DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development(HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

October 27, 1994

Reckitt & Colman Pharmaceuticals, Inc.
Attention: Mr. Charles O'Keeffe
Executive Vice President
1901 Huguenot Road
Richmond, VA 23235

Dear Mr. O'Keeffe:

Reference is made to your orphan drug application of November 29, 1993 submitted pursuant to Section 526 of the Federal Food, Drug, and Cosmetic Act (FFDCA) for the designation of buprenorphine in combination with naloxone as an orphan drug (application [redacted].

We have completed the review of this application and have determined that buprenorphine in combination with naloxone qualifies for orphan designation for the treatment of opiate addiction in opiate users under Section 526(a)(2)(B) of the FFDCA. Please note that it is buprenorphine in combination with naloxone and not its formulation that has received orphan designation.

Prior to marketing approval, sponsors of designated orphan products are requested to submit written notification to this Office of their intention to exercise orphan drug exclusivity if they are the first sponsor to obtain such approval for the drug. This notification will assist FDA in assuring that approval for the marketing of the same drug is not granted to another firm for the statutory period of exclusivity. Also please be advised that if buprenorphine in combination with naloxone were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA. Therefore, prior to final marketing approval, sponsors of designated orphan products are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

In addition, please inform this office annually as to the status of the development program, and at such time as a marketing application is submitted to the FDA for the use of buprenorphine in combination with naloxone as designated. If you need further assistance in the development of your product for marketing, please feel free to contact Dr. John McCormick at (301) 443-4718.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

Marlene E. Haffner, M.D., M.P.H.
Director

cc:
HFD-85/M.A.Holovac
HFD-007
HF-35/OP File [redacted]
HF-35/B.Steeves
HF-35/chron
HF-35/P.Vaccari 10/27/94 dsg.790

10/27/94

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Review of a Request for Orphan Drug Designation

[redacted]

Date of submission: November 29, 1993
Received by reviewer: December 2, 1993
Review initiated: June 15, 1994
Review completed: October 21, 1994

Designation [redacted]

Drug Name:
code name:
generic name: buprenorphine hydrochloride in combination with naloxone (Buprenorphine/Naloxone)

trade name: not yet assigned

Sponsor's Name:
Reckitt & Colman Pharmaceuticals, Inc.
1901 Huguenot Road
Richmond, Virginia 23235

Contact Person:
Charles O'Keeffe, Executive Vice President
Reckitt & Colman Pharmaceuticals, Inc.
1901 Huguenot Road
Richmond, Virginia 23235
(804) 379-1090

Drug Manufacturer:
Active drug substances and finished dosage form are manufactured by:
[redacted]

Proposed Designation:
For use in opiate detoxification and maintenance treatment schedules.

Regulatory Status:
Buprenorphine is presently marketed in the United States as an injectable analgesic under NDA 18-401. The sublingual formulation has not been approved; however, it is being studied under 4 IND's in the U.S.. Buprenorphine is marketed as an analgesic under the trade names Temgesic, Buprenex, Lepetan, and Buprex in numerous countries outside of the U.S. as an analgesic. The injectable is available in 42 countries, and the sublingual in 31. Naloxone has been added to the sublingual tablet in NZ to discourage diversion.

The buprenorphine/naloxone combination is currently marketed in New Zealand as Temgesic Nx; buprenorphine is also marketed as a mono product under the tradename Temgesic and New Zealand

regulates both products as controlled substances but places the mono product in a higher, more controlled schedule, than the combination product.

Naloxone is currently marketed in the United States as an injectable for adults and neonates by various manufacturers as a narcotic antagonist.

Disease/Condition Background Information:
The primary characteristic of opiates which promotes abuse is the feeling of euphoria, described as a high. The euphoria in addition to the analgesic effect also makes the opiates a very effective treatment for disease initiated pain. Most opioid abuse begins when users are in their teens, and if use continues, addiction develops in one to two years.

Chronic use is accompanied by delayed or arrested development in most areas of an addict's life, including their educational, occupational, and psychosexual lives. Chronic use also results in tolerance and the addict needs ever increasing doses to achieve a high. With the development of tolerance the addict also develops physical dependence which results in a withdrawal syndrome 8 to 10 hours after the last injection. Withdrawal, in most instances, is comparable to a severe case of the flu and is not life threatening; however, prevention of withdrawal syndrome seems to be a significant motivator in the addict's search for drug.

In addition to withdrawal, other side effects of opiate addiction include criminal behavior to secure the money necessary to purchase drug, acute heroin reaction, which is usually caused by the ingredients used to cut street heroin, and spread of diseases such as HIV, hepatitis, and others.

Addiction treatment consists of two phases, the first involves reducing or eliminating withdrawal syndrome, and the second is to eliminate drug seeking behavior. Medically assisted withdrawal is usually accomplished by treating the withdrawing addict with methadone which is gradually tapered over seven days. An alternative therapy is treatment with clonidine when methadone is not available. Multiple therapies have been tried to eliminate the drug seeking behavior and include maintenance of addicts on methadone, psychoanalysis, group therapy, and opioid antagonist.

