

The following is a list of action items.

- ACTION:** The Sponsor will submit the information about the characterization of the impurities to the Division.
- ACTION:** The Sponsor will clarify the COA listed in the meeting package for the Suboxone extract used in the pre-clinical studies on impurities.
- ACTION:** The Sponsor agreed to send in a request for another meeting prior to the next submission.
- ACTION:** The Sponsor will provide the appropriate data for acceptance criteria for the drug product tests.
- ACTION:** The Sponsor will provide the appropriate data on individual degradation products.
- ACTION:** The Sponsor will provide the acceptance criteria for individual degradation products. The Sponsor has improved their identification and monitoring process.
- ACTION:** The Sponsor will provide the test and acceptance criteria for individual tablet dissolution. In the submission the data were reported as mean data but the individual tablet data are available.
- ACTION:** The Sponsor will provide data to cross correlate the different degradation products found in Subutex and Suboxone.
- ACTION:** The Sponsor will provide identification of the site of packaging used for drug product stability batches and the proposed commercial drug product packaging site.
- ACTION:** No agreement was reached on a PK study design and this issue will need to be resolved by telecon or another meeting.
- ACTION:** The Sponsor will submit a summary of all the stability studies conducted on the drug product (manufacturing site, packaging, formulation, storage conditions, etc.).

The meeting adjourned at ~12:30 PM

NOTE: The Sponsor provided a package of their overheads used during the meeting.

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Sara Shepherd
3/13/01 08:57:35 AM

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

M E M O R A N D U M**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

Date: January 25, 2001

To: Director, Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170)

Through: Deborah B. Leiderman, MD, MA
Director, Controlled Substance Staff (HFD-009)

From: Michael Klein, Ph.D.
Controlled Substance Staff (HFD-009)

Subject: Controlled Substance Staff Proposals on Scheduling and Risk Management for Buprenorphine and Buprenorphine-Naloxone Sublingual Tablets (NDA #20-732 & 20-733)

The purpose of this memo is to summarize the basis for the proposal to reschedule buprenorphine under the Controlled Substances Act (CSA) to Schedule III and to reschedule the combination products of buprenorphine-naloxone to Schedule IV. Rescheduling will occur soon after approval of NDAs 20-732 and 20-733, and prior to marketing. For the purposes of CSA scheduling, buprenorphine is defined as the drug substance and all possible products, mixtures and combinations, except for approved drug products that contain buprenorphine and naloxone. CSS additionally proposes that a Risk Management Program be developed to ensure safe use of the buprenorphine-containing drugs.

DRUG SCHEDULING & RISK MANAGEMENT PROPOSALS

The criteria for listing a drug in a CSA schedule derive from an assessment of its relative abuse and dependence potential properties. A drug listed in Schedule III must have a potential for abuse less than drugs in Schedules I and II and must produce moderate or low physical dependence or high psychological dependence. A drug in Schedule IV has a lower potential for abuse than drugs in Schedule III and produces limited physical or psychological dependence. Sublingual buprenorphine tablets produce predominantly opiate agonist effects with little or no contributing antagonist effect of naloxone. By contrast, buprenorphine combined with naloxone and parenterally administered to opioid-dependent individuals may precipitate a withdrawal syndrome. Actual abuse documented from France, New Zealand, and other countries largely involves opiate addicts extracting and injecting the active ingredient of the buprenorphine tablets. Therefore, if this pattern repeats in the United States, the addition of antagonist to buprenorphine would be expected to reduce its intravenous abuse, although other routes for the "street addict" to abuse the drug would not be significantly affected.

In addition to listing buprenorphine in more restrictive CSA schedules, a Risk Management Program (RMP) is needed and needs to be part of the NDAs. Such a program will ensure safe use of buprenorphine and prevent abuse by other at-risk populations, including the drug naïve individual and non-dependent intravenous opioid abuser. Features of the Program should include the following:

1. A post-marketing surveillance plan for diversion and safety
2. Development of _____
3. Voluntary restriction of take-home medication
4. An _____
5. Educational material to be distributed to patients, doctors, pharmacies
6. A plan to monitor signals for off-label use
7. 1-800 number to report diversion
8. A Dear Pharmacy/Healthcare letter
9. A plan for physician/pharmacist interaction
10. Monitoring of existing databases to provide periodic updates to FDA

ABUSE AND DEPENDENCE POTENTIAL

The evaluation of buprenorphine considers the profile of effects related to (1) abuse potential and (2) physical dependence capability.

Buprenorphine has high affinity for, and slow dissociation from, the mu-opioid receptor. Buprenorphine produces a typical opioid-like spectrum of effects. These include euphoria, drug liking, pupillary constriction, respiratory depression and sedation. In both preclinical and clinical studies, buprenorphine manifests a shallower dose response curve and “ceiling effect” for many actions compared to pure agonists such as morphine (C-II) and hydromorphone (C-II). Buprenorphine is thus considered a partial opioid agonist.

The withdrawal syndrome that develops after continued use is typical of opioids and is evidence of the capacity of buprenorphine to produce physical dependence. The intensity of the withdrawal syndrome has been evaluated by clinical investigators to vary from moderately severe to moderate to mild. Drug craving has been reported after discontinuing use of buprenorphine, which has in some patients resulted in the need to resume use of heroin. This craving is indicative of psychophysiological dependence. Individuals dependent on buprenorphine can easily return to heroin use and vice versa. Twenty percent of newborns born to mothers in treatment with buprenorphine substitution for opiate dependence have exhibited a narcotic abstinence syndrome (NAS) severe enough to require treatment. For mothers maintained on methadone (C-II), 60-80% NAS of varying severity was reported.

The presence of the opiate antagonist, naloxone, in the combination product is expected to reduce its abuse. The antagonist may diminish the euphoria produced by buprenorphine. Withdrawal in opiate dependent individuals may be precipitated, if the drug combination is

parenterally administered. Dependence production is thus limited in this at-risk population. Naloxone administered by the sublingual route is not bioavailable.

MORBIDITY AND MORTALITY

In France, sublingual buprenorphine has been available by prescription. During the first three years of marketing, approximately — individuals were treated with the drug for heroin addiction. More than 100 buprenorphine-related deaths were reported. The deaths involved individuals who were not in treatment for addiction, but who obtained the drug through diversion. Most cases involved diverted medication and concomitant use of other psychoactive drugs, especially benzodiazepines. Risks associated with misuse of the tablet form of buprenorphine were primarily by intravenous injection.

Benzodiazepines ranked first in association, (present in 91 observations, of which 64 were nordiazepam). There were 37 cases involving neuroleptics, of which 26 were with cyamemazine. Eighteen cases (8 with tricyclics and 10 SSRI's) were with antidepressants. Concomitant use of other narcotics was observed with morphine (12 cases), codeine (2 cases), methadone (4 cases), meperidine (1 case) and *dextro*-propoxyphene (4 cases). There were 4 reported fatalities involving ethanol and buprenorphine.

ACTUAL ABUSE

Numerous articles have been published in the scientific literature on buprenorphine abuse. Thus far, in the United States, buprenorphine has been marketed as a Schedule V, injectable product (0.3 mg/mL). Abuse of the injectable formulation has been low, because of limited marketing and availability. Parenteral formulations are not available to patient populations to the same extent as are oral, sublingual, or transdermal formulations. Many national governments have increased the regulatory controls on buprenorphine as a result of abuse and diversion. The reports from other countries need to be examined in relation to how the new drug products will be marketed in the United States. The proposed additional CSA restrictions and Risk Management Program will offer deterrents to abuse, diversion, overdose, and deaths, which differ from the manner in which buprenorphine has been marketed elsewhere after approval.

