

Background

Buprenorphine is a thebaine-derived partial agonist of the opioid (morphine-type) μ -receptor and an antagonist of the opioid (dynorphin-type) κ -receptor initially approved by the FDA (1982) in an injectable formulation, Buprenex, for the treatment of moderate to severe pain.

Since initial approval addiction researchers have explored its utility as a maintenance treatment for opiate addiction. Most of the research on buprenorphine in this clinical context was performed through NIH funding (National Institute on Drug Abuse) through individual research grants. NIDA-MDD opened IND#35,877 for the sublingual solution, and obtained a CRADA (cooperative research and development agreement) with Reckitt & Colman, the commercial sponsor, under which IND# 45,219 for buprenorphine sublingual tablets was filed.

The development of buprenorphine in high doses as a treatment for opiate dependence began with a sublingual ethanolic solution. Indeed most of the clinical research that has been conducted with this drug substance used that formulation. The sublingual ethanolic solution of buprenorphine

— a problem that was not appreciated until late in development. Thus, the sponsor initiated a new development program using a sublingual tablet. Since alcohol increases the bioavailability of buprenorphine, it was soon discovered that the new sublingual tablet was not bioequivalent to the sublingual solution, milligram for milligram. The ensuing development program for the tablet formulation, therefore, focused on three factors (1) establishing a relationship between the tablet and the sublingual solution which, in the absence of bioequivalence, would allow for the treating physician to accurately approximate the dosing regimen shown to be effective and safe in clinical trials using the solution. (2) absent the above relationship, adequate and well controlled studies demonstrating the efficacy of the sublingual buprenorphine tablet in the treatment of opiate addiction and (3) the development of a combination product with naloxone and buprenorphine which would have equivalent efficacy but would, by virtue of the small dose of naloxone present, and the poor sublingual bioavailability, be a deterrent to intravenous abuse, therefore improving its safety profile.

NDA# 20-733 for Suboxone (buprenorphine and naloxone) was submitted on June 7, 1999. The NDA contains a single adequate and well-controlled trial of Suboxone vs placebo (and vs Subutex), two controlled studies of the sublingual buprenorphine solution (without naloxone), and a variety of clinical pharmacology studies, pharmacokinetic studies, and small, generally investigator-initiated studies.

The current NDA is for the — treatment of opiate dependence when added to a comprehensive program of psychiatric counseling and support. Buprenorphine is thought have some hypothetical advantages over existing therapies as a partial agonist, including

a purported protective effect in the setting of overdose, a purported ceiling effect limiting its subjective effects with increasing dose, and a slightly lower abuse potential.

Pharmacokinetics

The studies using the sublingual buprenorphine solution can be linked with pharmacokinetic data to buprenorphine tablets, both buprenorphine alone and buprenorphine with naloxone, to provide corroborative evidence for the safety and efficacy of buprenorphine. While the two different formulations of buprenorphine have different bioavailability, there is sufficient basis to correlate the findings in one series of studies using the more bioavailable solution with higher doses of the less bioavailable tablets.

Dr. Doddapaneni has undertaken an analysis that compares the dose vs. AUC plots for Suboxone and solution formulations. These are found to be reasonably parallel indicating that the relative bioavailability of Suboxone compared to the solution is relatively constant across doses of 4 mg to 16 mg for Suboxone. The relative bioavailabilities for the doses of 4 mg, 8 mg and 16 mg were 0.72, 0.66, and 0.72. This bracketing of doses allowed for the clinical studies of the sublingual solution to be linked to the current NDA for buprenorphine/naloxone tablets. This is discussed in greater detail in the pharmacokinetics review.

While doses of 16 mg were studied and found to be effective (see below) the lower effective dose of 12 mg (equivalent) were studied only in the liquid form. The means for delivering 12 mg by tablet has not been completely worked out—as the tablets only exist as 8 mg and 2 mg. Therefore a 12 mg dose would have to be delivered as 8 mg + 2mg + 2mg. The mechanics and bioavailability of delivering this lower dose have not been studied. This will be requested of the sponsor as a phase 4 commitment.

Efficacy

There are three well-controlled studies adequate to demonstrate the effectiveness of buprenorphine. These are described in detail by Dr. Lee and Dr. Fermutt and summarized by Dr. Winchell in her memorandum and I will discuss them briefly here.

Study 1008 was a placebo-controlled trial in which both the sublingual buprenorphine tablet at a dose of 16mg/day and the buprenorphine: naloxone tablets also at a dose of 16 mg:4 mg/day were compared with each other and with placebo as maintenance therapy for opiate addiction. Endpoints included “clean” urines and retention in therapy. The duration of the study was only one month, and for a chronic disorder such as opiate addiction, this duration is clearly not sufficient to conclude that the product will be effective over time. Nevertheless, this study was strongly positive in support of the efficacy of buprenorphine with naloxone.

Study CR88/130 compared buprenorphine sublingual solution 8 mg² to oral methadone 20mg and 60 mg in a double dummy parallel group trial with a one-week induction phase and a 4 month maintenance phase. Counseling was an integral part of treatment.

² Approximately comparable to 12 mg Suboxone, based on PK linkage studies.

Outcome measures included retention in treatment and clean urines (for nonstudy opiates).

Both methadone 60 mg and buprenorphine 8 mg by sublingual route were shown to be more effective than methadone 20 mg in keeping heroin addicts in treatment and in reducing their opiate use while in treatment.

Study CR92/099 was a 16-week dose ranging trial comparing four doses of buprenorphine sublingual solution in the treatment of opiate addiction in the setting of daily clinic visits and counseling sessions. The study compared doses of 1 mg, 4 mg, 8 mg, and 16 mg following a 1-4 day induction period. Outcome measures again included retention in treatment and clean urines (for nonstudy opiates). As in the previous study, 8 mg and 16 mg buprenorphine were shown to be superior to doses of 4 mg and 1 mg of buprenorphine, providing corroboration of the previous findings.

In part, the basis for accepting the buprenorphine SL solution efficacy data in support of the Suboxone application was the premise that the naloxone in Suboxone was inactive when used as directed. It was known that there were extremely low but detectable levels of naloxone associated with the 8:2 and 16:4 doses of Suboxone. The application had to therefore demonstrate that these low levels did not affect the overall efficacy of the product. The efficacy of both Suboxone and Subutex in study 1008a was established with a placebo control and the success rate, albeit for one month of treatment, was comparable. In addition, the absence of precipitated withdrawal in patients treated with Suboxone or in patients switching from Subutex to Suboxone (following induction) is the most compelling evidence in support of this premise.

The findings of these three clinical trials provide evidence that buprenorphine at doses of 12 mg (based on 8 mg sublingual solution) and 16 mg (bracketed by 16 mg (equivalent to 24 mg tablet formulation in Study CR92/099) both confirmed in two separate studies, is effective in the treatment of opiate addiction, when administered in the context of a treatment program that includes psychiatric support and counseling.

Safety—Nonclinical

The nonclinical safety was evaluated in acute, subacute and chronic studies in rats, dogs and primates. Target organ toxicity was observed only in dogs with chronic administration of up to 76-fold higher doses than the highest anticipated human dose. The toxicity that was observed was moderate bile duct hyperplasia with associated biliary fibrosis. The NOAEL was 3.5 mg/kg/day.

While certain isolated genotoxicity studies were positive for both naloxone and buprenorphine in isolation, the genotoxicity panel was negative for the combination product.

Carcinogenicity studies performed in rats demonstrated a higher incidence of testicular interstitial adenoma at 17-fold higher doses than the highest projected human dose. Carcinogenicity studies in mice were negative. The sponsor is currently undertaking a 2-year carcinogenicity study in rats using the buprenorphine/naloxone combination product.

In the context of treatment of this serious and in many cases life threatening clinical condition, potential benefit of treatment can be judged to outweigh this low risk of carcinogenicity, as long as the product is appropriately labeled.

Reproductive toxicology studies of buprenorphine and the combination of buprenorphine and naloxone were conducted. No teratogenicity was found with either buprenorphine or the combination of buprenorphine and naloxone in various ratios. As the review team points out, while none of the reproductive toxicology studies were performed using the 4:1 ratio of buprenorphine to naloxone, no interactions have been seen using higher ratios in several studies conducted in two species and two different routes of administration. Thus, they posit that it is reasonable to predict that no interactions would be present at a lower naloxone concentration. Post-implantation losses were observed in animals treated with buprenorphine and buprenorphine/naloxone in combination at doses up to 50 mg/kg administered orally.

Clinical Safety— buprenorphine

Subjects participating in clinical trials of various buprenorphine formulations with CRF's include 472 exposed to Suboxone, 105 exposed to Subutex, and 813 exposed to buprenorphine sublingual solution, for a total of 1390. Additional, less well-documented exposures have also been noted by the sponsor and adverse events of significance arising in the context of studies without CRFs, post-marketing surveillance, and published studies were also described.

In the context of the review of NDA 20-732 for Subutex, the division previously concluded that there was evidence to support the safety of buprenorphine *sublingual solution* at doses up to 32 mg/day. Further examination of the buprenorphine/naloxone database as described by Dr. Winchell, who teased apart the contributions of the various components of this development plan, confirmed this finding.

There have been a series of isolated reports of buprenorphine-associated deaths related to hepatocellular damage, based largely on postmarketing passive reporting, but a clear association with buprenorphine was difficult to establish. This relationship was not clearly corroborated in the NDA database. The placebo-controlled trials did not provide adequate cases of treatment emergent liver function abnormality or frank hepatitis to be able to definitively answer this question. Clinical laboratory monitoring demonstrated some effect of buprenorphine on hepatic function. While baseline LFT abnormalities are common in this population, and are attributed to viral causes and drugs of abuse and alcohol, an effect of buprenorphine on LFTs was observed earlier in development, causing the sponsor to define for future studies LFTs >8x ULN as serious adverse events. In fact, this was the most commonly reported SAE in the database (46 subjects). Identifying other contributing factors, which often included viral hepatitis and alcohol, was used to assess the relatedness of these events to buprenorphine treatment. Many subjects were seropositive at baseline for Hepatitis B and/or C. However, as Dr. Winchell points out not all elevations in enzymes could be explained away by exacerbation of pre-existing viral hepatitis or substance abuse but lacking adequate comparators in did not allow for a full exploration of these findings. These findings

should be incorporated into the package insert with inconclusive language regarding causality.

In addition to the above, Dr. Doddapaneni has identified concerns related to the metabolism and excretion of buprenorphine and naloxone in patients with hepatic failure. No studies were conducted to determine the pharmacokinetics of buprenorphine and naloxone in hepatic failure patients. Population PK indicated that the clearance of buprenorphine was decreased in patients with elevated bilirubin and ALT levels. Since naloxone is also metabolized by the liver, the increased levels in patients with hepatic failure might precipitate withdrawal. A Phase 4 study will be recommended to assess this further. Alternative treatment with buprenorphine alone should be considered for patients with hepatic failure until further evaluation is complete.

There were many subjects who had elevated eosinophil counts. There appeared to be a dose-dependent trend in the shift from normal to abnormally high eosinophil counts. Line listings reveal counts as high as 30 in one case, and several in the mid-20s. In many subjects, the finding was transient and resolved by the end of treatment. Eosinophilia is not unexpected in injection drug users.

Serious Adverse Events were largely related to complications of underlying disease but also included seizure, endocarditis, vomiting and diarrhea, suicidal ideation, and elevated liver function studies. These are not unanticipated and were infrequent.

Common adverse events included headache, insomnia, constipation, anxiety, sedation, nausea, and dizziness.

Safety—Naloxone

Naloxone in buprenorphine/naloxone is not absorbed sublingually, and therefore, the entire dose is available for GI absorption. There has not been a robust evaluation of the chronic oral toxicity of naloxone, which was initially developed as a single-use agent for intravenous administration. The development plan for buprenorphine/naloxone should, therefore, have included a up to a minimum of 6-months to a year of safety data for the combination product doses of naloxone of up to 6 mg/day (more typically 2 mg/day). In the open label extension, Study 1008(b) approximately 250 patients were exposed to naloxone for up to 6 months in doses for which this product will be labeled. No unexpected adverse events were noted in this experience. Longer studies are ongoing which are expected to provide additional chronic oral exposure of approximately 600 patients up to and including 1 year.

