[

]

IV. RECOMMENDATIONS

A. OPDRA has no objections to the use of the proprietary name, Suboxone.

B. OPDRA recommends the above labeling revisions which might lead to safer use of the product.

OPDRA would appreciate feedback of the final outcome of this consult (e.g. copy of the revised label/labeling/packaging). We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Lauren Lee, Pharm.D. at (301)827-3243.

[/S/] 11/1/99

Lauren Lee, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

[/S/] 11/1/99

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

APPEARS THIS WAY
ON ORIGINAL

ABUSE LIABILITY REVIEW

NDA #: 20-733

TRADE NAME: SUBOXONE®

DRUG: Buprenorphine Hydrochloride /Naloxone Hydrochloride Sublingual Tablets

SPONSOR: Reckitt & Colman Pharmaceuticals, Inc.
(The National Institute on Drug abuse (NIDA) and Reckitt & Colman have entered a Cooperative Research & Development Agreement (CRADA) to develop the product for the indication. Through NIDA-funded studies, buprenorphine has been studied for the indication under 47 different INDs)

PROPOSED INDICATION: Treatment of Opiate Dependence

DOSAGE FORMS: Sublingual tablets of 2 mg buprenorphine + 0.5 mg naloxone and 8 mg buprenorphine + 2.0 mg naloxone

DATE OF NDA SUBMISSION: June 7, 1999

DATE OF REVIEW: October 7, 1999

REVIEWER: Michael Klein, Ph.D. [/S/]

The Sponsor submitted for Agency review the following data and information in NDA # 20-733, as the abuse liability section of the NDA:

1. Summary and description of drug abuse and dependence studies on buprenorphine dosage forms.

   This includes some preclinical studies described in the original buprenorphine product (Buprenex; NDA # 18-401) which are applicable to the abuse liability assessment of the NDA # 20-733 and # 20-732.

2. Actual experience reports of abuse of sublingual preparations of buprenorphine marketed worldwide:

   a. France
   b. New Zealand
   c. United Kingdom
   d. Ireland

APPEARS THIS WAY ON ORIGINAL

e. Scotland
f. Spain
g. India
h. Australia
i. Others (Belgium, Sri Lanka, Germany)

3. Description of issues related to abuse in NDA clinical, pharmacokinetics and chemistry sections.

4. Recommendation in the form of an eight factor analysis to place the combination product and the single entity buprenorphine (Subutex®) product (NDA # 20-732) into Schedule V. Although buprenorphine was recommended for Schedule III in the pharmacology/toxicology review (March 12, 1981), final placement of the product and substance was in Schedule V (1985).

In addition, subsequent to filing the original submission, the National Institute on Drug Abuse (NIH/NIDA/MDD) provided additional data:

1. Information on overdoses of buprenorphine reported in France.

2. Results of a NIH-funded study (U.S. Public Health Service Research Scientist Award K05 DA00050, Scientist Development Award K02 DA 00332, and R01 DA08045 from the National Institute on Drug Abuse) entitled "Effects of buprenorphine versus buprenorphine/naloxone tablets in non-dependent opioid abusers" that has been sent to the journal Psychopharmacology for publication.

BACKGROUND:

Jasinski *et al.* (1978) were the first to look at the pharmacology and abuse potential of buprenorphine. Incarcerated male volunteers with histories of narcotic addiction were given single or repeated doses of buprenorphine. The single dose study showed buprenorphine to have typical morphine-like effects. However, unlike morphine which produces effects for approximately 4 to 5 hours, buprenorphine was found to produce effects through a 72-hour observation period following administration. Initially in the repeated dose study, 5 subjects were administered daily doses of buprenorphine. Three of the 5 subjects completed the experiment and received buprenorphine for 57 consecutive days. After the 57th day, buprenorphine was abruptly discontinued. Several days after the cessation of buprenorphine was abruptly discontinued. Several days after the cessation of buprenorphine, subjects began experiencing severe withdrawal symptoms which were alleviated by gradual, decreasing doses of morphine and diazepam.

Jasinski *et al.* felt that any substance that has the ability to produce subjective morphine-like feelings of euphoria, and which can lead to physical dependence has the potential for abuse. Buprenorphine was shown to have both of these properties. However, because of its long-lasting effects and the low doses needed to induce morphine-like euphoria, the

potential for abuse was judged to be less than that of heroin and addicts might be successfully maintained on doses administered less frequently than once daily. However, with increasing numbers of reports of abuse of buprenorphine, that conclusion has been increasingly questioned. (Jasinski D. R., Pevnick J. S., Griffith J. D. Human pharmacology and abuse potential of the analgesic buprenorphine. Arch. Gen. Psych., 35:501-516, 1978).