Buprenorphine was first marketed in France in 1987 as an analgesic. Its approval for treatment of opiate addiction followed in 1996. Abuse and diversion was identified soon after it first became available. Due to misuse of the sublingual form, special narcotic restrictions on the prescribing and dispensing of buprenorphine in treating pain were instituted in December 1992. Prescriptions had to be written on a voucher taken from a counterfoil prescription book that was specifically designed for narcotic drugs and monitored by the French Medical Association. Records had to be retained by the pharmacist for 3 years. The prescription could be filled by any pharmacy. As of 1996, general practitioners were permitted to prescribe the buprenorphine tablets for treating opiate dependence for up to 28 days per prescription, by use of the counterfoil prescription book. Doses prescribed were in the range of 4 to 16 mg/day. In September 20,

1999, because of continuing reports of abuse and diversion, dispensing was restricted to a 7-day supply at one time from the prescription.

In New Zealand, buprenorphine was launched as a noncontrolled drug in April 1982. Within 2 months, the first report of intravenous abuse appeared. Opioid users described using 4-5 tablets intravenously twice daily to produce euphoria lasting for hours. Buprenorphine was reported as the drug of choice during heroin shortages. Data from the — indicated that, of 110 new patients in 1983, 56 (51%) reported buprenorphine abuse. Escalating abuse, theft, and forged prescriptions led to control of buprenorphine in September 1983. Nevertheless, abuse continued to rise in 1984. In 1986, more than 50% of drug abusers in New Zealand were abusing buprenorphine.

In March 1991, because of a continuing iv drug abuse problem, buprenorphine was reformulated with naloxone. Abuse of the naloxone combination product was compared to abuse of the single ingredient drug product. In 1990, 81% of the subjects reported buprenorphine abuse in the 4-week period prior to intake and 65% had buprenorphine in their urine. In 1991, after introduction of the combination product, 57% reported abuse of products containing buprenorphine, and 43% had buprenorphine in their urine. One-third of the patients abusing the buprenorphine-naloxone product intravenously reported withdrawal symptoms and felt that it was less appealing as a drug of abuse. Users reported injecting three tablets of the single entity product versus two tablets of the combination product. The illicit importation of buprenorphine single entity product was documented, as large seizures of the drug occurred at New Zealand airports.

Thus, it appears that the combination of buprenorphine with naloxone reduced abuse and diversion of buprenorphine in the country where both products are available. We anticipate that in the United States the likelihood of abuse of the combination product by the "street addict" will be less than that of the single ingredient product after approval. The institution of an adequate Risk Management Program, the features of which are described above, with the rescheduling of buprenorphine are expected to be significant deterrents to abuse, diversion, overdoses, and deaths resulting from the buprenorphine-containing products.

CC:

Orig NDA #20-732

Orig NDA #20-733

HFD-009/ KleinM/LeidermanD/MoodyC/LocklearD

HFD-170/McCormickC/WinchellC/ShepherdS

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Michael Klein
1/25/01 11:56:50 AM
CHEMIST

This is the same memo, however it is for the combo NDA.

Deborah Leiderman
1/25/01 12:10:46 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL



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

MEMORANDUM

To: File, NDA 20-732

NDA 20-733 ✓

From: Celia Winchell, M.D., Medical Team Leader, Addiction Drug Products

Through: Cynthia G. McCormick, M.D., Director, HFD-170

Date: 1/22/01

Re: Pediatric Studies for Subutex (Buprenorphine HCl) Sublingual Tablets

I believe that pediatric studies for Subutex (Buprenorphine HCl) Sublingual Tablets
— at this time for the following reasons:

1. The drug substance, buprenorphine, is already known to be safe in children, and the injectable product is labeled for pediatric use. The doses for children 13 and over are the same as for adults.

2. The indication for this product is — Although the rates are reported to be increasing, opiate addiction in teenagers remains relatively rare. Opiate maintenance treatment of children under age 16 has been prohibited under the methadone treatment regulations, and treatment of patients between 16 and 18 has been permitted only under limited circumstances; therefore maintenance treatment in adolescents is not a common part of clinical practice. Given what is known about the drug substance, based on experience with the injectable formulation, it is reasonable to expect that those few patients between the ages of 16 and 18 who require maintenance therapy can be treated with the doses used in adults.

3. Should the epidemiology of this disorder change so that extensive use in patients under age 16 becomes more common, pediatric studies may be indicated in the future. —

APPEARS THIS WAY
ON ORIGINAL

/s/

Celia Winchell
1/22/01 03:05:33 PM
MEDICAL OFFICER

Cynthia McCormick
1/24/01 10:20:28 AM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**



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 (301) 827-7410

**ADDENDUM TO REVIEW AND EVALUATION OF CLINICAL AND
STATISTICAL DATA**

NDA #: 20-733
Supplement #: Response to Approvable
Sponsor: Reckitt & Colman Pharmaceuticals
Generic Name: Buprenorphine HCl/Naloxone Sublingual
Tablets
Proprietary Name: Suboxone (TBD)
Pharmacologic Class: Opioid
Proposed Indication: Treatment of Opioid Dependence
Submission Date: 7/28/00
Dosage forms: Buprenorphine 2 mg/Naloxone 0.5 mg
sublingual tablet;
Buprenorphine 8 mg/Naloxone 2 mg
sublingual tablet
Route: Sublingual
Clinical Reviewer: Celia Jaffe Winchell, M.D.
Date: 1/22/01

Financial Disclosure:

The sponsor submitted financial disclosure information for studies cited in the NDA. The studies were primarily sponsored by NIDA, but Reckitt & Colman, Schering-Plough, and various other entities provided financial support for some studies.

Form FDA 3454 was submitted for 42 studies cited in the NDA, including the three studies deemed pivotal to the demonstration of safety and efficacy of buprenorphine for treatment of opiate addiction.

/s/

Celia Winchell
1/22/01 03:15:09 PM
MEDICAL OFFICER

Cynthia McCormick
1/24/01 10:22:48 AM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**



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)827-7410

Division Director Review of NDA and Basis for Action

Drug: Buprenorphine HCl/Naloxone, Sublingual Tablets
Sponsor: Reckitt & Colman Pharmaceuticals, Inc.
NDA: #20-733
Review Cycle: 2, Response to approvable action
Received: July 28, 2000
Indication: Treatment of —

This review summarizes the basis for the action to be taken on the New Drug Application for Suboxone, buprenorphine and naloxone sublingual tablet, for the treatment of opiate dependence. The previous review (memorandum) dated December 7, 1999 summarized the basis for the findings of safety and efficacy for this application, but delineated a number of significant deficiencies which were to have been corrected before the application could be approved. These deficiencies were explained in the approvable letter of December 7, 1999. This application represents a response to that letter and each of these deficiencies will be discussed. The previous findings that were not in dispute will not be reviewed at this time. Additional related problems identified during this review cycle will also be noted.

Chemistry, Manufacturing, and Controls

The stability of naloxone in Suboxone was a significant issue that arose during the review of this NDA. During the previous review cycle it was learned that the product was unable to meet the naloxone content specifications at room temperature storage of 25 C/60%RH beyond —. The approvable letter stated that

The stability data are not sufficient to assess a reasonable expiry date for the product. Information on any new packaging material should be provided. Provide information demonstrating compliance with USP standards, including — e data. Submit a written stability protocol prior to conducting the stability studies that includes, but is not limited to, the following items

- a. _____ lots of the packaged product based on accelerated _____ and
long-term stability testing per ICH Q1A&B guidance conditions
- b. _____ testing time stations; i.e., _____ for accelerated and _____

Provide the first 3 months of data at time of resubmission and the additional data as they become available.

The sponsor has responded by submitting data for the NDA stability batches, which failed under ICH conditions. The sponsor writes "ICH storage conditions are not ideal for Suboxone, since the proposed pack is _____

_____ . Results from the first ICH study of _____ batches of 2 mg and _____ batches of 8 mg Suboxone tablets were presented to the Division in an Amendment dated October 5, 1999. This study was terminated after _____." The sponsor also stated, however, that additional studies conducted showed that _____ did not help the stability of naloxone. Two additional developments are in progress, however there is insufficient information in the NDA to review these.

_____ The determination of approvability must be made on the data that are present in this NDA, not those that are anticipated. Therefore the data provided for the NDA stability batches using the initially proposed formulation do not support even a _____ shelf life. There is a _____

_____ The individual dissolution data have not been provided. It has been noted that the use of _____ rpm for dissolution testing rather than the recommended _____ rpm may in addition be delivering a falsely optimistic result. Due to the trends on stability, the more discriminating method should have been employed.