Abuse Liability and the Combination Drug Policy

In order to satisfy the requirements of the combination policy, approval under 21CFR300.50(a)(2)³ the naloxone component of Suboxone must be shown to minimize

³ 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 be added to minimize the potential for abuse of the principal active component.

the abuse potential of the buprenorphine when intentionally self-administered intravenously. Clinical pharmacology studies are provided which demonstrate that the combination of buprenorphine and naloxone, given intravenously in a 4:1 ratio, precipitates withdrawal in subjects maintained on other opiates.

Suboxone may, however, be abused sublingually or intranasally, as it has euphorogenic effects by these routes, unaffected by the presence of naloxone, which is not expected to be bioavailable sublingually as buprenorphine is. The intranasal bioavailability of naloxone has not been studied. These alternate routes of abuse may be important in the United States given a recent increase in intranasal or smoked heroin use, particularly among youth.

Nevertheless, the abuse of buprenorphine by the intravenous route could be reduced based on theoretical clinical grounds with the addition of naloxone, and is justified under 21CFR 300.50.

Chemistry, Manufacturing, and Controls

The stability of naloxone in Suboxone was an issue that arose during the review of this NDA. The specification for naloxone assay is _____ of the labeled amount. During the course of review it was learned that the product was unable to meet the _____

Current data suggest that _____

_____ seemed to be erratic in the lots tested.

Currently stability data provided by the Sponsor support _____ expiration dating,

An _____

_____ package used in clinical studies also appears to have improved stability, but this was not tested using NDA specified methods.

The sponsor has provided preliminary data to suggest that the degradation is caused by _____

_____ degradants were identified as _____

The full degradation profile has not been fully worked out.

The degradation of naloxone in this formulation raises two specific concerns. The first concern is the potential for toxicity of the breakdown products when taken under conditions directed. The degradation products of naloxone have not been completely 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 be provided. The degradation products should be qualified with respect to safety in accordance with the ICH Q3 A and Q3B guidance.

The second and greater concern with the

is that the product may not be an adequate deterrent for abuse as purported. The important question is the minimum dose of naloxone required to deter intravenous abuse of the product. As Dr. Winchell has pointed out, only a very small amount of naloxone is generally needed to precipitate withdrawal in heroin-dependent individuals, the 8:2 mg tablet is likely to continue to be aversive if injected in its entirety, despite loss of some of the naloxone contained in the tablet. However, addicts (particularly those without a high level of dependence) may find that, by using the 2: 0.5 mg tablet or divided portions of the 8:2 mg tablet, it is possible to abuse the buprenorphine intravenously without receiving a sufficient dose of naloxone to precipitate withdrawal. 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 and Combination Drug Policy). If the presence and stability of naloxone cannot be assured, there is no basis for approving this product. In order to evaluate the integrity of the unpackaged product under conditions of intentional degradation, the tablets should be stressed under forced degradation conditions for sufficient time to predict the extent of degradation under abuse conditions. It must be pointed out that this stability issue should not affect the overall efficacy of the product.

The current product packaging does not provide

and must also comply with the provisions of the Poison Prevention Packaging Act as an oral dosage form of a controlled substance, and be child resistant. Any new packaging will have to comply with the USP standards for , and long term stability data.

Control of buprenorphine under the CSA (Controlled Substances Act)

Buprenorphine for parenteral use is currently controlled in Schedule V. The basis for this level of control was reviewed and new information considered. An Eight-Factor Analysis was conducted and a recommendation for Schedule III 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. Methods to improve the bioavailability of buprenorphine either by crushing the tablets to increase the surface area or dissolving the tablets in alcohol to increase absorption have been reported among abusers.

The presence of naloxone in the Suboxone formulation is likely to be a deterrent only to intravenous abuse, and due to the instability of naloxone in this formulation, it may provide less of a deterrent than was anticipated.

Treatment under the NATA (Narcotic Addicts Treatment Act)

No data have been developed to establish the optimal treatment setting or ancillary support and counseling which should be used with buprenorphine. However, it should be noted that investigators experienced in addiction treatment carried out the efficacy studies

within the context of comprehensive treatment, including counseling, thus it could be concluded that the efficacy of buprenorphine is a function of the setting under which the studies were performed, and that buprenorphine as otherwise "monotherapy" has not been established. Opiate dependence is considered a complex disorder that requires the proper controls, surveillance and counseling services. The current system of dispensing controlled substances for the treatment of opiate addiction in methadone clinics, as prescribed by regulations emanating from the NATA, is currently undergoing assessment and restructuring but these measures may not be completed by the time of approval of buprenorphine.

Action: Approvable pending satisfactory resolution of the stability issues, and revision of the draft package insert

The following are Phase 4 Commitments will be required once approved to be completed within one year of approval:

1. Pharmacokinetic studies to determine the appropriate method of delivering doses of more than two tablets should be required, leading to a labeling amendment that provides more precise instructions to clinicians as quickly as possible.
- 2.
3. Study the effect of hepatic impairment of varying degrees upon the pharmacokinetics of buprenorphine and naloxone should be evaluated.
- 4.
5. Develop data on buprenorphine with naloxone to confirm the efficacy of this drug product, specifically that, is not likely to exert an opiate antagonist effect when the product is used sublingually in the maintenance phase of treatment.
6. 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.

**APPEARS THIS WAY
ON ORIGINAL**

Electronic Mail Message

Date: 12/7/99 11:25:00 AM
From: Khairy Malek (MALEKK)
To: Indira Kumar (KUMARI)
Subject: Suboxone Inspections

The inspections revealed that the data for this NDA are acceptable,
I will send you the summary this afternoon.

Malekk

**APPEARS THIS WAY
ON ORIGINAL**

Electronic Mail Message

Date: 12/6/99 12:35:17 PM
From: Indira Kumar (KUMARI)
To: Khairy Malek (MALEKK)
Subject: NDA 20-733 Suboxone - Status of DSI Reports.

Hello Khairy,

I am following up on the status of the pending DSI reports for this NDA.
The Division is getting ready to take an action on this NDA today.
Please let me know what is the status of these inspections/reports.

Thanks.
Indira Kumar
827-7424
(New PM covering this NDA in place of Tony).

APPEARS THIS WAY
ON ORIGINAL

2 Page(s) Withheld



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ADDENDUM TO 11/15/99 MEMORANDUM

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

From: Celia Winchell, M.D., Medical Team Leader, Addiction Drug Products [/S/]

Date: November 22, 1999

Re: NDA 20-733

Reckitt & Colman Pharmaceuticals, Inc.

Suboxone (Buprenorphine/Naloxone) Sublingual Tablets

This memo serves as an addendum to my team leader memo of 11/15/99 regarding the NDA for Suboxone (Buprenorphine/Naloxone) Sublingual Tablets, 20-733. Although the safety and efficacy of the product *when used as directed* appear to be adequate to support approval, the sole justification for inclusion of naloxone is the prevention of misuse. To satisfy the requirements of the combination combination drug policy (21CFR 300.50), the inclusion of naloxone must reduce the abuse potential of the product. The intention of the sponsors in formulating this product was that persons misusing the buprenorphine/naloxone tablet by the intravenous route would experience precipitated opiate withdrawal, a very unpleasant phenomenon that is not considered dangerous. It is predicted that the reputation of the product "on the street" would be affected by reports of persons experiencing this phenomenon, and that further diversion of the combination product would be discouraged through lack of demand. The ability of a 4:1 ratio of buprenorphine:naloxone to precipitate withdrawal in opiate-dependent individuals¹ has been demonstrated by the sponsor in experimental settings. I believe this begins to address the issue, and, in keeping with the action taken on the pentazocine-naloxone combination product, would be sufficient to permit approval with post-approval data collection to confirm the prediction of reduced abuse compared to the single-entity product. However, this use of naloxone in the combination has already forced us to consider issues arising when the product is used other than "as directed."

Materials submitted to the Chemistry review team suggest that the _____
_____ noted previously may be associated with the development of an as-yet-
uncharacterized degradation product. _____

_____, may potentially slow the degradation and
could be used to establish a commercially viable shelf-life. However, because it is
believed that the degradation of naloxone may be _____

¹ Although not those dependent on buprenorphine, and not non-dependent drug abusers.

— it may be anticipated that deliberate mis-handling of the product will occur, in order to remove the naloxone to facilitate diversion for intravenous abuse. This mis-handling would be expected to accelerate formation of this uncharacterized compound, and full assessment of the safety of this product requires further information on the degradation product and its safety. Exposure to a compound with an unknown safety profile would not be considered an appropriate deterrent to abuse. More information about the safety of the degradation products is needed in order to weigh the risks of including naloxone against the potential benefits.

I recommend approval be withheld pending the submission of further safety information about the naloxone degradation products.

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sara Shepherd
10/3/02 03:53:50 PM
CSO
Comments from CMC sent to Sponsor via e-mail on
Oct 3, 2002.

**APPEARS THIS WAY
ON ORIGINAL**



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

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MEMORANDUM

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

From: Celia Winchell, M.D., Medical Team Leader, Addiction Drug Products [/S/]

Date: November 15, 1999

Re: NDA 20-733

Reckitt & Colman Pharmaceuticals, Inc.

Suboxone (Buprenorphine/Naloxone) Sublingual Tablets

This memo conveys my agreement with the primary medical reviewer that the New Drug Application for Suboxone, Reckitt & Colman's sublingual tablet which combines buprenorphine and naloxone, is approvable with modifications to the proposed labeling.

The key conclusions of this review which support approval of this product are:

- Buprenorphine, the drug substance, is safe and effective fo.
- Buprenorphine can be delivered, using sublingual tablets, in doses which 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 somewhat, thus providing the justification for its inclusion in this combination drug product, as required under the combination drug policy (21CFR 300.50).

The evidence in support of these conclusions are discussed according to the table of contents below.

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1 Background:

Buprenorphine HCl is a narcotic analgesic which has been marketed since 1982 as Buprenex, an injectable formulation, for the treatment of moderate to severe pain. For two decades, drug abuse researchers have been exploring its utility as a maintenance treatment for opiate addiction. Although the manufacturer and commercial sponsor is a pharmaceutical company, Reckitt & Colman Pharmaceuticals, Inc., most of the development has been conducted by the National Institute on Drug Abuse under a cooperative research and development agreement, as well as under more than 40 different investigator-initiated INDs sponsored largely by NIDA grantees. This NDA represents the final step in making this product commercially available.

This product, Suboxone, and its “companion” product, Subutex (buprenorphine sublingual tablets, NDA 20-732), have had a long and complex administrative history and development plan. The potential utility of buprenorphine for the treatment of opiate dependence was identified over 15 years ago, and research has been conducted by NIDA and its grantees over the ensuing years,

— The studies were funded by the National Institute on Drug Abuse (NIDA), who served as the importer of the drug substance and formulated it for use in

clinical trials by various investigators, each operating under his or her own IND. After the establishment of the Medications Development Division (MDD) of NIDA, NIDA-MDD opened their own IND (35,877), and also succeeded in negotiating a Cooperative Research and Development Agreement (CRADA) with Reckitt & Colman (effective 4/29/94), who opened IND 45,219. Orphan Drug designation and waiver of fees were sought (and granted) based on the projected limited sales revenue. According to the principals in the agreement, Reckitt & Colman have deferred to NIDA-MDD in much of the design and execution of the development plan and the preparation of the NDA study reports. However, business decisions at Reckitt & Colman have influenced some of the timing and content of submissions.

