the labeling for each benzodiazepine product describes the half-life of the drug, so physicians already have access to the information you describe. Contrary to the table in the Petition, which implies that half-life translates to interchangeability and equivalence of different benzodiazepines at different doses, each benzodiazepine should be considered individually, not as equivalent to other benzodiazepines at different dosage strengths. FDA does not agree with the contentions in the Petition regarding equivalencies or interchangeability of benzodiazepine products. Without data to support a precise dose reduction and discontinuation regimen for each benzodiazepine product, your suggested modification of benzodiazepine labeling to include a table of benzodiazepine equivalencies is not appropriate. For these reasons, your request is denied.

2. Require that Pharmacists Supply Leaflets, or Medication Guides

You request that pharmacists be required to hand out leaflets with every benzodiazepine prescription with the following warning:

> "In general, benzodiazepines should be prescribed for short periods only (e.g., 2 – 4 weeks). Extension of the treatment period should not take place without reevaluation of the need for continued therapy. Continued long-term use is not recommended. Withdrawal symptoms (e.g., rebound insomnia, dizziness, agitation, palpitations, etc.) can appear following cessation of the recommended dose after as little as one week of therapy. Abrupt discontinuation of product should be avoided and a gradual dosage-tapering schedule followed after extended therapy. Protracted withdrawal (symptoms lasting months or years after the drug is stopped) is a risk with this class of drug."

FDA Response

As explained above, a Medication Guide must be distributed when a drug product poses a serious and significant public health concern, and patient labeling is necessary to ensure the safe and effective use of the product (§§ 208.1(a) and (b)). As noted previously in our response, we decline to add the warnings suggested for your "leaflet" to the labeling for benzodiazepines at this time. For the same reasons discussed in section II.A. of this

[47] See Guidance for Industry and FDA Staff: Dear Health Care Provider Letters: Improving Communication of Important Safety Information, available at: http://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

letter, we do not believe that these warnings are appropriate to be provided to patients in a "leaflet" as you suggest.

The Agency believes that the information and warnings currently presented in the labeling of benzodiazepine products are sufficient to inform physicians of the risks associated with these products, which they can then discuss with their patients. For these reasons, your request that FDA require a patient "leaflet" articulating the warnings listed above is denied.

3. Include Toll-Free Numbers and Web sites in Product Labeling

You request that a toll-free number and Web site address be given for all benzodiazepine manufacturers as part of the labeling for benzodiazepine products.

FDA Response

All drug product labels must "bear the name and place of business of the manufacturer, packer, or distributor."[48] The place of business must include "the street address, city, state, and ZIP Code."[49] There is no requirement that manufacturers include a Web site address or toll-free number on drug product labels, but some manufacturers choose to do so. In addition, through FDA's MedWatch system, patients and health care providers may always contact FDA to report an adverse event or pose a question to FDA's Division of Drug Information about a specific product.[50] FDA believes these resources are adequate to inform patients of safety problems associated with any benzodiazepine products and answer their questions regarding the safety of those products. For these reasons, your request is denied.

4. Require Manufacturers to Include Updated Labeling Information on Their Web sites

You note in your Petition that it is important for both patients and doctors to be able to access updated labeling from the manufacturer's Web site, and you request that FDA require manufacturers to post this information.

FDA Response

We agree that access to current labeling is important. As noted above, the current labeling for benzodiazepine products, and all FDA-approved products, is available on our Web site as well as other Web-based sources. We believe that these resources provide adequate access for patients and health care providers to the current approved labeling for benzodiazepine products and additional access is not warranted. For this reason, your request is denied.

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[48] FD&C Act 502(b); 21 CFR 201.1(a).
[49] See § 201.1(i).
[50] See http://www.fda.gov/safety/medwatch/default.htm.

III. CONCLUSION

After careful consideration, and in light of the foregoing, we hereby deny your Petition in its entirety. Please be assured, however, that FDA remains committed to ensuring an appropriate balance of safety and efficacy for all approved drugs. FDA will continue to monitor the safety of benzodiazepines, and, if necessary, will take appropriate action to protect the public health.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research