The stability problems with this formulation must be satisfactorily resolved before this drug is placed on the market.

The degradation of naloxone in this formulation had previously raised two additional specific concerns. The first was the potential for toxicity of the breakdown products when taken under conditions directed. The degradation products of naloxone had not been identified and the toxicity of these degradation products has not been determined. Identification of all degradation products occurring at or above _____ of the active ingredient, naloxone, should have been provided. The degradation products should have been qualified with respect to safety in accordance with the ICH Q3 A and Q3B guidance. The approvable letter stated

The identity and toxicity of the degradation products have not been determined. Provide identification of all degradation products occurring at or above _____ of the active ingredient, naloxone. You must follow ICH Q3B guidance for qualification of degradation products.

In response, the sponsor provided some data on the identity of naloxone degradation products, but a complete impurity profile was not provided. Of those that were identified, _____ occurred in clinical batches in quantities that exceeded the _____ threshold for individual impurities requiring safety qualification. Furthermore, the preclinical testing submitted to this NDA did not expose animals to these breakdown products, since the relevant formulation was not used in those studies. These impurities have, therefore, not been safety qualified as required. The sponsor has indicated that nonclinical studies are underway, but that the histopathology has not yet been completed. These data have not been submitted. This deficiency has not been corrected.

The sponsor was further required to

(2) Develop and validate analytical methods and specifications to provide a full accounting for all degradation products of naloxone. Additionally provide linkage between the analytical methods used by the _____ for generating the data at _____ and the regulatory methods that are suitable for detecting and quantifying the degradation products of naloxone. Without confirmation of this determination, the _____ stability data may not be considered to support the expiration dating of the product.

Dr. Al-Hakim has reviewed these materials and has found them unsatisfactory. These materials were not stored under ICH conditions. The shelf life of the product must be based on stability data generated using the ICH guidelines.

A second and greater concern with the _____ is that the product may not be an adequate deterrent for abuse as purported. This has important implications for the justification for including naloxone. The stability of naloxone in this product is critical to its approval under 21CFR300.50(a)(2) (See Abuse Liability in Fixed Combination Prescription Drug Regulation). It was reasoned that if the presence and stability of naloxone could not be assured, there would be no basis for approving this product. The approvable letter stated:

(5) The stability of naloxone in this product is critical to its approval under 21CFR300.50(a)(2), in which it is stated that 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 is such that the combination is safe and effective. It is permissible that a component is added to minimize the potential for abuse of the principal active component. Therefore in order to

satisfy the requirements of the combination policy, the naloxone component of Suboxone must be shown to minimize the abuse potential of the buprenorphine component. If the presence and stability of naloxone cannot be assured, there is no basis for approving the product with the addition of naloxone. In order to evaluate the integrity of the unpackaged product under conditions of intentional degradation, additional testing is required. The tablets should be stressed under forced degradation conditions for sufficient time to predict extent of degradation under abuse conditions.

In response, the sponsor provided stability testing under stressed conditions. Under the conditions tested, _____ here was no selective degradation. Testing from two independent FDA laboratories, however, was able to demonstrate nearly 100% extraction of buprenorphine from Suboxone using readily available methods and inexpensive equipment. This information will be considered in the overall plan to increase the schedule of buprenorphine under the CSA.

The product packaging finally also did not provide adequate _____
_____ did not comply with the child resistance provisions of the Poison Prevention Packaging Act as an oral dosage form of a controlled substance. The approvable letter stated

*(3) Provide packaging that affords adequate protection from _____
and is compliance with 16CFR 1700.14(a)(4) for controlled drugs.*

In response, the sponsor did provide child resistant packaging, but it was learned that the _____ could not be readily opened _____ Additional testing is underway but the results have not yet been submitted to the FDA. As the package stands, however, the current solution to child resistant packaging is unsatisfactory in that the integrity of the dosage form, and therefore, likely, its bioavailability and its efficacy, cannot be ensured.

Control of buprenorphine under the CSA (Controlled Substances Act)

An Eight-Factor Analysis was conducted and a recommendation for a higher schedule for buprenorphine and buprenorphine with naloxone was developed based on new data on comparative binding at the opiate receptors, information about the product's ability to cause physical dependence, including reports of neonatal withdrawal syndrome, and reports of actual abuse worldwide using the sublingual formulations by intranasal, sublingual and intravenous routes. The stability of naloxone continues to be an issue in the scheduling of Suboxone, as it may prove less of a deterrent to abuse than was anticipated.

**APPEARS THIS WAY
ON ORIGINAL**

Pharmacokinetics

Pharmacokinetic studies to determine the appropriate method of delivering doses of more than two tablets still have not been submitted. These have been requested throughout the review cycles for Subutex and Suboxone by telecon and discussions with the sponsor. Studies were formally requested in the text of the Subutex NDA approvable letter and was implied in the labeling which was to have been adopted with the Suboxone AE letter also. Clearly, instructions for use cannot be written without these data, which should ultimately provide the regimen for dosing and the corresponding pharmacokinetic profile for multiple tablet delivery. This continues to remain a deficiency plaguing both applications. This will be requested again.

Treatment under the Drug Addiction Treatment Act of 2000

The Drug Addiction Treatment Act of 2000 was passed during the review of buprenorphine and amends the Controlled Substances Act (CSA) to provide a system for physicians to prescribe drugs in schedules III, IV, and V in the setting of a doctor's office rather than dispensed in a specialized clinic setting. As a new addiction medication about to be approved in a new health care system for delivery ample care should be taken to minimize the risks anticipated with this new treatment, based on European experience. Discussions have been initiated with the sponsor who will be expected to develop a risk management program to assess the success of this new treatment. The sponsor will be asked to develop a plan for postmarketing surveillance to assess the extent abuse and diversion, the effectiveness of naloxone as a deterrent to intravenous abuse, and the extent of abuse by other routes, particularly as it relates to the appropriate control of this drug substance.

Action: Approvable pending satisfactory resolution of the stability issues, appropriate revisions in the package insert in accordance with previous recommendations, and development of a satisfactory program of Risk Management and Postmarketing Surveillance in conjunction with the appropriate government agencies.

151

January 24, 2001

Cynthia G. McCormick, MD,
Director,
Division of Anesthetics, Critical Care, and
Addiction Drug Products

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Cynthia McCormick
1/24/01 11:29:35 AM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**

Electronic Mail Message

Date: 1/17/01 2:11:53 PM
From: Bona, James (JBona@OC.FDA.GOV)
To: Shepherd, Sara (Shepherds@A1)
Subject: Re: ORPHAN DRUG QUESTION

Sara:

Sorry I took so long to answer but I wanted to be certain of our position.

Orphan designation for a single product does NOT cover a combination of the designated product and one or more other active ingredients. A separate designation application would have to be submitted and approved for the combination.

However, in this case, buprenorphine was designated on 6/15/94 (application _____ and the combination w/naloxone designated on 10/27/94 (application _____). So both products appear to be covered by orphan designations. However, the firm should have provided a copy of the combination's designation before the User Fees were waived.

You should ask to have that submitted for completion sake. Hope this helps.

!! Cathie I said hi!