The buprenorphine ethanolic solution used in NIDA-sponsored trials proved to be

However, the sublingual route was felt to be practical based both on the NIDA-sponsored trials of the solution, and on the commercial success of low-dose (0.2 and 0.4) mg sublingual tablets marketed as an analgesic by Reckitt & Coleman in 30 countries (not including the U.S., where the product has not been approved and is not under active development for an analgesic indication). Reckitt & Colman chose to develop buprenorphine sublingual tablets, Subutex, containing 8 mg, 2 mg, and 0.4 mg for the opiate addiction indication. When the sponsors chose to develop a sublingual tablet, they also elected to develop a second product, Suboxone, which would incorporate naloxone to deter diversion for intravenous abuse, similar to Talwin-Nx. Naloxone is not active orally, and was expected to be poorly bioavailable sublingually and therefore was viewed as an inactive ingredient when the product was used as directed. However, should the product be crushed and injected, the naloxone would precipitate withdrawal in opiate-dependent individuals. The sponsors hope that this will translate into reduced street value and abuse potential, thereby facilitating the use of the product outside the traditional methadone clinic setting. Because their expectation is that the naloxone will not affect the efficacy of buprenorphine when used as directed, they have based much of their application for the combination product on studies of buprenorphine alone, in solution and tablet form.

FDA has previously reviewed NDA 20-732 for Subutex Sublingual Tablets. The Subutex NDA was problematic because much of the data therein was derived from NIDA's studies of a sublingual solution of buprenorphine. Unfortunately, it became apparent that the sublingual tablet formulation was not well-linked to the dataset on the sublingual solution via pharmacokinetic data. The division met with Reckitt & Colman and NIDA on 3/27/98 to discuss the deficiencies in NDA 20-732, and the applicability of the advice to the Suboxone NDA. The division issued an approvable letter on 6/30/98, accompanied by very restricted labeling (calling for use of only a single dose, rather than titration to effect, as proposed by the sponsor) and an extensive list of deficiencies. Those deficiencies were also intended as guidance for the preparation of the Suboxone NDA, and were so understood by the sponsor.

The Suboxone NDA, 20-733, was submitted on June 7, 1999. It contains much of the same safety and efficacy data submitted in support of NDA 20-732 (Subutex), but was organized somewhat differently in response to agency advice. The NDA contains a single adequate and well-controlled trial of Suboxone vs placebo (and vs Subutex), two controlled studies of the sublingual buprenorphine solution (without naloxone), and a variety of clinical pharmacology studies, pharmacokinetic studies, and small, generally investigator-initiated studies. It was reviewed by Dr. Chang Lee, Medical Officer, who focused on the two controlled studies of buprenorphine sublingual solution already reviewed by Dr. Monte Scheinbaum under NDA 20-732, the single adequate and well-controlled trial of Suboxone, and selected smaller studies cited by the sponsor in support of specific claims. He also examined the integrated safety database which incorporates information on Suboxone, Subutex, and buprenorphine sublingual solution, as well as post-marketing information on other formulations of buprenorphine.

I have reviewed Dr. Lee's report and some of the material submitted by the sponsor. I agree with his conclusion that the drug may be approved. In order to arrive at this decision, it was necessary to determine that the sponsor had submitted substantial evidence of safety and efficacy of buprenorphine, and that their formulation could deliver the safe and effective doses. Because much of their evidence was drawn from studies of buprenorphine without naloxone, the sponsor had to demonstrate that the naloxone in Suboxone was inactive when the product was used as directed in the intended population. I will outline the evidence provided in support of these assertions below, and will also describe several assertions made by the sponsor for which adequate support was not provided.

2 Efficacy of Buprenorphine

Four studies of buprenorphine in the treatment of opiate addiction were submitted to this NDA as full reports with Case Report Forms (CRFs). These included a study comparing buprenorphine sublingual solution, 8 mg/day, to methadone (CR88/130), a dose-controlled study of buprenorphine sublingual solution (CR92/099) with a flexible-dose open-label follow-on (CR92/100), a study of buprenorphine sublingual solution comparing daily and alternate-day dosing, which included a brief placebo-controlled initial phase (CR92/102), and a four-week study comparing Subutex 16 mg/day, Suboxone 16 mg/day, and placebo, with an open-label, flexible-dose follow-on (CR96/013 and CR96/014, also known as 1008a&b¹). All but CR92/102 were previously

¹ This study was conducted under a single protocol calling for a placebo-controlled 4-week study, followed by open-label, flexible dose treatment open to completers of the placebo-controlled study as well as new entrants. Several reference numbers have been assigned to the study. For consistency, the reference numbers for the sponsor's study report (CR number), and not the protocol numbers, have been used in this memo. Study 1008 included substudies 1008a and 1008b. The subjects who participated in placebo-controlled portion were considered to have enrolled in 1008a. New entrants directly into open-label treatment were considered to have enrolled in 1008b. The study report given reference number CR96/013 comprises the open-label phase of Study 1008a. Study CR96/014 included participants in 1008a who continued into the open-label, flexible dose extension (1008a, Phase II), and new subjects enrolled directly into open-label, flexible dose treatment (1008b). Other terms used by the sponsor are "the efficacy study" (CR96/013 a.k.a 1008a, Phase I) and "the safety study" (CR96/014, a.k.a. 1008a, Phase II + 1008b).

reviewed under NDA 20-732. The sponsor also submitted many manuscripts and publications representing additional experience with buprenorphine as sublingual solution and as sublingual tablets. Only a few used the Suboxone tablet. Many of the studies were small and/or uncontrolled. Only where the sponsor cited these reports in support of a particular claim, they were reviewed for adequacy to support the claim. Generally speaking, they were found to be too small to support definitive conclusions about efficacy claims but were regarded as support for the primary studies.

In the context of the approvable action for NDA 20-732, Subutex, the division previously concluded that there was substantial evidence of efficacy of Subutex (two 8 mg tablets) in retaining heroin addicts in treatment and reducing use of heroin. I will reiterate briefly the descriptions of the studies upon which this conclusion was based, which are CR88/130, CR92/099, and CR96/013. More detail may be found in memos to NDA 20-732.

2.1 Studies of Buprenorphine Sublingual Solution

Two studies of the sublingual ethanolic buprenorphine solution were submitted to this NDA. Dr. Monte L. Scheinbaum (Medical Officer) and Dr. Thomas Permutt (Mathematical Statistician/Team Leader) examined the primary data from these two trials of buprenorphine sublingual solution during the review of NDA 20-732.

2.1.1 Study CR88/130

The first study, given Reckitt & Colman reference number CR88/130, was a double-blind, double-dummy, parallel-group, trial comparing buprenorphine sublingual solution 8 mg/day with oral methadone 20 and 60 mg/day, and consisting of a one-week induction phase, 16-week maintenance phase and a 7-week detoxification phase. In this study, 162 subjects were randomized to receive sublingual buprenorphine 8 mg/day (a dose which is roughly comparable to a dose of 12 mg/day of Subutex or Suboxone), or two relatively low doses of methadone, 20 mg/day and 60 mg/day. Buprenorphine was titrated to maintenance dose by day three; methadone doses were titrated more gradually according to the table below.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6-9	Day 10-Week 17
Buprenorphine	2 mg	4 mg	8 mg	8 mg	8 mg	8 mg	8 mg
Methadone 20	20 mg	30	30	30	30	25	20 mg
Methadone 60	20 mg	30 mg	40 mg	50 mg	60 mg	60 mg	60 mg

Maintenance dosing continued through week 17. Subjects received individual and/or group counseling weekly. Based on retention in treatment and the percentage of thrice-weekly urine samples negative for non-study opiates, the reviewers concluded that the study provided evidence that buprenorphine was more effective than methadone, 20 mg p.o. q.d., in keeping heroin addicts in treatment and in reducing their use of opiates while in treatment. The effectiveness of buprenorphine was in the same range as methadone, 60 mg p.o. q.d., but neither superiority nor equivalence was demonstrated.

At the conclusion of the maintenance period, medications were tapered by approximately 20-30% per week over weeks 18-24, with placebo dosing for the last two weeks.

2.1.2 Study CR92/099

The second study, CR92/099, was a twelve-center, double-blind, parallel-group, 16-week trial of four doses of buprenorphine sublingual solution. The primary aim of this study was to determine the safety and effectiveness of 8 mg/day buprenorphine sublingual solution as compared to 1 mg/day in decreasing illicit opiate use. The 1 mg dose was envisioned as an ethical alternative to placebo. A secondary purpose was to gather experience with 4 mg and 16 mg daily dosing. In this study, 731 subjects were randomized to receive one of four doses of buprenorphine ethanolic solution. Buprenorphine was titrated to maintenance doses over 1-4 days (see table below) and continued for 16 weeks. Subjects received at least one session of AIDS education and additional counseling ranging from one hour per month to one hour per week, depending on site. Subjects completing the study could enroll in an open-label, flexible-dose extension study which included at least one hour per month of counseling or psychosocial services.

Buprenorphine dose	Day 1	Day 2	Day 3	Maintenance dose
1 mg	1 mg	1 mg	1 mg	1 mg
4 mg	2 mg	4 mg	4 mg	4 mg
8 mg	2 mg	4 mg	8 mg	8 mg
16 mg	2 mg	4 mg	8mg	16 mg

Based on retention in treatment and the percentage of thrice-weekly urine samples negative for non-study opiates, the reviewers concluded that this study provided evidence that sublingual buprenorphine solution, 8 mg/day, is more effective than 1 mg/day in keeping heroin addicts in treatment and in reducing their use of heroin. There was an indication that 16 mg/day is somewhat more effective than 8 mg/day, and that 4 mg/day is more effective than 1 mg/day. There was no indication that 4 mg/day was different from 8 mg/day.

2.2 Studies of Buprenorphine Sublingual Tablets

One study in support of the to-be-marketed tablet formulations (both the buprenorphine-only and the buprenorphine + naloxone tablet) was submitted to NDA 20-732. The study was a multicenter, clinical trial conducted in two phases. The first, 4-week phase (Study CR96/013 or 1008A) was conducted at eight sites as a randomized, placebo controlled, double blind efficacy assessment. Subjects were to be randomly assigned to one of three treatment groups: placebo, buprenorphine 16 mg per day, or buprenorphine 16 mg/naloxone 4 mg per day. The second phase of the study (phase 2 of Study 1008A and Study 1008B conducted at four additional sites, known together as CR96/014) was a 48- to 52-week open label safety assessment of the buprenorphine/naloxone arm only, in doses up to 24 mg/6 mg per day.

In the double-blind phase of the study, 326 subjects were randomly assigned to one of three treatment groups: placebo, buprenorphine 16 mg per day, or buprenorphine 16 mg/naloxone 4 mg per day. Subjects were seen daily in the clinic (Monday through Friday) for dosing and efficacy assessments. Drug was to be taken once daily sublingually. The subject was to be instructed to hold the medication under his/her tongue for approximately 5 to 10 minutes until completely dissolved in order to ensure maximum absorption. Induction (for those in the active drug treatment groups) was accomplished using buprenorphine 8 mg SL tablet on day one, and buprenorphine SL tablet 2 x 8 mg beginning on day two. (Subjects in the buprenorphine/naloxone condition began treatment with the combination tablet on day three.) Subjects received a session of HIV education and one hour of individual counseling per week. The data showed that subjects treated with buprenorphine, whether administered as monotherapy or in combination with naloxone, had a statistically significantly higher percentage of urine samples that were negative for opiates when compared to the subjects who were treated with placebo: 19.7% clean urines following monotherapy, and 16.7% following combination therapy, and 5.7% for placebo. There was no statistically significant difference between the two buprenorphine treatment arms, nor was equivalence demonstrated.

2.3 Efficacy conclusions: Buprenorphine

Taken alone, the single study of Suboxone and Subutex vs. placebo (CR96/013) would not provide the substantial evidence needed for approval of either product. Information from trials using other formulations can be used to support the claim of efficacy. Current information about the pharmacokinetics of the to-be-marketed formulation suggests that the 16 mg dose of the Suboxone tablet (2 x 8 mg tablets) is bioequivalent to a dose approximately 12 mg of solution. Two trials using buprenorphine sublingual solution have demonstrated the efficacy of the 8 mg/day dose of solution. One of those trials also provided evidence of efficacy of the 16 mg/day dose of solution. Therefore, since there is substantial evidence of efficacy for a dose *lower than* the 2 x 8 mg tablet regimen (i.e. 8 mg sublingual solution), and some evidence of efficacy for a dose *higher than* the 2 x 8 mg tablet regimen (i.e. 16 mg sublingual solution), I feel that these studies of the sublingual solution should be viewed as confirmation of the findings of Study CR96/013. Furthermore, since the studies of the sublingual solution showed that doses across a range which brackets the 2 x 8 mg regimen demonstrated efficacy in longer studies (16 weeks), I think the short duration of the CR96/013 study, which would otherwise render it somewhat unpersuasive, is offset by the available data from the other studies.

