Edwin Thompson
President
PMRS, Inc.

November 14th, 2018

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-011/S-003

Xanodyne Pharmaceuticals, Inc.
Ove Riverport Place
Newport, KY 41071-4563

NDA 21-011/S-003

your supplemental new drug application dated January 13, 2009,

provides for the addition of a 5-mg strength tablet.

and it is approved,

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format submitted on March 26, 2009.

We remind you of your March 8, 2009, agreement to implement the carton and container label changes listed below.

Carton Labels and Container Labels

For all strengths, delete the blue horizontal stripe which separates the trade name and established name/dosage form from the product strength.

Blister Labels

For all strengths, delete the reverse numbering on each blister.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care and Addiction Drug Products

MEMORANDUM

to: Division File, NDA # 21-011

from: Cynthia McCormick, MD

September 16, 1999

Currently oxycodone exists in the marketplace in many forms by virtue of DESI evaluation for the immediate release product, 5 mg. in combination with aspirin (Percodan),

The currently available oxycodone IR 5-mg product that is being marketed as a single entity analgesic has no historical basis for approval.

This NDA contains no efficacy data,

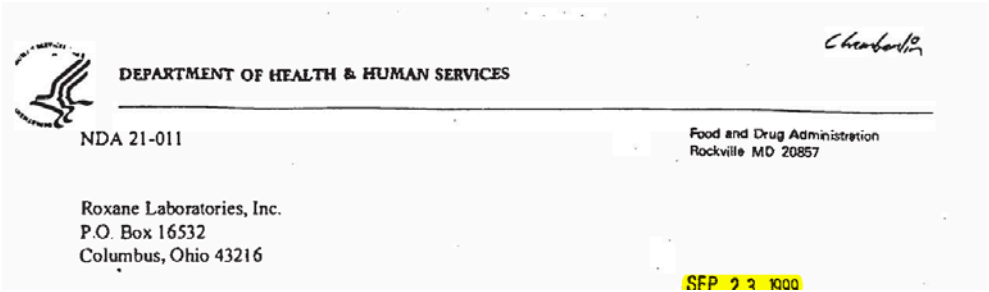
It presents a problem the root of which is the basis for the determination of efficacy of single entity oxycodone immediate release.

a single entity analgesic has no historical basis for approval.

This NDA #20-011 is intended to provide for an extension of the IR oxycodone line beginning as a 5-mg tablet to now include 15 and 30 mg. This NDA contains no efficacy data, but rather pharmacokinetics and limited safety supporting the higher doses. It presents a problem the root of which is the basis for the determination of efficacy of single entity oxycodone immediate release. The relevant regulatory history of oxycodone is reviewed below.

Oxycodone was first marketed in the United States in 1926.

The National Research Council/National Academy of Sciences Panel on Drugs for Relief of Pain, Panel on Drugs used in Rheumatic Diseases, and Panel on Neurologic Drugs all reviewed



DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-011

Food and Drug Administration
Rockville MD 20857

Roxane Laboratories, Inc.
P.O. Box 16532
Columbus, Ohio 43216

SEP 23 1999

SEP 23 1999

1. There are no data submitted in support of the effectiveness of immediate release 15 and 30 mg oxycodone in this application. There is also no link to any product for which the FDA has made the findings of efficacy.

3. Clinical safety in the higher doses has not been adequately established with the database submitted. There is also no link to any product for which the FDA has made the findings of safety in higher doses.

30 mg oxycodone in this application. There is also no link to any product for which the FDA has made the findings of efficacy.

2. There is no request for a waiver of such studies and no justification provided for the claim that clinical studies are not needed.

Safety:

3. Clinical safety in the higher doses has not been adequately established with the database submitted. There is also no link to any product for which the FDA has made the findings of safety in higher doses. There may be adequate safety data for oxycodone 15 and 30 mg that you can bring to bear on this application. This may include data that you have developed. However, if these data are derived from studies on products other than that to which you have linked your application for purposes of establishing efficacy, an additional biopharmaceutical link must be provided.

NDA 21-011
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4. The safety database as presented, correlating adverse events by tablet size rather than dose does not provide appropriate information about adverse events from which labeling can be written.

Regulatory:

5. This application has relied upon the finding of efficacy of oxycodone and has provided no clinical efficacy data of its own. If you intend to file a bridging study which will enable

1. A bridging study or studies will be required from which the Agency can link its prior findings of efficacy for immediate release oxycodone to your product seeking approval. Such a bridging study is generally a biopharmaceutical study demonstrating relative bioavailability to the reference listed product.

2. An adequate rationale will be required for the extension of the dosage form to 15 and 30 mg without having provided clinical studies demonstrating efficacy at higher doses.

1. A bridging study or studies will be required from which the Agency can link its prior findings of efficacy for immediate release oxycodone to your product seeking approval. Such a bridging study is generally a biopharmaceutical study demonstrating relative bioavailability to the reference listed product.