Jim

-----Original Message-----

From: Sara Shepherd FAX t- [SMTP:SHEPHERDS@cder.fda.gov]
Sent: Tuesday, January 16, 2001 11:36 AM
To: JBONA@OC.FDA.GOV
Subject: ORPHAN DRUG QUESTION
Sensitivity: Confidential

Cathie Schumaker suggested I talk to you about the orphan drug status of Subutex (buprenorphine HCl, NDA 20-732) and Suboxone (buprenorphine/naloxone, NDA 20-733). The letter we have on file (dated June 15, 1994) stated that "it is buprenorphine and not its formulation that has received orphan designation". The company submitted this letter to both NDAs (listed above). Does this orphan drug status cover the buprenorphine/naloxone product?? Both NDAs have gone thru several review cycles and the next PDUFA date is Jan 26, 2001. Thanks

Sara Shepherd
Project Manager
Division of Anesthetic, Critical Care and Addiction Drug Products.
827-7430



**DEPARTMENT OF HEALTH & HUMAN
SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-732
NDA 20-733

Reckitt & Colman Pharmaceuticals, Inc.
1909 Huguenot Road
Richmond, VA 23235

Attention: Alan Young
Director, Regulatory Affairs

Dear Mr. Young:

Please refer to the teleconference between representatives of your firm and the FDA on December 14, 2000. The purpose of the telecon was to discuss the development of a risk management plan, and chemistry issues for Subutex and Suboxone.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

If you have any questions, contact Sara Shepherd, Project Manager, at (301) 827-7430.

Sincerely,

A handwritten signature in black ink, appearing to read "S/".

Sara E. Shepherd
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELECON

DATE: December 14, 2000

APPLICATION NUMBER: NDA 20-732, NDA 20-733

DRUGS: Subutex and Suboxone

BETWEEN: Reckitt & Colman (waiting for list)

Name: Charles O'Keeffe, President Reckitt & Colman Pharmaceuticals, Inc
Alan Young, Director, Regulatory Affairs
Chris Chapleo, Director, Buprenorphine Business Group
Don Walter, Buprenorphine Development Manager
Sharon James, Director R&D for Buprenorphine
Paul Field, Formulation Development Manager
Neil Hyde, Buprenorphine Project Manager
Tim Baxter, Medical Director

AND

Name: Division of Anesthetic, Critical Care, and Addiction Drug Products
Cynthia McCormick, M.D., Director
Celia Winchell, M.D., Medical Team Leader
Ali Al-Hakim, Ph.D., Chemistry Reviewer
Sara E. Shepherd, Project Manager
Controlled Substance Staff
Corrine Moody, Project Manager,
Michael Klein, Ph.D., Senior Interdisciplinary Scientist,
Deborah Leiderman, M.D., Director

SUBJECT: To discuss chemistry issues and the development of a risk management plan

Chemistry

1. The Division is still reviewing the chemistry issues for Subutex and Suboxone and has the following concerns:
 - a. The instability of Suboxone under ICH guidelines.
 - b. The limited shelf-life (12 months or less) based on submitted data
 - c. The new manufacturing method may require an additional PK study for Suboxone
 - d. The new manufacturing method may impact the specifications for Suboxone

Reckitt & Colman stated that the new manufacturing method should not be evaluated during this review cycle. The Division agreed that only the previous manufacturing process and data, submitted on July 28, 2000, would be reviewed.

2. There will be no action letter issued in December because the Division needs the full 6 months to review the submission.

Reckitt & Colman stated that approval of Subutex alone would not be beneficial without approval of Suboxone. However due to the unresolved chemistry issues, the Division stated that another cycle may be needed. In the meantime, the company should begin to consider the development of a risk management plan.

Risk Assessment Plan

1. The Division informed Reckitt & Colman of the need to develop a risk management and surveillance plan. Examples of items to be addressed in the plan include:
 - a. Analyze the path from the pharmacy to the patient, in detail.
 - b. Examine the possibility of diversion (at home and at the pharmacy).
 - c. Propose a plan to monitor risks and develop a surveillance plan.
 - d. Examine the development of _____
 - e. Consider voluntary restriction of take-home medication for new stable patients.
 - f. Develop an _____
 - g. Develop educational material to be distributed to patients, doctors, pharmacies.
 - h. Develop plan to monitor signals for off-label use.
 - i. Develop 1-800 number for diversion.
 - j. Develop Dear Pharmacy/Healthcare letter.
 - k. Develop plan for physician/pharmacist interaction.
 - l. Monitor existing databases (provide periodic update to Division).

Action: Reckitt & Colman have started a risk assessment plan and will send a proposal to the Division prior to January 28, 2001 (action date) for review/comments. A face-to-face meeting may also be beneficial to discuss the overall proposal.

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Sara Shepherd
12/28/00 01:27:45 PM

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELECON

DATE: December 1, 2000

APPLICATION NUMBER: NDA 20-732, Subutex (buprenorphine)
NDA 20-733 Suboxone (buprenorphine/naloxone)

BETWEEN:

Name: John Spencer, Ph.D., Chemist, St. Louis
Jim Brower, Ph.D., Chemist, St. Louis
Mike Gurbarg, Ph.D., Chemist, Philadelphia
Representing: FDA field labs

AND

Name: Cynthia McCormick, M.D., Director HFD-170
Celia Winchell, M.D., Medical Team Leader
Dale Koble, Ph.D., Chemistry Team Leader
Ali Al-Hakim., Ph.D., Chemistry Reviewer
Sara E. Shepherd, Project Manager
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

SUBJECT: Discuss results of lab experiments to separate buprenorphine and naloxone.

Mike Gurbarg, (Philadelphia)

The _____ the buprenorphine from the naloxone. Only two tablets were initially used with the possibility of _____ with this method. The material eluted with _____ the separation was good and it was very simple method to use. The eluted burprenorphine was approximately _____ pure.

_____ lid not separate the burprenorphine frm naloxone.

John (Jack) Spencer, (St. Louis)

A _____ was used for the separation of the two materials. This reusable _____ would be readily available and inexpensive to purchase from a standard scientific supplier. Clean separation was obtained _____ No other extractions were done by the St. Louis lab.

Actions

Dale Koble will send a list of questions to the field labs to assist the labs in compiling their final report for the Division. The final reports will be available by January, 2001.

Sara Shepherd will check on how the labs (Philadelphia) should report their time for this project.

|
S

Sara E. Shepherd
Project Manager

/s/

Sara Shepherd
12/11/00 01:12:07 PM
CSO

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ON ORIGINAL**



**DEPARTMENT OF HEALTH & HUMAN
SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-732
NDA 20-733

Reckitt & Colman Pharmaceuticals, Inc.
1909 Huguenot Road
Richmond, VA 23235

Attention: Alan Young
Director, Regulatory Affairs

Dear Mr. Young:

Please refer to the teleconference between representatives of your firm and the FDA on November 14, 2000. The purpose of the telecon was to discuss stability issues and child resistant packaging for Subutex and Suboxone.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

If you have any questions, contact Sara Shepherd, Project Manager, at (301) 827-7430.

Sincerely,

A handwritten signature in black ink, appearing to be "S" with a flourish, written over a horizontal line.

Sara E. Shepherd
Regulatory Project Manager
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELECON

DATE: November 14, 2000

APPLICATION NUMBER: NDA 20-732, NDA 20-733

DRUGS: Subutex and Suboxone

BETWEEN: Reckitt & Colman

Name: Charles O'Keeffe - President Reckitt & Colman Pharmaceuticals, Inc
Chris Chapleo, Ph.D. - Director, Buprenorphine Business
Don Walter, Ph.D. - Global Development Manager
Neil Hyde, Ph.D. - Buprenorphine Project Manager
Sharon James, Ph.D. - R&D Category Director, Buprenorphine
Paul Field, Ph.D. - R&D Manager, Buprenorphine
Alf Davis - Senior Chemist, Buprenorphine

AND

Name: Division of Anesthetic, Critical Care, and Addiction Drug Products,
Sara E. Shepherd, Project Manager
Cynthia McCormick, M.D., Director
Steve Koepke, Ph.D., Deputy Director, DNDCII
Dale Koble, Ph.D., Chemistry Team Leader
Pat Maturu, Ph.D., Chemistry Reviewer

SUBJECT: Discuss Subutex stability issues and child resistant packaging

1. *Explain the decrease in dissolution at 25°C as noted in the Subutex stability data.*

The Sponsor stated that these data are for product held at 25°C at 80% relative humidity (RH). The product is under stress conditions. There are additional storage data for — batches at 25°C /ambient humidity, 25°C /80% RH, 30°C /ambient humidity, 35°C /ambient humidity, 35°C /75% RH, and 40°C /ambient humidity. The — report was submitted to the application and a 3-year report is also available.