3 Efficacy of Buprenorphine/Naloxone Combination

One important issue remains to be resolved, however, with respect to Suboxone, the buprenorphine-naloxone combination product, specifically: is the buprenorphine-naloxone combination product clinically equivalent to the buprenorphine-only tablet, such that the finding of safety and efficacy can also be extrapolated from the studies of the buprenorphine solution to support the Suboxone tablet?

The purpose of adding naloxone to the buprenorphine sublingual tablet was to deter intravenous abuse of the product. The sponsor has submitted clinical pharmacology studies providing evidence that buprenorphine and naloxone, given intravenously in a 4:1 ratio, is capable of precipitating withdrawal in subjects stabilized on agonists such as morphine or hydromorphone. As mentioned above, naloxone is expected to be poorly bioavailable sublingually, and therefore, when the product is used as directed, naloxone is intended to be an inactive ingredient.

Evaluation of this prediction involves several bodies of information:

- Assessment of the sublingual bioavailability of naloxone
- Assessment of naloxone's oral activity at doses comparable to those in Suboxone
- Assessment of the likelihood of naloxone-precipitated withdrawal when naloxone is given in clinically relevant doses (i.e. doses comparable to those in Suboxone)
 - in subjects dependent on full opiate agonists
 - in subjects dependent on buprenorphine
 - based on experimental evidence from clinical pharmacology studies
 - based on clinical trial data

3.1 Sublingual Bioavailability of Naloxone in Suboxone

Pharmacokinetic studies of the combination tablet reveal low, but detectable, plasma levels of naloxone associated with 8mg/2mg and 16 mg/4 mg doses of Suboxone. The table below shows the data from Results are from two single dose studies of Suboxone tablets conducted in 8 subjects at Suboxone doses of 4 mg/1 mg, 8 mg/2 mg and 16mg/4 mg and 14 subjects at Suboxone doses of 4 mg/1 mg, 8 mg/2 mg, 16mg/4 mg and 24mg/6 mg. Plasma naloxone was measured by LC/MS/MS.

Mean Cmax and AUC of naloxone following acute sublingual administration of Suboxone tablets

Dose (mg)	Subjects	C _{max} (ng/ml)	Range (ng/ml)	Subjects	AUC (h.ng/ml)	Range (h.ng/ml)
4	20	0.12	0.06 - 0.25	14	0.12	0.02 - 0.35
8	21	0.23	0.09 - 0.42	14	0.30	0.15 - 0.50
16	20	0.39	0.07 - 1.15	13	0.53	0.16 - 1.26
24	12	0.47	0.08 - 1.12	12	0.60	0.03 - 1.18

3.2 Activity of Oral Naloxone

It should be noted that the naloxone which is not absorbed into venous blood through the sublingual veins is nevertheless swallowed. Naloxone is poorly bioavailable orally, not because of poor absorption but because of extensive first-pass metabolism. Oral doses of naloxone have been used for the treatment of constipation (primarily opiate-induced). The mechanism of action is unknown, but is believed to involve local action in the gut. Published studies and case series have used doses as high as 100% of the daily oral morphine dose in cancer pain patients (expected to be not less than 30 mg/day). Other studies have suggested that doses as low as 2 mg, dosed more than once daily, might be effective. This suggests that the amount of naloxone ingested by some patients (as much as 6 mg/day for a 24 mg/6 mg dose of Suboxone) may be high enough to be active. It is difficult to predict whether this would be manifested as diarrhea (sometimes seen in studies of oral naloxone)—an adverse effect which could be interpreted as withdrawal,

and might lead to treatment drop-out, or as a reduction in the incidence of constipation—a benefit which might promote treatment retention. There was a suggestion of a U-shaped dose dependency of constipation in the open-label flexible dose extension study of Suboxone (CR96/014), with increasing incidence up to a dose of 20 mg/5 mg and a lower incidence in the patients receiving 24 mg/6 mg. Diarrhea was more common in subjects receiving more than 4 mg naloxone/day in Suboxone than in subjects receiving less, but dose dependency was not clear across the range of doses. However, the number of patients and the design of the study prevents definitive conclusions.

3.3 Precipitation of Opiate Withdrawal Using Sublingual Naloxone

A clinical pharmacology study of sublingual effects of naloxone in opioid dependent subjects was undertaken by Preston and colleagues². In this study, six heroin addicts and three methadone-maintained patients were challenged with ascending doses of sublingual naloxone solution in three cohorts of three. The first two cohorts included 6 heroin addicts seeking detoxification who were given a 20 mg dose of methadone on day -1 and on each of two study days, followed by gradual detoxification after the study. The first cohort of three was given three challenges per study day, separated by 2-2.5 hours. Challenges involved the administration of naloxone in a sublingual solution in doses of 0, 0.4, and 0.8 mg (day 1) and 1, 2, and 4 mg on day 2. The subjects were not aware of the ascending dose order. The protocol called for discontinuation if withdrawal symptoms were so intense that the subject wished to discontinue participation or if the investigator believed higher doses would be unethical. All of the first three subjects were able to tolerate the maximum dose without a measurable response on parameters including heart rate, blood pressure, skin temperature, respiration, pupil diameter, subjective scales, and observer ratings. The protocol called for the second cohort to receive challenges of 0 and 2 mg (day 1) and 4 and 8 mg (day 2). In this group, the first subject was able to tolerate the maximum dose without consistent signs or symptoms of withdrawal. The second and third subjects showed slight signs and symptoms of withdrawal at the 2 mg dose, and were able to identify the drug as an antagonist. Both showed marked signs and symptoms of withdrawal at the 4 mg dose (including vomiting in one patient) and were not exposed to the 8 mg dose.

The third cohort of subjects were patients undergoing methadone detoxification who had been on methadone for at least a month and on 30 mg/day for at least a week. These subjects were challenged with sublingual naloxone solution doses of 0, 0.25, and 0.5 mg on day 1 and 1, 2, and 4 mg on day 2. Two of the subjects were able to tolerate all of the challenges given, but did show signs and symptoms of withdrawal at 2 mg and were able to identify the drug as an antagonist. One subject showed moderate precipitated withdrawal at 1 mg and was not exposed to the higher doses.

This study demonstrates that 2-4 mg of sublingual naloxone solution can precipitate withdrawal in some heroin addicts, and that lower doses may be sufficient to precipitate withdrawal in methadone-maintained patients, even those on a dose as low as 30 mg/day.

² Preston KL, Bigelow GE, and Liebson IA, *Drug and Alcohol Dependence*, 25 (1990)27-34.

Although the naloxone in Suboxone is expected to be less bioavailable than a naloxone solution, it is reasonable to expect that the naloxone contained in Suboxone doses recommended for clinical use could precipitate withdrawal in some patients beginning treatment.

3.4 Naloxone-precipitated Withdrawal in Buprenorphine-Dependent Subjects

Although Preston's study showed that the administration of sublingual naloxone at doses within the range delivered by clinically relevant doses of Suboxone could precipitate withdrawal in some patients, it is predicted that these doses would not result in adverse clinical events (e.g. precipitation of withdrawal) in patients maintained on buprenorphine, because naloxone competes less effectively with buprenorphine at the μ -receptor than with other opioids. It is important to examine this prediction. If the naloxone in Suboxone does precipitate withdrawal in the intended population—patients beginning or continuing in buprenorphine treatment, this might be expected to affect retention in treatment compared to buprenorphine alone, and therefore calls into question the use of data on buprenorphine alone in support of the efficacy of Suboxone. Because the CR96/013 study used Subutex for two days before beginning Suboxone, this dosing scheme introduces the naloxone at a point where the patient might be thought of as "buprenorphine dependent," rather than dependent on the opioid used before entering treatment (although it should be noted that this assumption may not hold if the the pre-treatment opioid was very long-acting). When the drug is used in this way, Suboxone may be less likely to precipitate withdrawal than if it is given as an initial medication.

There are two sources of data to address this issue: the first is the body of literature on experimental naloxone-precipitated withdrawal in buprenorphine-maintained subjects, and the second is the adverse experience data from clinical trials submitted to the NDA. In CR96/013 and CR96/014, subjects treated with Subutex for two days (CR96/013) or four weeks (CR96/014) were then switched to Suboxone. Their experience may predict the effect of naloxone in Suboxone in patients initiating treatment or involved in ongoing treatment. Two small, investigator-initiated trials gave information about the use of Suboxone as the initial treatment for opiate-dependent individuals. These bodies of information are described and reviewed below.

3.4.1 Experimental Naloxone-Precipitated Withdrawal In Buprenorphine-Maintained Subjects

Several clinical pharmacology studies have examined the effect of naloxone on subjects stabilized on buprenorphine. In fact, early studies of buprenorphine which demonstrated difficulty in precipitating withdrawal with naloxone have often been cited as evidence that buprenorphine does not produce physical dependence. A more comprehensive view of the scientific information now available interprets these findings not as evidence that buprenorphine does not produce dependence, but as an expression of the relative affinities of buprenorphine and naloxone at the μ receptor.

In one study³ of precipitated withdrawal in buprenorphine-maintained subjects, subjects dependent on injected buprenorphine (1.33 ± .27 mg/day) experienced withdrawal when given 1.2 mg naloxone i.v. In a second study⁴, subjects maintained on 8 mg sublingual buprenorphine/day (presumably solution) were challenged with i.m. naloxone at doses of 0.3, 1.0, 3.0, and 10.0 mg/70 kg, and p.o. naltrexone 0.3, 1.0, and 3.0 mg/70 kg. Significant precipitated withdrawal occurred at 3 mg and 10 mg of naloxone and at 3 mg of naltrexone. Minimal symptoms were also noted with the 1.0 mg naloxone dose. In comparison, the “Narcain challenge test,” considered definitive demonstration of lack of dependence on opiates, entails the administration of 0.8 mg of naloxone. Doses as low as 0.1 mg i.v. naloxone have been known to precipitate withdrawal in subjects dependent on opiates. Therefore, the plasma levels seen with 8 and 16 mg doses of Suboxone would be predicted to be more of a problem for patients transitioning from illicit opiates or from methadone (either a maintenance program or illicit use). It should be noted, however, that no study cited examined the precipitation of withdrawal in patients stabilized on higher doses of buprenorphine. These patients, perhaps more dependent, might be more sensitive to naloxone than the subjects tested.

3.4.2 Withdrawal in Patients Switching from Subutex to Suboxone

In response to agency request, the sponsor provided an exploration of the data from Study CR96/013 giving close attention to the experience of subjects receiving their first dose of Suboxone after a two-day stabilization on Subutex. This is intended to support the theoretical data predicting that sublingual naloxone in Suboxone will not precipitate withdrawal in patients dependent on buprenorphine. Listings of adverse events attributable to withdrawal were provided by subject. The terms included in the AE listings were diarrhea, nausea, vomiting, dyspepsia, chills, fever, sweat, vasodilation, leg cramps, myalgia, spasm general, hypertonia, tremor, rhinitis, lacrimation disorder, pain, abdominal pain, back pain, bone pain, insomnia, anxiety, nervousness, agitation, thinking abnormal, dizziness, yawning, anorexia, asthenia, somnolence, hair disorder, as well as withdrawal syndrome *per se*. Thus, the preparers of the report cast a wide net for withdrawal-related AE's. In addition, listings of the incidence and severity of “withdrawal syndrome” and of “withdrawal effects” were provided. The latter refers to adverse events attributed to withdrawal by the investigator.

I examined these data to compare the occurrence of adverse events with onset on day 3 across treatment groups. Next, I counted the number of patients coded as having withdrawal syndrome on day 3, the number coded as having “withdrawal effects” on day 3, and the number for whom the severity on day 3 was greater than the severity on day 2. The results are listed in the table below.

