DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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Charles E. Weber
1908 Country Club Road
Hendersonville, NC 28739

Re: Docket No. 2006P-0508/CP1

Dear Mr. Weber:

This letter responds to your citizen petition (Petition) that we received on December 5, 2006, requesting that the Food and Drug Administration (FDA) "make 2 to 5 milligram pills of naltrexone to have an over the counter status." We have reviewed your Petition, your comments, and other comments received in the docket. For the reasons described below, your Petition is denied.

I. BACKGROUND

There are currently one approved new drug application (NDA) and four approved abbreviated new drug applications (ANDAs) for prescription (Rx) naltrexone hydrochloride tablets. The tablets are available in 25-, 50-, and 100-milligram (mg) strengths. The INDICATIONS AND USAGE section of the naltrexone hydrochloride labeling states that the drug product is indicated

> in the treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids. Naltrexone hydrochloride has not been shown to provide any therapeutic benefit except as part of an appropriate plan of management for the addictions.

There are no approved NDAs or ANDAs for naltrexone hydrochloride in 2- to 5- mg strength tablets.

II. LEGAL FRAMEWORK

A. Marketing Over-the-Counter (OTC) Drug Products

Under the Federal Food, Drug, and Cosmetic Act (the Act) and FDA's regulations, a drug product can be made available OTC in the following ways[1]:

- *Marketing Under the Authority of an NDA or ANDA*

Section 505 of the Act (21 U.S.C. 355) grants us the authority to approve or reject a drug application for a new drug product (see 21 U.S.C. 355(b) and (j)). The applicant must submit adequate data to satisfy the applicable statutory and regulatory requirements for approval of a

[1] These are post-1938 pathways for OTC marketing of a drug product.

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new drug product. An NDA must generally demonstrate that the product is safe and effective for the indication for use. An ANDA must generally demonstrate that the product is both pharmaceutically equivalent (identical active ingredient) and bioequivalent (behaves the same way in the body) to an approved NDA product. A drug product may be approved as an Rx or OTC product or may be switched from Rx-to-OTC status under the applicable legal and regulatory standards. The Rx-to-OTC switch process is described in further detail below.

- *Marketing in Compliance With an OTC Monograph*

An OTC monograph represents regulatory standards for the marketing of non prescription drug products that are found to be generally recognized as safe and effective for use in self treatment. These products marketed under an OTC monograph are not covered by NDAs. These monograph standards provide the marketing conditions for certain categories of OTC drug products, including the active ingredients, labeling, and other general requirements.

B. Rx-to-OTC Switch

Under section 503(b)(1) of the Act, a drug that is not safe for use except under the supervision of a practitioner licensed by law to administer the drug may only be dispensed by prescription. A drug will be restricted to Rx-only status when FDA finds that "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, [it] is not safe for use except under the supervision of a practitioner licensed by law to administer such drug" (21 U.S.C. 353(b)(1)).

Section 503(b)(3) (21 U.S.C. 353(b)(3)) of the Act provides us with the authority to issue a regulation changing the status of an Rx drug to an OTC drug when such prescription-only requirements are not necessary for the protection of the public health. The Act also grants us the authority to approve and reject a drug application (see 21 U.S.C. 355(c) and (d)), including an application to switch a drug from Rx-to-OTC status. FDA's regulations at 21 CFR 310.200(b) identify processes for initiating consideration of an Rx-to-OTC switch. A proposal to exempt a drug from Rx-only requirements may be initiated by the Commissioner, by "any interested person" in the form of a sponsor submitting a supplement to an approved NDA, or by a third party petitioning FDA (see 21 CFR 310.200(b)). Regardless of who initiates a request for an OTC switch, the evidence must demonstrate that (1) the prescription-only dispensing requirements are no longer necessary to protect the public health by reason of the drug's toxicity or other potentiality for harmful effect, or by reason of the method of the drug's use, and (2) the drug is safe and effective for use in self-medication as directed in proposed labeling (see 21 CFR 310.200(b)).

III. DISCUSSION

In requesting that 2- to 5-mg tablets of naltrexone hydrochloride be made available OTC, the burden is on you, as the petitioner, to provide FDA with sufficient evidence to demonstrate that

the drug is safe and effective for OTC use,[2] and that all the statutory and regulatory requirements have been met. As described below, we find that you have not met this burden.

Naltrexone hydrochloride 2- to 5- mg tablets are not the subject of an approved NDA or ANDA. To obtain approval of naltrexone hydrochloride tablets in 2- to 5- mg strengths, an applicant would need to submit an NDA that contains adequate safety and efficacy data and satisfies the applicable statutory and regulatory requirements. Furthermore, there is no applicable OTC monograph for such a product.[3]

Because naltrexone hydrochloride 2- to 5- mg tablets are not the subject of an approved NDA or ANDA, a switch from prescription to OTC status is not possible. Even if these tablets were the subject of an approved NDA or ANDA, you do not provide the following information and data to support your request for OTC status:

- Which indication(s) you request for the OTC drug product

  You state that naltrexone hydrochloride appears to be especially effective for minimizing symptoms and retarding progression of multiple sclerosis and advantageous in rheumatoid arthritis, Crohn's disease, and Parkinson's disease, and that some doctors have seen improvement in chronic fatigue syndrome and even to some extent in cancer (Petition at 1-2). In your comments, you provide additional references to studies using naltrexone hydrochloride for various treatments. You do not clearly specify which indication(s) for use you propose for naltrexone hydrochloride as an OTC product, and FDA cannot assume that your request is for any particular indication. This information is essential to evaluate the overall rationale and justification for an Rx-to-OTC switch. FDA cannot determine whether a prescription drug can be used safely and effectively in an OTC setting unless the proposed indications for use are clearly set forth by the petitioner.

- Evidence (i.e., safety data, studies, or trials (actual use or labeling comprehension)) to suggest that naltrexone hydrochloride may be used safely and effectively in an OTC setting

- Evidence to demonstrate that consumers would be able to self-diagnose their condition and use the drug effectively without a medical diagnosis or supervision by a health care practitioner, evidence that FDA considers for any Rx-to-OTC switch (see 21 CFR 310.200(b))

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[2] Data to support an Rx-to-OTC switch generally comes from the following sources: safety and efficacy data in an original NDA for the prescription drug, safety and efficacy data from trials conducted to support the OTC use, other available safety data, actual use trials, and label comprehension trials.

[3] An applicant may submit a time and extent application to request that applicable conditions be considered for inclusion in the OTC monograph system if certain criteria are met (see 21 CFR 330.14).

IV. CONCLUSION

For the reasons discussed in this response, your Petition requesting that the Agency make 2- to 5-mg tablets of naltrexone hydrochloride available as an OTC drug is denied. We thank you for your interest in the work of FDA to ensure the safe and effective use of drug products.

Sincerely,

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