The Division requested that the Sponsor fax the — report and provide the location (citation) for the data from the — report.

The Division noted that the shelf-life of the product will have to be estimated for ICH conditions based on the available non-ICH data submitted with the application. The decreases observed for dissolution on stability are of concern. The post-approval stability protocol will be according to ICH conditions.

The Sponsor indicated that _____ tablets consist of a _____

2. *Explain the design of the child-resistant Subutex packaging.*

3. *Provide additional information on the components of the Subutex and Suboxone packaging.*

The Sponsor agreed to provide a summary of the components of the packaging including the DMFs (submission date to the DMF, DMF page number, item number, etc.) and which components were used for the stability studies and child-resistant studies versus those to be used in the to-be-marketed product.

4. *Discuss the change in dimensions from the _____ tablet to the oval Subutex tablet.*

The Sponsor stated that the majority of the studies were done with the oval tablet. The _____ tablet was initially used in a small group prior to the change to the oval configuration. In addition, a comparison was done on the surface area of the _____ versus the oval tablet.

The Division requested a summary of the clinical and biopharmaceutic studies which use the _____ and the oval tablets.

5. *Have studies been done to demonstrate bioavailability using more than one sublingual tablet?*

The Sponsor stated that the 1008 study has PK data pertaining to the use of more than one tablet (suboxone). They used 4, 8, 12, 16, 20 and 24 mg doses and the results showed a linear relationship. It was compared to the solution in the pivotal study.

6. *The specifications for the drug substance assay and for impurities need to be tightened (e.g., see USP monograph for buprenorphine). In addition, provide a specification of no more than — for any individual unspecified drug related impurity.*

The Sponsor stated that their current specifications (although not those currently in the NDA) are tighter than the USP. They will provide the revised specification to the Division.

7. *Provide an update on the dissolution test method used for stability testing of Subutex and summarize any changes.*

The Sponsor agreed to provide the information.

8. *What is the status of the method validation for the Suboxone impurities as discussed in the October 25, 2000, telecon?*

The Sponsor stated that the updated methods validation for drug product impurities will be sent at the end of November.

9. *When will the additional ICH stability data for Suboxone be sent to the Division?*

The Sponsor will send the — stability on the original manufactured material by November 17, 2000.

10. *Is the summary of the hepatotoxicity in patients taking buprenorphine available?*

The Sponsor stated that the report is done and will be sent to the Division by November 17, 2000.

11. *How much stability data have been generated with the new drug product manufacturing process?*

The Sponsor stated that they have — stability data on — batch at each strength under ICH guidelines. The Sponsor did a side-by-side comparison of the stability data from batches manufactured with the original and modified manufacturing process. The Sponsor stated that there is a reduction in the impurities for the batches from the modified manufacturing process. The Sponsor did not think that it was necessary to show bioequivalence since the only difference between the two manufacturing processes was

The Sponsor will submit the comparative stability data at the end of November.

The Division agreed that the Sponsor should submit the data. However the PDUFA goal date is January 28, 2001 and the reviewers may not have enough time to review the comparative data since it will not be submitted until the end of November. The Sponsor requested a meeting with the Division to discuss the new data but it was denied because the Division did not think it would be a productive meeting and would take away crucial review time from the reviewers. The action may have to be taken on the original amendment and the remaining new data handled as a correspondence, to be submitted later to the NDA as a supplement. It should be noted that the available data will dictate the shelf-life of the drug product.

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Sara Shepherd
11/27/00 04:53:24 PM

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ON ORIGINAL**



OCT 30 2000

NDA 20-733

Reckitt & Colman Pharmaceuticals, Inc.
1909 Huguenot Road
Richmond, VA 23235

Attention: Alan Young
Director, Regulatory Affairs

Dear Mr. Young:

Please refer to the teleconference between representatives of your firm and the FDA on October 25, 2000. The purpose of the telecon was to discuss several chemistry issues concerning the July 28, 2000, submission for Suboxone (buprenorphine/naloxone).

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

If you have any questions, contact Sara Shepherd, Project Manager, at (301) 827-7430.

Sincerely,

[/S/]

Sara E. Shepherd
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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ON ORIGINAL

9 Page(s) Withheld



DEPARTMENT OF HEALTH & HUMAN SERVICES

White/Shepherd

Food and Drug Administration
Rockville MD 20857

JUN 2 2000

Paul P. Casadonte, M.D.
New York Veterans Affairs Medical Center
423 E. 23rd Street, Room 17021 W.
New York, New York 10017

Dear Dr. Casadonte:

Between November 17 and 29, 1999, Mr. Thomas Hansen, representing the Food and Drug Administration (FDA), inspected your conduct as the investigator of record of a clinical study (protocol CSP1008) of the investigational drug Suboxone (buprenorphine/naloxone) sublingual tablets, that you conducted for the National Institute of Drug Abuse (NIDA) and the drug was submitted by Reckitt and Colman Pharmaceuticals, Inc for marketing approval. This inspection is part of the FDA's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

At the close of the inspection, Mr. Hansen presented his inspectional observations (i.e., Form FDA 483) and discussed these observations with you. From our evaluation of the inspection report, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note discrepancies in study documentation for subject 1041 in that the case report form documents clinical laboratory results for a blood sample taken on — however, the source lab data did not document a — sample. In addition, we note a protocol violation in that for at least two subjects (#1093 and #1063), the blood sample needed for pharmacokinetic assessment of the investigational drug was not collected prior to the phase II dosing, as required by the protocol.

Please ensure that corrective actions will be taken to prevent similar problems in your current and future studies.

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Page 2 - Dr. Casadonte

We appreciate the cooperation shown Investigator Hansen during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,



/S/

]

David A. Lepay, M.D., Ph.D.

Director

Division of Scientific Investigations

Office of Medical Policy, HFD-45

Center for Drug Evaluation and Research

7520 Standish Place, Suite 103

Rockville, MD 20855

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cc:

HFA-224
HFD-170 Doc. Rm. NDA 20-733
HFD-170 Review Div.Dir. McCormick
HFD-170 MO Chang
HFD-170 PM/CSO Chite
HFD- 45 Reading File
HFD- 46 Chron File
HFD- 46 CIB File 09984
HFD- 46 Malek
HFR- NE150 DIB Woyshner
HFR- NE1500 BIMO MONITOR Hansen
HFR- NE1500 FIELD INVESTIGATOR Hansen

FEI: 3002872485

Field Classification: VAI

Headquarters Classification:

- 1)NAI
- 2)VAI no response required
- 3)VAI-R response requested
- 4)OAI-W warning letter
- 5)OAI NIDPOE letter

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Deficiencies noted:

- inadequate consent form
- inadequate drug accountability
- deviations from protocol
- inadequate and/or inaccurate records
- failure to report ADRs
- other (specify)

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drafted/KM 4/24/2000

reviewed/AEH:5/23/00

f/c:mrb:6/1/00

Note to Review Division and DSI Recommendation:

The field investigator inspected the records for 15 of the 60 subjects enrolled in protocol 1008 at Dr. Casadonte site. The data appear acceptable for use in support of drug claims.



NDA 20-733

MAY 8 2000

Reckitt & Colman Pharmaceuticals, Inc.
1901 Huguenot Road
Richmond, Virginia 23235

Attention: Alan N. Young
Director, Regulatory Affairs

Dear Mr. Young:

Please refer to your June 3, 1999, new drug application for Suboxone (buprenorphine HCl/naloxone) Sublingual Tablets, 0.5 mg/2 mg, 2mg/8mg).

We also refer to your February 29, 2000, submission providing a draft protocol for your proposed carcinogenicity study of Suboxone in rats. The Executive Carcinogenicity Assessment Committee's recommendations and conclusions have been faxed to you on April 10, 2000.

Our review of the statistics section of your submission generated the following comments.