³ Nigam AK, Srivastava RP, Saxena S, et al., Naloxone-induced withdrawal in patients with buprenorphine dependence, *Addiction*, 1994 Mar 89(3):317-20

⁴ Eissenberg T, Greenwald MK, Johnson RE, et al., Buprenorphine's physical dependence-potential: antagonist-precipitated withdrawal in humans, *J Pharmacol Exp Ther* 1996 Feb 276(2):449-59

	Placebo N = 110	Subutex N = 106	Suboxone N = 110
Reported withdrawal-related AE's with onset on day 3	13 (12%)	4 (4%)	12 (11%)
Withdrawal syndrome day 3	24 (22%)	9 (8%)	17 (15%)
Withdrawal effects day 3	45 (41%)	29 (27%)	34 (31%)
Withdrawal effects more severe on day 3 than on day 2	9 (8%)	3 (3%)	7 (6%)

These data are not clear-cut. On one hand, for each parameter examined, the incidence of withdrawal on the first day of Suboxone treatment is higher in those receiving Suboxone than in those who continued to receive Subutex. This would argue against the notion of naloxone's lack of activity in the buprenorphine-stabilized patient. On the other hand, for each parameter, the incidence of withdrawal on the third day of the study is highest in patients who received neither buprenorphine nor naloxone. It is difficult to attribute indicators of withdrawal on day 3 to the introduction of naloxone when these indicators also occurred—at higher rates—in patients on placebo.

To further explore this issue, Dr. Lee and I examined the adverse event data from the first week of the open-label extension study (CR96/014). In this study, 103 subjects continuing from the Suboxone group in the placebo-controlled study, 81 subjects continuing from the Subutex group, and 86 subjects continuing from the placebo group began receiving Suboxone 16 mg/day on the first day of the study. Titration up or down was permitted over the remaining weeks of the study. However, I was most interested in whether subjects who had been receiving Subutex for a month would be susceptible to naloxone-precipitated withdrawal when given Suboxone. Dr. Lee identified subjects for whom an adverse event coded as "withdrawal" was recorded during week 1. I identified subjects for whom an adverse event was recorded coded as any of the terms used in the sponsor's search described above. The exception was when "pain" was the only adverse event, I did not include the subject if the lower level term clearly suggested another etiology, such as toothache or twisted ankle. The results of this search are shown in the table below.

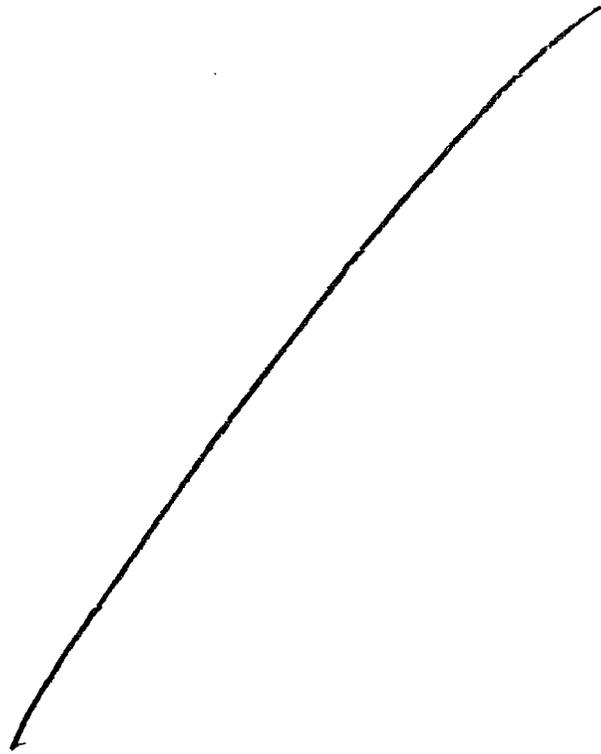
Medication prior to initiation of Suboxone→	Suboxone N = 103	Subutex N = 81	Placebo N = 86
Reporting withdrawal during week 1	25 (24%)	12 (15%)	29 (34%)
Reporting AE consistent with withdrawal during week 1	60 (58%)	48 (59%)	60 (70%)

Although this seems to be a rather high rate of withdrawal and other possibly withdrawal-related symptoms, it does suggest that patients who are stabilized on Subutex are less likely to experience withdrawal when naloxone is introduced (in Suboxone) than are patients who have been receiving placebo, and presumably some unknown amount of illicit street opiates.

3.5 Use of Suboxone



2 Page(s) Withheld



3.8 Buprenorphine Solution Studies Cited in Support of Suboxone's Efficacy: Implications for Labeling

A key limitation of the product is that it is available in only two tablet sizes, 2 mg/0.5 mg and 8 mg/2 mg. However, the efficacy data supports the use of doses in the range of about 12 mg/3 mg (roughly analogous to 8 mg solution, used in two sublingual solution trials) to 16 mg/2 mg (used in CR96/013, and bracketed by data on 4 mg through 16 mg solution). This submission contains some additional pharmacokinetic data which was not available at the time of the review of NDA 20-732, which shows that doses of 4 mg/1 mg (two 2 mg/0.5 mg tablets), 8 mg/2 mg (one 8 mg/2 mg tablet), and 16 mg/4 mg (two 8 mg/2mg tablets) are dose proportional, and that, importantly, *the dose proportionality curve is parallel to the dose proportionality curve for the solution*. This provides the elusive "conversion factor" not available at the time of the Subutex review. It appears that a rough conversion factor of 70% relative bioavailability (tablets 70% bioavailable compared to solution) can be used across a range which encompasses most of the doses tested in controlled trials of either tablet or solution formulations. This makes it possible (if challenging) to provide understandable labeling describing the studies which provide the evidence of efficacy, and to convert the range of doses studied into a range of doses which might be administered.

One problem remains. The data show that when more than two tablets are administered simultaneously (as when a dose of 24 mg is administered), the plasma levels fall off the dose-proportionality curve. This is due to the limitations of the sublingual space and the amount of saliva available.

However, many intermediate doses require the administration of three or more tablets. To use 12 mg/3 mg, for example, a patient must take one 8 mg/2 mg tablet and two 2 mg/0.5 mg tablets. Theoretically, these could be given sequentially, with the third tablet being taken sublingually after the first two have dissolved. However, there do not appear to be any data confirming that this administration procedure would result in plasma levels on or near the dose-proportionality curve. Without this data, it may be difficult to describe a practical and well-supported approach to dose titration, which is important in the therapeutic setting where dose is adjusted to individual effect. Because the only dose actually demonstrated to be effective when administered in tablet form is 16 mg/2 mg (2 x 8 mg/2 mg tablets), the product could be labeled with this dose and only the 8 mg tablet marketed. However, the treatment of opiate addiction requires titration to individual effect, so this would be clinically impractical labeling.

From a clinical standpoint, it is essential to know that a change in the dose provided would actually translate into a change in the plasma level generated, so that a patient who needs more or less medication can be given a dose that will provide the needed change. However, the specific amount more or less may be less critical. The sponsor has provided data to show that a dose of 12 mg/3 mg, delivered as one 8 mg/2 mg and two 2 mg/0.5 mg tablets given simultaneously, provides a blood level that is greater than that seen after a dose of one 8 mg/2 mg tablet and less than that seen after a dose of two 8 mg/2 mg tablets. It cannot be shown to fall on the dose-proportionality curve. Dr. Suresh Doddapaneni, Clinical Pharmacology and Biopharmaceutics Reviewer, has concluded that if dose changes are made in 4 mg/1 mg increments, a meaningful, although not entirely dose-proportional, change in plasma level can be expected. Dr. Doddapaneni did not feel that dose changes in 2 mg increments would reliably produce clinically meaningful changes in plasma levels.

The proposed labeling calls for titration of patients to a target dose of 16 mg, with titration upward or downward by 4 mg within a range of 4-24 mg. This envisions the use of the following doses:

Dose	2 mg/0.5 mg tablets	8 mg/2 mg tablets	Total tablets
4 mg/1 mg	2	0	2
8 mg/2 mg	0	1	1
12 mg/3 mg	2	1	3
16 mg/4 mg	0	2	2
20 mg/5 mg	2	2	4
24 mg/6 mg	0	3	3

Because there is no data on the sequential use of more than two tablets, it seems at this time to be more appropriate to accept the somewhat approximate increases in dose associated with the use of three (and rarely four) tablets, pending the development of more definitive data on the optimal administration of dose combinations requiring more than two tablets. It is recommended that the labeling recommendation be deleted, but that the recommendation for titration by 4 mg must remain. As this is a recommendation that will not be intuitive to clinicians, the label should provide an explanation about the limitations of the data on titration, until these limitations can be remedied.

4 Safety

4.1 Safety of Buprenorphine

In the context of the review of NDA 20-732 for Subutex, the division previously concluded that there was evidence to support the safety of buprenorphine *sublingual solution* at doses up to 32 mg/day. Dr. Lee has reviewed the integrated safety database submitted to NDA 20-733, which relies upon much of the same data. Subjects participating in clinical trials of various buprenorphine formulations with CRF's include 472 exposed to Suboxone, 105 exposed to Subutex, and 813 exposed to buprenorphine sublingual solution, for a total of 1390. Additional, less well-documented exposures have also been noted by the sponsor and adverse events of significance arising in the context of studies without CRFs, post-marketing surveillance, and published studies were also described.

4.1.1 Deaths

Three deaths in buprenorphine-treated subjects were noted in the studies of buprenorphine solution, and an additional death in a published, NIDA-sponsored study without CRFs was also reported. One death, a drug overdose, occurred 4 days after the last dose of buprenorphine. The other deaths (coronary thrombosis, sepsis in an HIV-positive subject, and cancer) were not judged attributable to buprenorphine. The sponsor also included reports of death in post-marketing surveillance of Subutex in France and low-dose buprenorphine tablets worldwide. Although post-marketing reports offer incomplete information, in over half of the Subutex-related deaths, clinical or laboratory data was available to suggest abuse of Subutex in conjunction with other drugs, often benzodiazepines. Deaths in the post-marketing experience with Subutex also included some related to hepatocellular damage, but a clear association with Subutex is difficult to establish, despite its known effect on hepatic enzymes.

4.1.2 Serious Adverse Events

The pre-specified definition of SAEs included elevations of hepatic enzymes ($>8 \times$ ULN) in CR96/013, CR96/014, CR92/099, and CR92/100. In addition, under the traditional definition of SAEs, inpatient detoxifications (often at patient request) were included because hospitalization was involved.

Excluding hospitalization for detoxification, there were 5 (of 216) buprenorphine-treated subjects who experienced SAEs during the controlled portion of the clinical trial of the

tablet formulations. These included one seizure, one episode of endocarditis, one episode of vomiting and diarrhea, and two occurrences of suicidal ideation. In the placebo-treated group (103), there were one report of infection, one of cancer, and one of elevated LFTs.

There were 57 (of 497) subjects who experienced SAEs during open-label treatment. Five events (in subjects who may or may not have reported other events) were inpatient detoxifications. In the solution studies, 98 of 813 buprenorphine-treated subjects experienced SAEs. The most commonly-reported SAE was elevated LFTs (46 subjects), discussed below.

4.1.3 Discontinuations Due to Adverse Events

Overall, there were few discontinuations attributed to adverse events. Many of these were attributed to withdrawal symptoms, which might be an adverse event associated with the drug but is more probably a result of lack of efficacy, rather than lack of tolerability. The rate of discontinuations due to adverse events was similar in the pooled solution studies and in the combination treatment arm of the tablet study (which included the open-label extension).

4.1.4 Common Adverse Events

Comparisons to placebo or control (methadone) are difficult for non-serious adverse events because the placebo-controlled phase of the tablet study (CR96/013) was only four weeks long. The methadone-comparison study, while a more clinically relevant duration, used a 14-item checklist for collecting non-serious events and did not elicit information about other adverse events. The dose-controlled solution study, CR92/099, gives some opportunity to compare incidence across doses. In addition, the two flexible dose extensions (CR96/014 and CR92/100) allow some dose comparisons, but it should be noted that these allowed titration and may be confounded both by time and by differences among patients requiring different maintenance doses.