2. An adequate rationale will be required for the extension of the dosage form to 15 and 30 mg without having provided clinical studies demonstrating efficacy at higher doses.

3. Information establishing safety at higher doses or a bridging study or studies will be required from which the Agency can link its prior findings of safety for lower doses of oxycodone to the proposed higher doses of oxycodone. Such a bridging study will likely be a biopharmaceutical study demonstrating relative bioavailability to an approved oxycodone product. New clinical safety data using the immediate release (IR) Oxycodone 15 and 30 mg would also be acceptable.

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)443-3741

NDA 21-011 was originally submitted on September 30, 1998. The application requested approval of new 15 mg and 30 mg dose strengths of the sponsor's marketed, although unapproved, 5 mg oxycodone tablets [see Division Director's Memo to File dated September 21, 1999].

1. No data to support effectiveness were included in the NDA as comparative studies included only the subject of this application and/or the unapproved 5 mg tablets.

4. The application had been filed as a 505(b)1, although it provided little to no clinically useful effectiveness data.

approval of new 15 mg and 30 mg dose strengths of the sponsor's marketed, although unapproved, 5 mg oxycodone tablets [see Division Director's Memo to File dated September 21, 1999]. The application was found to be approvable and the following deficiencies were presented to the sponsor in a letter dated September 23, 1999:

1. No data to support effectiveness were included in the NDA as comparative studies included only the subject of this application and/or the unapproved 5 mg tablets.
2. Neither waiver of the necessary studies to establish efficacy nor justification for why these studies were not needed were included in the application.
3. Clinical safety had not been adequately established at the higher doses based on the database submitted, which correlated adverse events by tablet size rather than dose.
4. The application had been filed as a 505(b)1, although it provided little to no clinically useful effectiveness data.

The letter requested that the sponsor correct those deficiencies by:

1. Performing a relative bioavailability study, bridging their product to a previously approved product.
2. Providing an adequate rationale for extension of the dosage form to the 15 and 30 mg tablets in the absence of clinical evidence of efficacy.
3. Providing sufficient evidence of safety at the higher doses either by clinical studies or by a bridging study which demonstrates relative bioavailability to a previously approved product, including retabulation of all adverse events by total daily dose for

1. Performing a relative bioavailability study, bridging their product to a previously approved product.
2. Providing an adequate rationale for extension of the dosage form to the 15 and 30 mg tablets in the absence of clinical evidence of efficacy.

This submission included the results of a bioequivalence [BE] study (XIR0299) which assessed the dose-adjusted bioavailability of oxycodone comparing immediate release oxycodone HCl 15-mg tablet with three tablets of Percodan®.

is also a line extension of the 5-mg product that has been in use for decades.

DSI

An inspection of the pivotal biopharmaceutics study was not requested. There were no irregularities in the data that would suggest due cause for an inspection and this NDA, while officially a 505b2 application for the immediate release product, is also a line extension of the 5-mg product that has been in use for decades.

PRECLINICAL TOXICOLOGY:

Also included in this submission were four preclinical Segment II reproductive toxicity studies of oxycodone hydrochloride which, although not responses to the deficiencies

Electronic Code of Federal Regulations

e-CFR data is current as of November 7, 2018

Title 21: Food and Drugs
PART 300—GENERAL
Subpart B—Combination Drugs

§300.50 Fixed-combination prescription drugs for humans.

(a) Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug. Special cases of this general rule are where a component is added:

that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug. Special cases of this general rule are where a component is added:

(1) To enhance the safety or effectiveness of the principal active component; and

(2) To minimize the potential for abuse of the principal active component.

(b) If a combination drug presently the subject of an approved new-drug application has not been recognized as effective by the Commissioner of Food and Drugs based on his evaluation of the appropriate National Academy of Sciences-National Research Council panel report, or if substantial evidence of effectiveness has not otherwise been presented for it, then formulation, labeling, or dosage changes may be proposed and any resulting formulation may meet the appropriate criteria listed in paragraph (a) of this section.

(c) A fixed-combination prescription drug for humans that has been determined to be effective for labeled indications by the Food and Drug Administration, based on evaluation of the NAS-NRC report on the combination, is considered to be in compliance with the requirements of this section.

[40 FR 13496, Mar. 27, 1975, as amended at 64 FR 401, Jan. 5, 1999]

Page 105 (103 of 168), #3:

Following oral and intranasal MNK-812, and intranasal Oxycodone HCl IR, the mean maximum plasma levels of oxycodone achieved were 57.7, 55.0, and 55.7 ng/mL, respectively. Time to achieve Cmax (Tmax) following oral administration was 1.51 hours, compared to the Tmax values of 2.41 hours and 2.06 hours for intranasal MNK-812 and intranasal Oxycodone HCl IR. Overall oxycodone exposure over the first hour was highest for intranasal Oxycodone HCl IR (AUC0-1hour = 33.29 ng x h/mL) compared to either oral MNK-812 or intranasal MNK-812 with AUC0-1hour of 27.55 and 22.32 ng x h/mL, respectively.