ABUSE POTENTIAL STUDY OF SUBLINGUAL BUPRENORPHINE PRODUCTS

Study: Effects of Buprenorphine Versus buprenorphine/Naloxone Tablets in Non-dependent Opioid Abusers

Investigators: [redacted]

Rationale: The characteristics and abuse potential of intact buprenorphine and buprenorphine/ naloxone tablets in non-dependent opioid abusers has not been determined. Non-parenteral abuse of opioids such as buprenorphine may be more likely in people who have less severe substance abuse disorders (that is, are not physically dependent upon opioids). While non-dependent opioid abusers may dissolve and inject tablets, such populations with less severe levels of opioid abuse will have lower rates of injecting drug use. These non-dependent abusers may experiment and abuse buprenorphine tablets via the sublingual route, if sufficient opioid agonist effects are produced. The purpose of this study was to examine the pharmacologic characteristics of sublingual buprenorphine/ naloxone tablets in non-dependent abusers, determining if buprenorphine effects are modulated by the addition of naloxone, and assessing the relative abuse potential of sublingual buprenorphine/naloxone tablets in this population.

Objectives: To assess the abuse potential of sublingual buprenorphine and buprenorphine/ naloxone tablets in non-dependent opioid abusers.

Subjects: 7 Adult volunteers with active opioid abuse, but not physically dependent (6 males/ 1 female); average age 38.4 years (range 33-47 years). The number of illicit opioid uses per week was between 1 and 4.

Study Setting: In-patient. Urine samples collected at admission and intermittently throughout participation and tested for the presence of illicit drugs using an EMIT system.

Study Procedure: Participants were monitored drug-free for a minimum of 48 hours after admission to study site to ensure they had no evidence of physical dependence on opioids. Each subject participated in a minimum of 13 experimental sessions and resided on the ward for 7 weeks.

Laboratory Sessions: Subjects were informed they may receive combinations of buprenorphine and naloxone, and other opioid agonist medications or placebo. Subject and observer questionnaires were presented and responses entered. Examples of opioid agonists and antagonists and the types of effects produced by each were described to participants. Sessions lasted 3½ hours. 15 minutes after the start of each session, 15 minutes of baseline physiological data were obtained, all subject and observer questionnaires were completed. 30 Minutes after the start of the session, participants received an intramuscular injection followed by the administration of sublingual tablets. The session then continued for 3 hours, with collection of data.

Drugs & Doses: Sublingual buprenorphine (4, 8, 16 mg) sublingual buprenorphine/naloxone (1/.25, 2/.5, 4/1. 8/2. 16/4 mg), as well as intramuscular hydromorphone (2, 4 mg) [serving as positive opiate agonist control] and placebo in laboratory sessions conducted twice per week. All medications were administered using double-blind and double-dummy procedures.

Measures:

1. Physiological measures: heart rate, blood pressure, skin temperature, respiratory rate, pupil diameter, and oxygen saturation.
2. Subject and Observer measures: Subjective effect reports and observer rating questionnaires were completed 15 minutes before and at 15 minute intervals up to 180 minutes following drug administration. Subjects completed visual analog scales (High, Drug Effects, Good Effects, Bad Effects, Liking, and Sick), a pharmacological class questionnaire, and an adjective rating questionnaire. Each scale was a horizontal line on the computer screen, and the subject positioned an intersecting vertical line along the horizontal line. Ends of the horizontal line were labelled "None" and "Extremely" and responses were scored proportionately on a 100-point scale. The pharmacological class questionnaire asked the subject to select one of 10 drug classes to which the administered drug was most similar. The adjective rating questionnaire consisted of 37 items which the participant rated on a 5-point sclae from 0 (not at all) to 4 (extremely); the items constituted 2 scales: a 16-item opioid agonist scale (morphine-like effects), and a 21-item Withdrawal scale (adjectives associated with opioid withdrawal-like effects). Ratings for individual item were summed for a total score for each scale. Observer ratings included the same adjective rating scale, as well as an assessment of 7 signs of opioid withdrawal (lacrimation, rhinorrhea, perspiration, piloerection, bowel sounds, yawing and restlessness). Each opioid withdrawal item was scored either 0, 1, or 2 (with higher scores corresponding to greater severity), and scores for all items were summed to prodcue a total observer Withdrawal Signs Score. These ratings were done at the same times as the subject ratings. Item ratings were summed to produce total scores for the Agonist and Withdrawal scale.
3. Psychomotor/Cognitive Performance measures: 3 Tasks were completed during the session: a computerized form of the Digit Symbol Substitution Task, a Circular Lights Task, and a computerized form of the Trail-Making Test. Results were summarized for sequence errors and length of work product. Each of the 3 tasks were

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.