1. The following comments pertain to adjustment of tumor rates for intercurrent mortality.

Intercurrent mortality refers to all deaths unrelated to a tumor being analyzed for evidence of carcinogenicity. Like human beings, older rodents have a many-fold higher probability of developing or dying of tumors than those of younger age. Therefore, in the analysis of tumor data, it is essential to identify and adjust for possible differences in intercurrent mortality (or longevity) among treatment groups to eliminate or reduce biases caused by these differences.

Before analyzing the tumor data, the intercurrent mortality data should be routinely tested first to see if the survival distributions of the treatment groups are different. It is recommended by Peto, et al. (1980) that, whether or not survival among treatment groups is significantly different, tumor rates should routinely be adjusted for survival when presenting experimental results. The Cox test (Cox, 1972; Thomas, Breslow, and Gart, 1977); the generalized Wilcoxon or Kruskal-Wallis test (Breslow, 1970; Gehan, 1965; Thomas, Breslow, and Gart, 1977); and the Tarone trend tests (Tarone, 1975) are routinely used to test for heterogeneity in survival distributions and significant dose-response relationships (trends) in survival.

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2. The following comments pertain to statistical analysis of tumor data with information about cause of death, tumor lethality, but without multiple sacrifices.

One way to choose appropriate survival-adjusted methods in the analysis of tumor data is to base on the role that a tumor plays in causing the animal's death. Tumors can be classified as "incidental," "fatal," and "mortality-independent (or observable)" according to the contexts of observation described in Peto, et al. (1980). Tumors that are not directly or indirectly responsible for the animal's death, but are merely observed at the autopsy of the animal after it has died of an unrelated cause, are said to have been observed in an incidental context. Tumors that kill the animal, either directly or indirectly, are observed in a fatal context. Tumors, such as skin tumors, whose detection occurs at times other than when the animal dies are said to have been observed in a mortality-independent (or observable) context. To apply a survival-adjusted method correctly based on this piece of information, it is essential that the context of observation of a tumor be determined as accurately and subjectively as possible.

Different statistical techniques have been proposed for analyzing data of tumors which contain the information of contexts of observation (cause of death) of tumors.

The prevalence method described in the paper by Peto, et al. (1980) should be used in testing for positive trends in prevalence rates of incidental tumors. This method focuses on the age-specific tumor prevalence rates to correct for intercurrent mortality differences among treatment groups in the test for positive trends or differences in incidental tumors.

It is recommended that the death-rate method described in Peto, et al. (1980) be routinely used to test for the positive trend or difference in incidence of tumors observed in a fatal context.

When a tumor is observed in a fatal context for some animals and is also observed in an incidental context for other animals in the experiment, data for the incidental and fatal tumors should be analyzed separately by the prevalence and the death-rate methods. Results from the different methods can then be combined to yield an overall result. The combined overall result can be obtained simply by adding together either the separate observed frequencies, the expected frequencies, and the variances, or the separate T statistics and their variances.

Tumors observed in a mortality-independent context, such as skin tumors and mammary gland tumors, which are visible and/or can be detected by palpation in living animals, are routinely analyzed using the onset-rate method. The onset-rate method for mortality-independent tumors and the death-rate method for fatal tumors are essentially the same in principle except that the endpoint in the onset-rate method is the occurrence of such a

tumor (e.g., skin tumor reaching some prespecified size) rather than the time or cause of the animal's death.

The above methods are based on normal approximation in the calculation of p-values. It is well known that the approximation results may not be stable and reliable, and tend to underestimate the exact p-values when the total numbers of tumor occurrence across treatment groups are small. In this situation, the exact permutation trend test (Lin, 1994) should be used to test for the positive trend (Gart, 1986). The exact permutation trend test is a generalization of the Fisher's exact test to a sequence of $2 \times (r+1)$ tables.

There are issues in the determination of the three contexts of observation of tumors, especially the first two contexts of most occult tumors. Some people argue that the determination whether a tumor causes an animal's death is a rather complicated and subjective process. Very often it is difficult for a pathologist to classify accurately and objectively a tumor type as to whether it has unequivocally caused or not caused the animal's death. In practice, there is a continuum between these two extremes. That is, many tumors contribute ultimately to an animal's death, but are not instantly (or even rapidly lethal). Such tumors technically are neither 'incidental' or 'fatal' and it is not clear how such tumors should be regarded. Also even if the information of contexts of observation is reliable and available, it will be overly simplistic to assume that all tumors of a given type are 100% fatal or 100% incidental. It is likely that the tumor type is a mixture of incidental and fatal tumors, that is, it is fatal to some but non-fatal to the other animals.

Alternative survival-adjusted statistical procedures such as the poly-k tests (Bailer and Portier, 1988) and the ratio trend test (Bieler and Williams, 1993) which do not need such information have been developed and used for tumor data analysis because of the complexity and subjectivity in the pathologist's determination of the cause of death of a tumor. The alternative procedures should be used to replace the procedures proposed in Peto, et al. (1980) in the analysis of tumor data in situations in which there is no such information available or such information although available is considered as not accurate enough.

References:

Bailer A. Portier C: "Effects of Treatment-Induced Mortality on Tests for Carcinogenicity in Small Samples," Biometrics, 44, 417-431, 1988.

Bieler GS. Williams RL: "Ratio Estimates, the Delta Method, and Quantal Response Tests for Increased Carcinogenicity," Biometrics, 49, 793-801, 1993.

Breslow N: "A Generalized Kruskal-Wallis Test for Comparing K Samples Subject to Unequal Patterns of Censorship," Biometrics, 57, 579-594, 1970.

Cox DR: "Regression Models and Life Tables (with discussion)," Journal of Royal Statistical Society, Series B, 34, 187-220, 1972.

Gart JJ, Krewski D, Lee PN, Tarone RE, Wahrendorf J: Statistical Methods in Cancer Research, Volume III – The Design and Analysis of Long-Term Animal Experiments, International Agency for Research on Cancer, World Health Organization, 1986.

Gehan EA: "A Generalized Wilcoxon Test for Comparing K Samples Subject to Unequal Patterns of Censorship," Biometrika, 52, 203-223, 1965.

Lin KK, Ali MW: "Statistical Review and Evaluation of Animal Tumorigenicity Studies," In: Statistics in the Pharmaceutical Industry, Second Edition, Revised and Expanded, edited by CR Buncher and JY Tsay, ed., Marcel Dekker, Inc., New York, 19-57, 1994.

Peto R, Pike MC, Day NE, Gray RG, Lee PN, Parish S, Peto J, Richards S, Wahrendorf J (1980), "Guidelines for Simple, Sensitive Tests for Carcinogenic Effects in Long-term Animal Experiments," In Long-term and Short-term Screening Assays for Carcinogens: A Critical Appraisal, World Health Organization.

Tarone RE: "Tests for Trend in Life Table Analysis," Biometrika, 62, 679-682, 1975.

Thomas DG, Breslow N, Gart JJ: "Trend and Homogeneity Analyses of Proportions And Life Table Data," Computer and Biomedical Research, 10, 373-381, 1977.

If you have any questions, call Sara Shepherd, Regulatory Project Manger, at 301-827-7410.

Sincerely,

[/S/]

Cynthia G. McCormick, M.D.

Director

Division of Anesthetic, Critical Care,
and Addiction Drug Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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NDA 20-733

Page 5

cc:

Archival NDA 20-733

HFD-170/Div. Files

HFD-170/SS/C.Schumaker

HFD-170/K.Lin/L.Jean

DISTRICT OFFICE

LS
5/8/20

Drafted by:SS/April 27, 2000

Initialed by:C.Schumaker/May 2, 2000

L.Jean/May 2,2000

final:SS/May 3, 2000

General Correspondence Letter

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END=APR-10 15:56

FILE NO. =436

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-CDER/FDA/PHARM/TOX -

***** -CDER/FDA/PHARM/ - ***** 301 594 5147- *****

C O V E R

FAX

S H E E T

To: Dr. Alan Young
Reckitt & Coleman Pharm

Fax #: 804/379-1215

Subject: Meeting Minutes re: NDA 20,733

Date: April 10, 2000

Pages: 3, including this cover sheet.