Commonly reported events included headache, insomnia, constipation, anxiety, sedation, nausea, and dizziness. In the blinded dose-controlled solution study (CR92/099) there appeared to be some reverse dose-dependence of certain terms attributable to withdrawal (diarrhea, vasodilation, lacrimation disorder) but other terms also attributable to withdrawal (e.g. vomiting) showed a positive association with dose (Table 20 in Dr. Scheinbaum's review of NDA 20-733). In the flexible-dose extension studies, Dr. Lee noted a dose-response pattern to a number of adverse events, many of which are attributable to withdrawal. Some, but not all, showed a dose-dependent pattern in both the solution study (CR92/100) and the Suboxone study (CR96/014); these might be explained by a need for higher doses in patients with more complaints of withdrawal.

Dr. Lee also undertook an assessment of the relationship between adverse events and hepatic enzymes. No adverse events were more common in subjects with abnormal LFTs than in subjects with normal LFTs. Conversely, where differences existed, they were in the opposite direction.

4.1.5 Laboratory Assessments

Clinical laboratory monitoring in CR96/013 and CR96/014 included assessments of serum chemistry, hematology, and urinalysis. Dr. Lee's review notes no treatment emergent, clinically significant changes in kidney function, hematologic parameters, or urinalysis. However, an effect of buprenorphine on hepatic function has been observed.

As noted above, abnormal LFTs were not unusual in the safety population. Baseline LFT abnormalities are common in this population, and are attributed to viral and chemical causes (e.g. drugs of abuse, alcohol). However, an effect of buprenorphine on LFTs was observed earlier in development, and Studies CR96/013, CR96/014, CR92/099, and CR92/100 defined LFTs >8x ULN as serious adverse events. In fact, this was the most commonly-reported SAE in the database (46 subjects). The relatedness of these events to buprenorphine treatment was assessed by identifying other contributing factors, which often included viral hepatitis and alcohol. Many subjects were seropositive at baseline for Hepatitis B and/or C. Elevations in enzymes in these subjects were occasionally attributed to exacerbation of pre-existing viral hepatitis, which, although plausible, does not argue convincingly against a drug effect. However, some seroconversions occurred during treatment, and these represent persuasive alternative explanations for acute transaminitides. Four of ten reports in CR96/013/014 can be thus explained. Insufficient detail is available to closely examine the relatedness of the 35 events in CR92/099/100 and the one in CR88/130, but the sponsor provided a table with brief comments on alternative etiologies for CR92/099/100. Thirteen of 35 listings offer an alternative explanation with some confidence. Therefore, over half of the reports of LFTs >8 x ULN might be attributed to buprenorphine, but lack of comparator makes this difficult to assess.

Analysis of shifts upwards or downwards from baseline in the four-week placebo-controlled study (CR96/013) showed no difference among Suboxone, Subutex, or placebo for AST, ALT, and LDH, with more shifts upwards than downward. The number of shifts from normal or high to "clinically abnormal" (possibly clinically significantly abnormal) was similar across groups for AST and ALT. For total bilirubin, four patients, two on each active treatment, showed shifts from normal to high or clinically abnormal, compared with none in the placebo group. For GGT, both active treatment had more downward shifts than upward shifts, compared to placebo which showed the opposite pattern. Shift tables from the 52-week extension (CR96/014) show that shifts from normal to abnormal appear to occur within the first four weeks and further shifts are not seen later in treatment. Similarly, the proportion of patients with possibly clinically significantly abnormal LFTs (about 1% at baseline) increases to about 4-5% by week 4 (the first measurement) and remains stable for the remaining weeks. Attrition does not seem to involve subjects with abnormal LFTs preferentially.

In the the solution studies, shifts from normal to abnormal AST occurred in 8-10% of buprenorphine subjects, without dose effect. By comparison, shifts were seen in 14% of methadone subjects. Shifts in ALT were seen in 8-17% of buprenorphine subjects, without dose effect, and in 16% of methadone subjects. As in the tablet study, an

increase in the proportion of subjects with possibly clinically significantly abnormal LFTs occurred early in the study (within 8 weeks), but greater fluctuation was seen thereafter than in the tablet study. It did not appear that late-onset hepatotoxicity explained the fluctuations; rather it was a result of the changing denominator due to attrition from the study.

Although Dr. Lee noted no treatment emergent, clinically significant changes in hematologic parameters, he observed that a large number of subjects had elevated eosinophil counts. I examined shift tables for the solution studies, which revealed a dose-dependent trend in the shift from normal to abnormally high eosinophil counts. Line listings reveal counts as high as 30 in one case, and several in the mid-20s. In many subjects, the finding was transient and resolved by the end of treatment. Eosinophilia is not unexpected in injection drug users, but a relationship to buprenorphine dose is difficult to explain.

4.1.6 ECGs

ECGs were obtained in CR96/013 and CR96/014 for all subjects at baseline and monthly visits. In Study CR92/099, 516 subjects had a baseline assessment and at least one additional assessment during treatment. The incidence of ECG abnormalities was high at baseline, and when evaluating the percent of subjects with abnormalities, no pattern emerges over time or across doses. A table of new abnormalities noted at week 4 or week 16 was provided (Appendix A), but it is not clear how many separate patients are encompassed. The abnormalities included most commonly sinus bradycardia, nonspecific ST/T wave changes (NSSTWΔ), and “other rhythm abnormalities.” Although sinus bradycardia was commonly noted on EKG, clinically significant bradycardia was not often observed during vital sign assessment. An apparent dose-dependence of new-onset NSSTWΔ at four weeks was less clear at 16 weeks. Although the dose-dependence is difficult to account for, non-specific changes suggestive of ischemia might be associated with cocaine use, common in this population. Other significant abnormalities suggestive of conduction defects included 1st and 2nd degree AV block, bundle branch blocks, and “other intraventricular conduction block.” Summing these together, there does not seem to be a dose-dependent pattern of conduction abnormality; similarly, summing together various non-sinus arrhythmias (including the non-specific category “other rhythm abnormalities”) does not reveal a dose-dependent pattern.

Shifts from overall normal to overall abnormal EKG occurred in 10 subjects in the 4 week double-blind study, CR96/013. This included 6 subjects on monotherapy, four subjects on combination therapy, and 0 subjects on placebo. The new abnormalities noted are listed in the table below.

Abnormalities Noted in ECGs with Shift from Overall Normal to Overall Abnormal at Week 4 in CR96/013

Site-subject #	Treatment	Abnormality
539-1013	Subutex	Prolonged QT (later normal)
689-1009	Subutex	Interval chg/wv [sic]
691-1013	Subutex	Sinus bradycardia; atrial complex
691-1096	Subutex	Sinus bradycardia, RBBB
578-1067	Subutex	Sinus bradycardia
691-1036	Subutex	Sinus bradycardia
578-1089	Suboxone	LVH, NSSTTA
578-1023	Suboxone	LVH
750-1060	Suboxone	Sinus bradycardia, low voltage QRS
750-1080	Suboxone	Ventricular conduction defect

Even focusing on abnormalities suggestive of conduction or rhythm disturbances, the absence of placebo-treated subjects in the group affected is striking. Closer review of the line listings reveals that some new abnormalities were reported in subjects whose baseline ECGs were overall abnormal, and some were reported in ECGs which were read as “overall normal.” One additional instance of new-onset QT prolongation occurred in a subject treated with placebo (662-1078), whose EKG was read as overall normal. This was the only treatment-emergent abnormality of rhythm or conduction seen in the placebo group on review of line listings. However, it should also be noted that this subject began open-label treatment at 12 mg/3 mg at week 5, and had an ECG without QT prolongation at week 8.

In the open-label safety study, four additional reports of new QT prolongation were noted. These included:

- Subject 629-2022, new entrant into open-label phase: QT prolongation at week 12. ECGs at weeks 24, 36 and 52 were overall abnormal, but QT prolongation was not reported. This subject remained in the study 364 days, and was receiving 16 mg/4 mg from week 2-week 37, then was tapered off.
- Subject 672-2068, new entrant into open-label phase: QT prolongation at week 4, no further ECGs reported. This subject was titrated from 8 mg/0 mg to 24 mg/6 mg by day 9, and remained on 24 mg/6 mg through the end of week 5. Reinduction was initiated on day 43 after 6 missed doses, and the subject was retitrated to 24 mg/6 mg and maintained on that dose through day 112.
- Subject 689-1064, assigned to combination treatment during double-blind phase: QT prolongation at week 36, week 52 ECG described as “no change.” This subject received 16 mg/4 mg from day 3 through 289 (week 42), followed by taper to 4 mg/1 mg through week 52.
- Subject 750-1070, assigned to combination treatment during double-blind phase: QT prolongation at week 24, later ECG read as “normal.” This subject received 16 mg/4

mg from day 3 through the end of week 25, then was increased to 20 mg/5 mg through the remainder of the 52 weeks.

In summary, QT prolongation in the open-label study was not associated in most cases with high doses, was usually transient, and resolved in the face of doses that were unchanged or, in some cases, increased.

Taken together with the lack of dose-dependence of significant abnormalities of rhythm or conduction in the dose-controlled solution study, it is difficult to attribute new ECG abnormalities unequivocally to buprenorphine.

4.1.7 Vital Signs and Weight

Vital signs were measured at baseline and monthly in Study CR96/013 and /014. Despite the frequency of “sinus bradycardia” noted on ECG, the incidence of vital sign abnormalities of possible clinical significance was low. Neither hypertension nor hypotension was noted in more than approximately 1% of the sample at any time point (except week 52, 2% systolic hypotension and 2% diastolic hypertension), and neither bradycardia nor tachycardia was observed in more than 1% of subjects. In the pooled data from the solution studies, where vital signs were also measured monthly systolic hypertension and diastolic hypotension were rare (<1% at all time points). Systolic hypotension was noted in 2-4% of subjects at various time points, and diastolic hypertension was also noted in 2-3% of subjects at various time points, but no clear pattern emerged.

The data on weight, however, showed a marked increase in the proportion of patients with “possibly clinically significantly high” values in Study CR96/014. Several patients gained substantial amounts of weight over the course of the 52 week safety study (20-50 lbs). No explanation or interpretation of this finding is offered, and because height data is missing, it is difficult to determine whether it may represent undernourished addicts attaining normal weight after a period of successful abstinence from illicit drugs.

4.2 Safety of Naloxone

The only additional safety issue concerns chronic exposure to orally administered naloxone at doses up to 6 mg/day (more typically 2 mg/day). Reckitt & Colman’s non-clinical studies show that the combination of buprenorphine and naloxone is not mutagenic, clastogenic, or teratogenic. Carcinogenicity studies are planned. Opiate antagonists are known to have effects on hypothalamic-pituitary function, but it is not known whether will be clinically relevant in this or other organ systems.. Naloxone was developed as a single-use agent for intravenous use, and a systematic evaluation of the chronic oral toxicity of naloxone is lacking. Four-week toxicity studies of orally administered combinations of buprenorphine and naloxone (although not in a 4:1 ratio) have been performed, but longer studies may be indicated to fully evaluate the safety of naloxone.

5 Effect of Naloxone on Abuse Liability of Buprenorphine Sublingual Tablets

Under 21CFR300.50(a)(2), 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 be 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.

The data presented in support of this conclusion consist of clinical pharmacology studies demonstrating that the combination of buprenorphine and naloxone, given intravenously in a 4:1 ratio, precipitates withdrawal in subjects maintained on other opiates. The validity of this claim is not in question.

The capacity of buprenorphine and naloxone (4:1) to precipitate withdrawal in many opiate addicts is expected to render it undesirable to intravenous drug users. It should be noted that individuals dependent on buprenorphine (licitly or illicitly obtained) and non-dependent drug abusers would likely be able to abuse Suboxone intravenously without experiencing withdrawal. Suboxone may also be abused sublingually or intranasally, as it has euphorigenic effects by these routes as well which are not expected to be affected by naloxone. This is expected to be of significance in the U.S. because a recent dramatic increase in heroin use, particularly among youth, has been attributed to the availability of increasingly pure heroin which does not need to be injected to achieve the desired effect. A series of questions and answers about buprenorphine, issued by NIDA, explains:

...there has been an increase in the amount of heroin of high purity. The high purity of this heroin has made it possible to nasally ingest (snort) or smoke heroin. This change in the route of heroin administration removes a major taboo, injection and its attendant use of needles, from initiation and experimentation with heroin use. The result of these new routes of administration is an increase in the number of younger Americans experimenting with, and becoming addicted to, heroin. The incidence of first-time use of heroin in the 12 to 17 year old group has increased fourfold from the 1980s to 1995.