COMMENTS:

I am faxing you minutes of the meeting of the FDA Center for Drug Evaluation and Research, Executive Carcinogenesis Assessment Committee. Further correspondence will come from the review division.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, this communication is not authorized. If you have received this document in error, please immediately notify us by telephone. Thank you.

Comis decision code = LS (letter sent)

From the desk of...
Adele E. Seffried, M.S.
Science Policy Analyst
Pharmacology/Toxicology Staff, HFD-24
1451 Rockville Pike, Woodmont II, Suite 6008
Rockville, MD 20852
301-594-5482
Fax: 301-594-5147

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Executive CAC
March 28, 2000

Committee: Joseph F. Contrera, Ph.D., HFD-901, Acting Chair
Nakissa Sadrieh, Ph.D., HFD-160, Alternate Member
Glenna Fitzgerald, Ph.D., HFD-120, Alternate Member
Lucy Jean, Ph.D., HFD-170, Team Leader
Anwar Goheer, Ph.D., HFD-170, Presenting Reviewer

Author of Draft: Anwar Goheer

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA # 20-733
Drug Name: Suboxone (buprenorphine HCl and naloxone HCl dihydrate
at a 4:1 buprenorphine : naloxone ratio as bases)
Sponsor: Reckitt & Colman Pharmaceuticals, Inc., Richmond, VA 23235.
Telephone (804) 379-1090, Fax (804) 379-1215.

Background:

Suboxone, sublingual tablets, is indicated for the treatment of opioid dependence. Naloxone is added to prevent abuse and diversion of the drug product.

Carcinogenicity of buprenorphine hydrochloride has been studied in Sprague-Dawley rats at dietary doses of 0.6, 5.6 and 56 mg/kg/day for 27 months. There was a statistically significant increase in testicular interstitial (Leydig's) cell tumors based on the trend test adjusted for survival. Pair-wise comparison of the high dose against the control failed to show statistical significance. In an 86-week study in CD-1 mice, buprenorphine hydrochloride showed no evidence of tumorigenicity at dietary doses of up to 100 mg/kg/day. Carcinogenicity data on naloxone and Suboxone are not available. Suboxone is not mutagenic in Ames, human lymphocyte and rat micronucleus assays.

A 13-week dose range finding toxicity study to support a future 2-year carcinogenicity study was carried out in male and female rats. Animals received suboxone in the diet at concentrations of 0 (control), 100, 500, 1500 or 2000 ppm (approximately 10, 50, 150 or 200 mg/kg/day). Satellite groups were fed appropriate diet for 13 consecutive weeks for toxicokinetics.

The study showed that males were more susceptible to effects on weight and appetite than females. The body weight gains in males were 13 % (100 ppm), 18 % (500 ppm), 22 % (1500 ppm) and 20 % (2000 ppm) lower than the control group. These decreases in body weight gain were accompanied by the reduction of food consumption. In females, there was no effect on body weight gain or food consumption. No mortality in either sex was observed.

The MTD could not be used because there was no target organ toxicity, no effects on body weight gain or food consumption in females, the decreases of body weight gain in

males were related to the decrease of food consumption, and there were no drug-related clinical signs that can limit the dosing.

The AUC values of buprenorphine in female and male rats at 2000 ppm of Suboxone (1424 & 1580 hr.ng/ml, respectively) are approximately 43-fold higher than the human AUC (34.89 hr.ng/mL) following single administration of 16 mg of Suboxone, a recommended human daily dose. The human AUC of naloxone from Suboxone is not available due to low oral bioavailability, consistent with the intent for naloxone not to contribute any activity following sublingual use, yet prevent illicit parenteral use of Suboxone. In rats, the mean plasma concentrations of naloxone at 2000 ppm are approximately 10-fold higher than the maximum concentration of naloxone detected in humans

Executive CAC Recommendations and Conclusions:

- (1) The Committee concurred with the sponsor's proposed doses (100, 450 and 1800 ppm i.e. approximately 5, 22.5 and 90 mg/kg/day) for the two-year carcinogenicity study in rats based on AUC values of buprenorphine in female and male rats at 2000 ppm of Suboxone (1424 & 1580 hr.ng/ml, respectively) that are approximately 43-fold higher than the human AUC (34.89 hr.ng/mL) following single administration of 16 mg of Suboxone, a recommended human daily dose.
- (2) If the sponsor plans histological evaluation of tissues from only control and high dose treatment groups, they will also need to conduct histopathologic examination of other dose groups under any of the following circumstances:
 - (a) For any macroscopic findings in the low and mid dose groups for a given tissue, they will need to look at that tissue for all of the dose groups.
 - (b) For an increase in the incidence of tumors (rare or common) in the high dose group for a tissue, even if not statistically significant, they will also need to look at the next lower dose group.
 - (c) For an increase in tumors in an organ for a tumor type that should be analyzed across tissue sites as well as by tissue site (e.g., hemangiosarcoma, lymphoma etc.; see McConnell et al, JNCI 76:283, 1986) they should look at all relevant tissues for that dose level and the next lower dose level.
 - (d) For an excessive decrease in body weight or survival in the examined dose group, they should examine lower dose groups.
- (3) The division recommends that animals be housed individually to manage the adverse effects of aggression (fighting behavior) seen in the 28-day palatability study and 90-day dietary toxicity study.

[/S/]

Joseph F. Contrera, Ph.D.
Acting Chair, Executive CAC

cc: \

/Division File, HFD-170
/Lucy Jean, HFD-170
/Anwar Goheer, HFD-170
/ASeifried, HFD-024

**APPEARS THIS WAY
ON ORIGINAL**

**Carcinogenicity Assessment Committee (CAC/CAC-EC) Cover Sheet
Review of Carcinogenicity Study Design/Dose Selection Proposals**

Application (IND/NDA) number: NDA 20-733
Division: DACCADP HFD-170
Drug Name: Suboxone [buprenorphine HCl and naloxone HCl dihydrate
at a 4:1 buprenorphine : naloxone base]
Pharmacological Classification: Buprenorphine: Opioid analgesic
Naloxone: Opioid antagonist
Indication: For the treatment of opioid dependence
Sponsor: Reckitt & Colman Pharmaceuticals, Inc., Richmond, VA 23235.
Telephone (804) 379-1090, Fax (804) 379-1215.
Submission Date: Feb. 29, 2000
Stamp Date: March 1, 2000
45-day date (from submission stamp date): April 14, 2000
P/T Reviewer: Anwar Goheer
Date Review Completed: March 20, 2000
Date of CAC review: March 28, 2000
CAC members: Joe DeGeorge, Ph.D., Joe Contrera, Ph.D., Nakissa Sadrieh, Ph.D.

Summary of Proposal for Review:

Species/strain: Rat/Alpk:AP,SD (Wistar derived)
Source: _____

Number /sex /dose: 52 for main study and 18 for toxicokinetics.
Route: Oral, in diet

	male	female
Doses Proposed:	100, 450, 1800 ppm ~5, 22.5 and 90 mg/kg/day	100, 450, 1800 ppm ~5, 22.5 and 90 mg/kg/day

Basis of dose selection:		
MTD	__x__	__x__
AUC ratio	__x (buprenorphine)	x (buprenorphine)
Saturation	_____	_____
MFD	_____	_____
PD	_____	_____
Other	_____	_____

Kinetics submitted:	rodent	human
pharmacokinetics	__x__	_____
metabolism	_____	_____
protein binding	_____	_____

Notable design feature: 2 control groups planned

Summary of Recommendations to CAC

	male	female
Doses recommended	100, 450, 1800 ppm ~5, 22.5 and 90 mg/kg/day	100, 450, 1800 ppm ~5, 22.5 and 90 mg/kg/day

Basis for recommendation (details): The 13 week Suboxone dietary toxicity study was conducted in rats at 0, 100, 500, 1500, and 2000 ppm [~0, 10, 50, 150 and 200

mg/kg/day]. The study showed that males were more susceptible than females. The body weight gains in males were 13 % [100 ppm], 18 % [500 ppm], 22 % [1500 ppm] and 20 % [2000 ppm] lower than the control group. There was no effect on body weight gain in females. No mortality was observed.