Therefore, it may be expected that Suboxone's abuse potential is reduced compared to Subutex, but by no means eliminated.

However, from a public health perspective, the prevention of injection use of Suboxone by a population with a high rate of HIV and Hepatitis C seropositivity is an important benefit, and provides justification for the inclusion of naloxone in this combination drug product, as required under the combination drug policy (21CFR 300.50), even if the decrement in abuse liability is insufficient to justify differential scheduling of the two formulations.

6 Pertinent Issues from Review of Chemistry, Manufacturing, and Controls

The stability of the naloxone in Suboxone has been questionable. Current data suggest that

the sponsor has been unable to provide, as of this date, data explaining or accounting for degradation products. Naloxone is normally very stable, but in the to-be-marketed formulation, appears not to be. It has been speculated that

The sponsor has provided stability data to support expiration dating, and has shown that

Furthermore, the clinical supply of tablets (which were rather than appear not to have similar problems with stability. An used in clinical studies also appears to have improved stability. The chemistry review team speculates that the degradation of naloxone may be related to Therefore, although it may be possible to specify storage conditions in the label which will allow for commercially viable expiration dating, it should be noted that patients may be able to accelerate the degradation of naloxone through improper storage, either inadvertently or deliberately.

Because a very small amount of naloxone is usually needed to precipitate withdrawal in heroin-dependent individuals, the 8 mg/2 mg tablet is likely to continue to be aversive if injected in its entirety, However, addicts (particularly those without a high level of dependence) may find that, by using the 2 mg/0.5 mg tablet or divided portions of the 8 mg/2 mg tablet, it is possible to abuse the buprenorphine intravenously without receiving a sufficient dose of naloxone to precipitate withdrawal. This has important implications for the justification for including naloxone, discussed above, and requires rapid resolution.

In the short run, however, it may be argued that the abuse of the drug is related as much to the street drug abusers' expectations of how the drug will perform as to the actual experience with the drug. Therefore, should the combination product achieve a reputation for having the potential to precipitate withdrawal, it would be less likely to be abused even if, at the end of its shelf-life, it might actually be used without risk of withdrawal. While manipulation of storage conditions by addicts might also reduce the likelihood of precipitated withdrawal by hastening the degradation of naloxone, the street desirability of the product would be reduced by the need to undertake such manipulations.

7 Pertinent Issues from Review of Pharmacokinetics

In addition to the pharmacokinetic linkage issues described above, Dr. Doddapaneni has identified concerns related to the metabolism and excretion of the two components of Suboxone patients with hepatic failure. Dr. Doddapaneni notes that no studies were conducted to investigate the pharmacokinetics of buprenorphine and naloxone in hepatic failure patients. However, a general statement in labeling indicates that buprenorphine's pharmacokinetics may be changed in hepatic failure patients due to its predominant hepatic metabolism. Furthermore, population PK indicated that the clearance of

buprenorphine was decreased in patients with elevated bilirubin and ALT levels. Dr. Doddapaneni points out that naloxone is also hepatically metabolized, and the increased levels in hepatic failure patients might precipitate withdrawal. He recommends further Phase IV study, and that :

Notably, Dr. Lee examined the adverse event database to determine if any adverse events were more common in subjects with abnormal hepatic enzymes than in subjects with normal levels. None were noted, and, to the contrary, any differences were in the opposite direction. Nevertheless, I agree that further investigation is indicated and recommend that the Phase IV study be sufficiently detailed to elucidate what degree of hepatic impairment should signal concern.

8 Treatment Setting/Context:

No data have been developed to establish the optimal treatment setting or ancillary support and counseling which should be used with buprenorphine. However, it should be noted that the efficacy studies were carried out by investigators experienced in addiction treatment within the context of comprehensive treatment, including ancillary counseling. Historical misadventures involving methadone “prescription mills” demonstrated that the mere provision of a prescription for an opiate maintenance therapy is neither safe nor effective. The current system of methadone clinics arose in the early 1970’s in response to the public health problem related to unscrupulous prescription of methadone. At the time of approval of LAAM, the only other agonist drug intended for maintenance treatment of patients addicted to illicit drugs, the clinic system was in place and LAAM was introduced within that framework. Therefore, apart from the methadone experience, there is no precedent for introducing an opiate agonist for use specifically by addicts without a strict system of controls. The current system is properly undergoing assessment and restructuring, and I do not propose that buprenorphine should be restricted to distribution through the current clinic system. However, I believe measures to ensure that the drug will be administered as a component of a comprehensive approach to treatment will enhance the safety and efficacy of the drug, and post-marketing surveillance should be undertaken to assess the extent of abuse and diversion.

9 Conclusions

- Buprenorphine, the drug substance, is safe and effective for maintenance treatment of opiate addiction.
- Buprenorphine can be delivered, using sublingual tablets, in doses which have been shown to be safe and effective.
- Naloxone, included in this drug product to deter intravenous abuse, is not likely to 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, but further post-approval confirmation may be warranted.

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- Additional data are needed on the optimal administration of doses requiring more than two tablets in combination.
- Systematic data on the chronic oral toxicity of naloxone are lacking. These should be identified or developed.
- Naloxone may be expected to reduce the abuse liability of buprenorphine by deterring the diversion of this product for intravenous abuse. This represents a public health benefit due to the impact on the transmission of AIDS and Hepatitis C, and provides justification for the inclusion of naloxone in this combination drug product, as required under the combination drug policy (21CFR 300.50).

10 Recommendations

I recommend that Suboxone be approved with modified labeling. My proposed modifications are annotated in the attached label.

Further study of the safety of naloxone should be required as a Phase IV commitment.

Pharmacokinetic studies to determine the appropriate method of delivering doses of more than two tablets should be required, leading to a labeling amendment that provides more precise instructions to clinicians as quickly as possible.

The effect of hepatic impairment of varying degrees upon the pharmacokinetics of buprenorphine and naloxone should be evaluated.

Because use of this product outside the current closed-distribution system used for methadone treatment is envisioned, post-marketing surveillance for abuse and diversion is recommended.

Appendix A

Table 111
Occurrence of New ECG Abnormalities by Treatment Group for CR92/099^{1,2}

Cardiac Pathology	Week 4				Week 16			
	1 mg	4 mg	8 mg	16 mg	1 mg	4 mg	8 mg	16 mg
No. Subjects Completing Week 16					N=74	N=83	N=98	N=110
1. Left atrial hypertrophy	0	1	0	0	0	1	0	0
2. Right atrial hypertrophy	0	1	0	0	0	1	0	0
3. Left ventricular hypertrophy	1	2	2	3	1	1	1	1
4. Right ventricular hypertrophy	0	0	0	0	0	0	0	0
5. Acute infarction	0	0	0	0	0	0	0	0
6. Subacute infarction	0	1	0	0	0	0	1	0
7. Old infarction	0	0	0	0	1	0	0	0
8. Myocardial ischemia	0	0	0	0	0	1	1	2
9. Digitalis effect	0	0	0	0	0	0	0	0
10. Symmetrical T-wave inversions	1	1	1	0	1	0	0	0
11. Poor R-wave progressions	1	0	0	1	1	0	0	0
12. Other non-specific ST/T	4	3	6	11	3	1	4	7
13. Sinus tachycardia	0	2	2	0	0	0	1	0
14. Sinus bradycardia	4	8	8	10	4	10	10	5
15. Supraventricular premature beat	0	1	1	0	0	3	3	0
16. Ventricular premature beat	1	2	0	1	1	3	0	1
17. Supraventricular tachycardia	0	0	0	0	0	7	0	0
18. Ventricular tachycardia	0	0	0	0	0	3	0	0
19. Atrial fibrillation	0	0	0	0	0	0	0	0
20. Atrial flutter	0	0	0	0	0	0	0	0
21. Other rhythm abnormalities	3	5	5	4	2	5	1	3
22. Implanted pacemaker	0	0	0	0	0	0	0	0
23. 1 st degree A-V block	1	1	2	2	0	0	3	0
24. 2 nd degree A-V block	0	1	0	0	0	0	0	0
25. 3 rd degree A-V block	0	0	0	0	0	0	0	0
26. LBB block ³	2	0	0	0	0	0	0	0
27. RBB block ⁴	0	1	0	0	0	1	1	0
28. Pre-excitation syndrome	0	0	0	0	0	0	1	0
29. Other intraventricular conduction block	2	3	1	2	2	2	2	2
30. Overall ECG results - abnormal	7	6	3	3	1	3	5	2

¹ Based on subjects who had a baseline assessment and 1 ECG assessment during treatment (N=516).

² If Week 4 and Week 16 assessments for a particular ECG parameter indicated an "adverse" change from baseline, each "adverse" change was counted for the respective period.

³ LBB= left bundle branch

⁴ RBB= right bundle branch



Chite

Food and Drug Administration
Rockville MD 20857

NDA 20-733

Reckitt & Colman Pharmaceuticals
1909 Huguenot Road (Suite 300)
Richmond, Virginia 23235

NOV - 2 1999

Attention: Alan N. Young
Director, Regulatory Affairs

Dear Mr. Young:

Please refer to the teleconference between representatives of your firm and FDA on October 27, 1999. The purpose of the teleconference was for the Agency's chemist to alert you of problems encountered while reviewing the stability for Suboxone tablets so that you could consider alternatives in packaging and storage conditions.

As promised, a copy of our minutes of that teleconference is enclosed. Please notify us of any significant differences in understanding you may have regarding the meeting outcomes. As you requested, also enclosed is a copy of the minutes of the teleconference between representatives of your firm and FDA on August 19, 1999.

If you have any questions, please contact Tony Chite, P.D., Regulatory Project Manager, at (301) 827-7410.

Sincerely,

[*/S/*]

Corinne P. Moody
Chief, Project Management Staff
Division of Anesthetic, Critical Care and
Addiction Drug Products, HFD-170
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

**APPEARS THIS WAY
ON ORIGINAL**



Memorandum of Telecon Meeting Minutes

Meeting Date: October 27, 1999

Time: 9:30 a.m.

Location: Parklawn Building – 9B 45

Type of Meeting: TELECON

NDA # / Drug Name: 20-733/ Suboxone

Sponsor: Reckitt & Colman Pharmaceuticals

Meeting Chair: Albinus D'Sa, Ph.D.

FDA Attendees:

Titles:

Albinus D'Sa, Ph.D.
Pramod Maturu, Ph.D.
Tony Chite, P.D.

Chemistry Team Leader
Chemistry Reviewer
Consumer Safety Officer

Applicant Attendees:

Titles:

Charles O'Keefe
Don Walter, Ph.D.
Grant Kelly
Neal Hyde
Alan Young

President, Reckitt & Colman

NIDA Attendees:

Nora Chiang

Purpose of the Telecon

The purpose of the teleconference was for the Agency's chemist to alert the applicant of problems encountered while reviewing the stability data for Suboxone tablets so that the applicant could consider alternatives in packaging and storage conditions.

Introduction:

The Agency's chemist, Pramoda Maturu, Ph.D., upon reviewing the applicant's submission dated October 5, 1999, noted that there were problems with the

stability of the tablet. The orange tablet did not appear to meet the assay specification for naloxone. The loss in potency for naloxone appeared to be due to . The room temperature data indicated that the product could not meet the specification for the orange tablet beyond . However, within the October 5, 1999, submission the Agency was provided with data from NIDA's files in the submission which indicated that a longer expiration date was possible if the applicant used packaging.

During the telecon the following information was requested from Nora Chiang of NIDA for the drug product.

1. The certificate of analysis (COA) for packaged Suboxone lots in
2. The retest results for these lots to support stability for the clinical study duration.
3. The test methods used for stability.
4. The suppliers for the with the corresponding DMF's and LOA to DMF.
5. CFN# if any for the packaging site,

Suboxone bulk tablets are identified as : 2mg/0.5 mg - Suboxone tablets: 6001/070, 6001/085, 6001/136, 6001/186;
8mg/2mg - Suboxone tablets: 6001/071, 6001/086, 6001/137, 6001/185

The applicant was informed that the stability data that was provided would qualify them for an expiration date of only . There was a mutual sharing of data to illustrate this point. The applicant was asked to comment on the stability of naloxone in the tablet. The applicant indicated that naloxone in the tablet was affected by

as illustrated in the fax dated October 27, 1999.

The applicant was asked if that generated this degradation product could be initiated by a . In response, the applicant agreed with the Agency that because the product did not show this degradation, therefore it is possible that the product is

The applicant maintained that the final packaged product . When asked if the applicant had any data for the agency was informed that no data existed as of October, 1999, and that such studies are currently in progress. On further inquiry, it appeared that the applicant was conducting studies to address the degradation of the naloxone. The agency was told that the degradants issue is now a research and development project.

The applicant was told by the Agency that a longer expiration date for the product could be considered only if the product was refrigerated or if the product was marketed in a package similar to the one NIDA used in their clinical studies.

The applicant took this advice under consideration and agreed to respond to the proposal. The applicant was also asked to have at least tentative specifications for degradation products of naloxone in categories of each individual specified, unspecified, and total impurities per ICH Q3B guidance. A commitment to finalize the specifications within 6 months was also requested and agreed upon by the applicant.

In addition, the applicant was asked to provide an explanation and amend the file to reconcile the methods validation data, which indicated ~~no~~ recovery and the new findings as reported in the October 5 submission on stability studies that showed ~~no~~ recovery of naloxone.

Finally, the applicant was asked to provide a complete response to address the issues raised in the August 19th telecon. The applicant was informed that the October 5th submission was incomplete because it did not address the full list on the information request. The seven items of information as indicated in the August 19 telecon were read as follows:

- 1 Provide all available stability data on Suboxone tablets.
- 2 Provide all available reports to examine why a drop in Naloxone potency did not result in an increase in related compounds.
- 3 Submit uniformity of drug substance in ~~the~~ development pharmaceuticals and process development reports.
- 4 Delete ~~the~~ as manufacturing site for Buprenorphine HCl drug substance.
- 5 Add tests for ~~the~~ and ~~the~~ impurities to release Suboxone tablets. You have proposed testing for ~~the~~ batch every 6 months.
- 6 Provide linkage between clinical protocol number and Suboxone lots, and Certificate of Analysis (COA) for Suboxone lots and drug substance lots.
- 7 Provide analytical test results, ~~the~~ test results and acceptance criteria for the release of ~~the~~ and ~~the~~ used for packaging primary stability lots and clinical test lots of Suboxone tablets.

In summary the applicant has to:

- Respond completely to the August 19, 1999 telecon requests
- Respond to the five items provided to NIDA
- Provide a commitment to set specs for impurities of naloxone which will be based on data and chromatograms submitted to the file.

- Respond to the Agency's proposal for storage and packaging.
- Reconcile the methods validation data.

Charles O'Keefe stated that he would have this information faxed to the chemists on Friday, October 29, 1999, with the exception of the reports loss, the permeation and moisture report, and the plans for degradation which will be sent on approximately November 18, 1999.

Minutes prepared by Tony Chite

Chair Concurrence by Albinus D'Sa, Ph.D. (Chemistry Team Leader)

Signature [|S|] 11/2/99

**APPEARS THIS WAY
ON ORIGINAL**

CONSULTATION REQUEST/RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE SENT: October 21, 1999

DUE DATE: N/A

OPDRA CONSULT #: 99-044

TO (Division): Cynthia McCormick, M.D.
Director, Division of Anesthetic, Critical Care, and Addiction Drug Products
(HFD-170)

PRODUCT NAME: Suboxone™
(Buprenorphine HCl/Naloxone HCl)
Sublingual Tablets

MANUFACTURER:

Reckitt & Colman Pharmaceuticals Inc.

NDA#: 20-733

CASE REPORT NUMBER(S): N/A

SUMMARY:

In response to the request by the Division of Anesthetic, Critical Care, and Addiction Drug Products, OPDRA conducted a review of the potential name confusion between the proposed proprietary name, Suboxone™, and other approved proprietary/generic names. This review includes a study conducted within OPDRA with emphasis on the evaluation of the potential medication errors in handwriting and verbal communication of this proposed proprietary name.

OPDRA RECOMMENDATION:

OPDRA has no objections to the use of the proprietary name, Suboxone™. See review.

[/S/] 11/1/99
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Center for Drug Evaluation and Research
Food and Drug Administration

**Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B-03
Center for Drug Evaluation and Research**

Proprietary Name Review

DATE OF REVIEW: **October 21, 1999**

NDA#: **20-733**

NAME OF DRUG: **Suboxone™ (Buprenorphine HCl/Naloxone HCl)
Sublingual Tablets**

NDA HOLDER: **Reckitt & Colman Pharmaceuticals Inc.**

I. INTRODUCTION

This consult is in response to a request sent on August 5, 1999, from the Division of Anesthetic, Critical Care, and Addiction Drug Products to review a proposed proprietary drug name, Suboxone, regarding potential name confusion with other proprietary/generic drug names. In addition, the container labels and carton labeling were reviewed for possible interventions in minimizing potential medication errors.

The proposed proprietary name, Suboxone, was previously reviewed by the Labeling and Nomenclature Committee (LNC) in September 1999 and was found to be acceptable. The LNC commented on the overemphasis of the naloxone component of the name.

PRODUCT INFORMATION

Suboxone sublingual tablets contain buprenorphine HCl and naloxone HCl dihydrate at a ratio of 4:1 (buprenorphine : naloxone). Suboxone is a partial agonist at the mu-opiate receptor and an antagonist at the kappa-opiate receptor for the treatment of opiate dependence. In studies, plasma levels of buprenorphine and naloxone increased with sublingual dose of Suboxone, but was not proportional to the dose. There was a wide inter-patient variability in the sublingual absorption of buprenorphine and naloxone from Suboxone tablets, but within subjects, the variability was low. The elimination half-life of buprenorphine from plasma was very long (overall mean 37.3h, range 16h to 160h) compared with naloxone (overall mean 1.06h, range 0.39h to 2.45h). Buprenorphine is conjugated in the liver and eliminated primarily via the bile resulting in about 70% of the dose excreted in the feces. Naloxone is metabolized in the liver by glucuronide conjugation and excreted in urine. Suboxone sublingual tablets are available in two dosage strengths, 2 mg buprenorphine/ 0.5 mg naloxone and 8 mg buprenorphine/ 2 mg naloxone. The sublingual tablets are dissolved within 2 to 10 minutes. Up to two tablets can be taken at any one time. A number of different regimens for the detoxification have been investigated.

II. RISK ASSESSMENT

In order to predict the potential medication errors and to determine the degree of confusion of this proposed proprietary name, Suboxone, with other drug names, the medication error staff of OPDRA searched American Drug Index (42nd Edition), Drug Facts and Comparisons (1998 Edition), PDR (53rd Edition, 1999), Drug Product Reference File (DPRF), and EES (Established Evaluation System) for possible sound-alike or look-alike names to approved and unapproved drug products. A focus group discussion was conducted to review all of the findings from the searches. In addition, OPDRA conducted a study of written and verbal analysis of the proposed proprietary name employing health practitioners within OPDRA to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate an actual practice setting.

Study conducted within OPDRA

1) Methodology

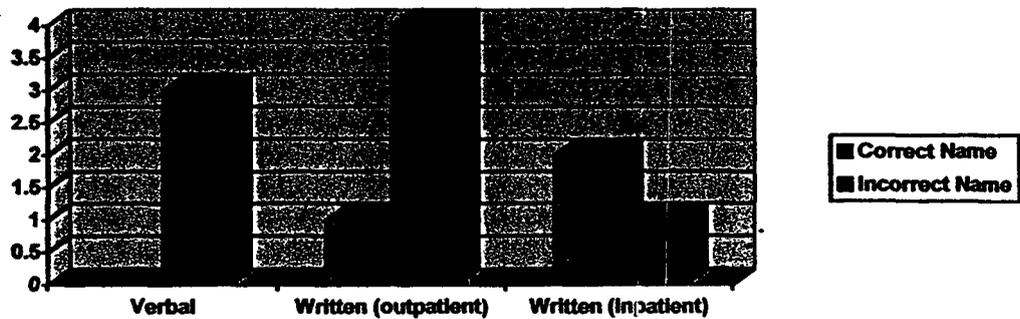
This study involved 18 health professionals comprised of pharmacists, physicians, and nurses within OPDRA to determine the degree of confusion between Suboxone and other drug names due to the similarity in handwriting and verbal pronunciation of the name. Random samples of the written orders, either inpatient or outpatient, were delivered to the participating health professionals via e-mail. In addition, verbal orders for Suboxone via voice mail were sent to the participating health professionals for their review. After receiving the prescription orders, the participants sent their interpretations of the prescriptions via e-mail to the medication error staff. After receiving the interpretations, the correct spelling of the proposed proprietary name was sent to the health professionals with a request for handwriting samples of the names. The medication error staff then reviewed the samples of the handwritten names.

Although this drug is indicated for the treatment of opiate dependence, this study involved written and verbal prescription orders since this drug may not be prescribed only by physicians registered for narcotic detoxification maintenance programs.

2) Results

We received responses from eleven participants, three of which correctly interpreted the proposed proprietary name, Suboxone. Three interpretations for verbal orders, five for outpatient written orders, and three for inpatient written orders were received. The results are as follows:

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Incorrect names include: Suboxon, Siloxone, Silroxone, Saboxon, Zeboxone, Suloxone & Subacone

Focus Group Findings

The proposed proprietary name, Suboxone, has a similar ending, “-oxone” as naloxone, which is a narcotic antagonist used in suspected acute opioid overdose. According to the United States Adopted Names Council (USAN), the stem, “nal-” is defined as narcotic agonists/antagonists. Although the stem, “-oxone” is not defined as the reversal of a drug, the combination of these two stems represents a drug which is a narcotic antagonist. However, this association is not sufficient to suggest that Suboxone will be mistaken for a narcotic antagonist and render the name objectionable.

Discussion

The results of the verbal and written analysis studies demonstrate that three out of eleven participants interpreted the proposed proprietary name correctly. We recognize that low scores of correct interpretations would be common for all unapproved drug product names because health professionals are not familiar with the name. However, in this case, the inaccurate interpretations of the proposed tradename, Suboxone, did not overlap with any existing approved drug products. Moreover, the searches in available texts, databases, and the handwriting samples did not produce any significant new information to render Suboxone objectionable.

Addendum

There is a safety risk for misuse of the sublingual form of buprenorphine. In order to deter use by injection, naloxone has been added as the second ingredient in Suboxone. OPDRA conducted a search in the Adverse Event Reporting System (AERS) to present medication error reports that were received regarding this issue and to increase awareness of the possibility of misuse.

Twenty-five reports were received from France of intravenous injection of buprenorphine (Subutex) sublingual tablets. In addition, there was one report of intranasal administration, one report of inhalation, and another report of intra-arterial injection of Subutex. In total, thirteen reports were received in 1998 and fifteen reports in 1999. There were two deaths and two amputations associated with the intravenous injection of Subutex. In addition, the misuse of buprenorphine sublingual tablets resulted in or

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prolonged twenty-two inpatient hospitalizations. Other reactions include respiratory distress, acute opiate intoxication, pulmonary embolism, acute chest pain, myocardial infarction, withdrawal symptoms, superficial venous thrombosis, abscess, agitation, fever, anemia, pancytopenia, skin necrosis, axillary adenopathy, acrocyanosis of fingers, vasculitis, arthralgia, DIC, cytolytic hepatitis, dyspnea, and local inflammation.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the packaging and the labeling of Suboxone, OPDRA has attempted to focus on safety issues relating to possible medication errors. Many of the items discussed in this consult involve issues normally reviewed by the chemist and the medical officer.

OPDRA has reviewed the current labeling and has identified several areas of possible improvement, which might minimize potential user error.

- **CARTON LABELING (2 mg/ 0.5mg & 8 mg/ 2 mg)**