Histopathological examination demonstrated an increased incidence/severity of mononuclear cell infiltration in the Harderian gland in all treated animals except low dose [100 ppm] males, but dose-related effects were seen only in the females. The significance of this finding is not clear. Minimal to moderate epithelial hyperplasia of both prostate gland (3/16 H vs 1/16 C) and seminal vesicles (3/16 H vs 0/16 C) were observed. Minimal to slight degenerative cardiomyopathy in males (3/16 H vs 1/16 C) and slight congestion/hemorrhage of thymus in females (2/16 H vs 0/16 C) were observed.

The AUC_{0-last} values of buprenorphine at 100, 500, 1500 and 2000 ppm of Suboxone were 123, 474, 1238 and 1580 hr.ng/mL in males and 134, 455, 1338 and 1424 hr.ng/mL in females. The AUC_{0-last} values of naloxone at 1500 and 2000 ppm of Suboxone were 51.0 and 53.8 hr.ng/mL in males and 31.7 and 37.8 hr.ng/mL in females. The AUC values of buprenorphine [1424 & 1580 hr.ng/mL] in male and female rats at 2000 ppm of Suboxone are approximately 43 fold higher than the human AUC [34.89 hr.ng/mL] following single administration of 16 mg of Suboxone. The human AUC of naloxone from Suboxone is not available. In humans mean peak naloxone levels ranged from 0.11 to 0.28 ng/ml in the dose range of 1-4 mg. In rats the mean plasma concentrations [ng/ml] of naloxone in 13 week toxicity study were 1.1-3.3 [m/1500 ppm], 0.8-1.8 [f/1500 ppm], 1.8-3.5 [m/2000 ppm] and 1.2-2.3 [f/2000 ppm].

Genotoxicity testing has been conducted with Suboxone. No genotoxicity was observed in the Ames test, the human lymphocytes chromosomal aberration assay and mouse micronucleus assay.

The sponsor proposes 1800 ppm as the highest dose in the carcinogenicity study. This dose is acceptable for male rats based on the effect on body weight gain (20% ↓) and buprenorphine AUC exposure (45 fold ↑). In the females, dose-dependent effects on APTT (15% ↑), mononuclear cell infiltration in Harderian gland [1/16 (control) to 9/16 (HD)], motor activity (22% ↓) and buprenorphine AUC exposure (41 fold ↑) were observed; although no effects on body weight gains and food consumption were observed. It is concluded that a high dose of 1800 ppm is also acceptable for females.

In summary, the dosing of both male and female rats at 100, 450 and 1800 ppm [~5, 22.5 and 90 mg/kg/day] for 2-year carcinogenicity study are acceptable. We recommend that animals be housed individually to manage the adverse effects of aggression seen in the 28-day palatability study and 90-day dietary toxicity study.

CAC Concurrence (y/n)

CAC Recommendations:

Comments:

**APPEARS THIS WAY
ON ORIGINAL**

SUBOXONE; 2 YEAR ONCOGENICITY STUDY IN THE RAT

Animals: 52/sex/group for main study and 18/sex/group for satellite group for toxicokinetics
4-5 weeks old,

Housing: Four animals/cage (main study) & 3 animals/cage (satellite study)

Doses: 100 [low], 450 [intermediate] and 1800 [high] ppm of Suboxone approximately 5, 22.5 and 90 mg/kg/day

Duration of dosing: 2 years by dietary administration.

Analysis of diets: Achieved concentration at all dose levels.
Homogeneity and stability at low and high doses

Clinical observations: Daily

Body weights: Weekly for 15 weeks, week 17 and then every 4 weeks.

Food consumption: Daily for weeks 1-13, weeks 14 & 16 and then every fourth week.

Clinical pathology: Blood samples at 53 & 79 weeks and scheduled termination for differential blood count [main study].

Toxicokinetics: Blood samples from 3 animals/sex/group at 0, 3, 6, 9, 18 and 22 hours after the start of the dark phase at 6 months dosing [satellite group].

Organ weight: 10 animals/sex/group at termination [Adrenal gland, brain, kidney, liver, testis, spleen, epididymis, ovary, uterus, heart]

Histopathology: All tissues from animals that die or are killed during the study, all tissues from control and highest dosed animals, and all macroscopic abnormalities (see page 7).

Data evaluation: SAS (1996) statistics package.

GLP/QA statements: Yes

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN 27 2000

John A. Renner, M.D.
Boston VA Outpatient Clinic
251 Causeway Street
Boston, MA 02114

Dear Dr. Renner:

The purpose of this letter is to inform you of our conclusions concerning your conduct of the clinical study (protocol # 1008A) of Buphenorphine/Naloxone (Suboxone), that you conducted for The National Institute on Drug Abuse.

Between September 8 to September 14, 1999, Ms. Ellen Madigan, representing the Food and Drug Administration (FDA), inspected the study identified above. From our evaluation of the inspection report and copies of study records obtained during the inspection, we conclude that you conducted your study in compliance with the applicable Federal regulations and good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

This inspection is part of the Agency's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

We appreciate the cooperation shown Ms. Madigan during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

[Signature]

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy, HFD-45
Center for Drug Evaluation and Research
7520 Standish Place, Room 103
Rockville, MD 20855

**APPEARS THIS WAY
ON ORIGINAL**

cc:

HFA-224
HFD-170 Doc. Rm. NDA # 20-733
HFD-170 Review Div.Dir. McCormack
HFD-170 MO Li
HFD-170 PM/CSO Chite
HFD-340/Reading File
HFD-344/Chron File
HFD-344/CIB File # 09900
HFD-344/ Malek
HFR-NE252 DIB Kravchuk
HFR-NE250 BIMO MONITOR Kelley
HFR-NE250 FIELD INVESTIGATOR Madigan

CFN: # 1284005

Field Classification: NAI

Headquarters Classification:

1)NAI
 2)VAI no response requested
 3)VAI-R response requested
 4)VAI-RR adequate response received prior to issuance of VAI-R letter
 5)OAI-WL warning letter
 6)OAI-NIDPOE

If the Field and Headquarters classifications are different, explain why:

Deficiencies noted: None

O:\ KM Malek
drafted/ KM 11/10/1999
reviewed/BLB/ 11/18/99
final/NLP/1/24/2000

Note to Review Division and DSI Recommendation:

The field investigator audited the study records for 10 of the 47 subjects enrolled in protocol # 1008A. Eighteen subjects completed phase 1 and were enrolled in phase 2 (16 were selected for the extension). The data appear acceptable for use in support of drug claims.

**APPEARS THIS WAY
ON ORIGINAL**



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)827-7410

MEMORANDUM

To: File NDA #20-733
File NDA #20-732

From: Cynthia McCormick, MD, [/S/]
Director, Division of Anesthetics, Critical Care, and Addiction Drug Products

Date: December 7, 1999

Re: NDA 20-733
Reckitt & Colman Pharmaceuticals, Inc.
Suboxone (Buprenorphine/Naloxone) Sublingual Tablets

cc: John K. Jenkins, MD
Director, Office of Drug Evaluation II

This memo summarizes for the file the basis for the action to be taken on the New Drug Application for Suboxone, buprenorphine and naloxone sublingual tablet, for the treatment of opiate dependence. The principal conclusions of the review team with which I concur are:

- Buprenorphine, the drug substance, is safe and effective for maintenance treatment of opiate addiction.
- Buprenorphine can be delivered, using sublingual tablets, in doses that have been shown to be safe and effective.
- Naloxone, included in this drug product to deter intravenous abuse, does not exert an opiate antagonist effect when the product is used sublingually in the maintenance phase of treatment. Thus, data on buprenorphine without naloxone may be used to support the finding of efficacy of this drug product.
- Naloxone may be expected to reduce the abuse liability of buprenorphine, thus providing the justification for its inclusion in this combination drug product, as required under the combination drug policy (21CFR 300.50)

There are additional factors regarding the safety of Suboxone, the drug product, which must be resolved prior to the issuance of an approval letter, however, and these will be detailed in this memorandum.