**VERIFICATION OF ORPHAN QUALIFICATION**

Population Estimate:
The sponsor states that there are approximately 115,000 patients enrolled in methadone maintenance programs in the United States, and 3,000 patients being treated with naltrexone. They then imply that this represents most "treatment seeking" patients in the country; however, they do mention other types of treatment programs, without giving enrolment estimates for these programs.

Economic Analysis:
The sponsor supplied full economic projects of costs and sales revenues, along with a report of a certified public accountant. The accounts, assumptions, and projections seem appropriate and reasonably documented.

Rationale for Use:
Buprenorphine appears to be a very long acting semi-synthetic opioid with both agonist and antagonist properties. When given to patients experiencing withdrawal, it will mitigate and delay the onset of symptoms. It has also be reported to be effective as a maintenance agent, with less physical dependency than methadone. The sponsor implies that it will be an effective agent to transfer patients from methadone maintenance to antagonist therapy.

The addition of a combination of naloxone, an opiate antagonist, is intended to lessen the abuse potential of the preferred dosage form, a sublingual tablet which can be self-administered and permit "take-home use" but which will be unsuitable for abuse via injection. Since a drug in sublingual dosage form must be readily soluble in water, some mechanism for blocking abuse potential must be part of the dosage form design. The sponsor has developed several sublingual and injectable products and postulates that in nontolerant/nondependent patients, an injection of the combination will act like buprenorphine but in tolerant/dependent subjects, it acts like naloxone and precipitates abstinence. Thus, diversion of the sublingual combination tablet in a population of dependent opiate users would be unlikely.

Evaluation and Recommendation:
There is adequate medical rationale and clinical evidence to support the designation of the buprenorphine/naloxone product.

Most sources estimate the number of opioid addicts at 1,000,000 to 1,500,000. The sponsor states that approximately 120,000 of these addicts are presently on drug therapy, and this represents the size of the population likely to use a pharmacologic agent. Without specifying some characteristic of the drug which would limit it's use, it is difficult for this office to accept such a limitation on a population. The law specifically uses the words disease or condition, and does not mention those who are likely to use the product or seek treatment; therefore, it would seem reasonable to assume that if there are 1,000,000 opioid addicts then the disease or condition which this drug is intended to treat contains a population of 1,000,000 patients. It should also be noted that for opioid addiction the number of addicts seeking treatment varies according to a number of factors such as the price of heroin, and the addicts access to funds to pay for illicit drugs; therefore, the number of patients seeking treatment may represent a very variable number.

"Treatment-seeking" is not a medically plausible subset of the potential patient population since there does not seem to be any characteristic of the product, or segment of the patient population, identified by the sponsor which would justify a conclusion that use of this product could not or should not be used in any opiate addicted patient.

However, the economic analysis and supporting documentation submitted by the sponsor as part of its application amply demonstrates that there is no reasonable expectation that the sales of the drug product will be sufficient to offset the costs of developing the drug for the U.S. market and the costs of making the drug available in the United States (21 CFR §316.21(a)(2)).

The sponsor submitted a financial spreadsheet showing its projected cumulative costs and returns for the years 1993 thru 2002 which included the assumption that the product would be first marketed in 1995. The financial submission was accompanied by "a report of an independent certified public accountant in accordance with [the] Statement on Standards for Attestation established by the American Institute of Certified Public Accountants on agreed upon procedures performed with respect to data estimates and justifications submitted . . . ." The [redacted] letter and attachments dated 11 November 1993 meets the requirement set forth in the orphan drug regulations, 21 CFR §316.21(b)(8). Since the certificate necessarily relates to projections of costs and allocations, it is not an audit of completed transactions and thus appropriately carries a caution that "actual results may vary considerably from those shown."

The sponsor also submitted excerpts from the CRADA with NIDA for the development of this drug which showed that in addition to th[redacted] future costs the sponsor was agreeing to expend on behalf of the CRADA, it had or would incur anothe[redacted] in expenses related to the development of buprenorphine and buprenorphine/naloxone for this indication. However, the sponsor declined to provide more precise expenditure expense estimates or records because it felt that the cost of collecting and evaluating the allocations for these records retrospectively over a period of years would not be cost effective; furthermore, the sponsor believed that the CRADA expenses alone would meet the requirements for designation.

Included within the listing was an item identified as "Preclinical Reckitt & Colman expenditures" for [redacted] Because the reviewer was aware of the close involvement of NIDA on the figures submitted as part of the CRADA, and the potential costs of the project, the reviewer requested NIDA estimate the cost and value of the buprenorphine preclinical studies (to independently verify the figures submitted by the sponsor). In a letter dated April 13, 1994, NIDA responded that "based on the list of preclinical studies supplied to NIDA and in consultation with scientists and administrators here, I would conservatively estimate the current value of the data base . . . to be in the range o[redacted] NIDA noted that it was of some importance to them that this data would require 3 to 5 years to obtain or recreate outside of the CRADA. This reviewer is satisfied that financial estimates and projections, including those fully incorporated in the request for designation, are fair and reasonable estimates.

To assess the likelihood that this request meets the statutory requirement that "there is no reasonable expectation" that sales over the first 7-year period will permit recovery of the developmental costs, the sponsors spreadsheet was reconstructed (Lotus 1-2-3) and subjected to additional hypotheses that might affect the first 7 years of marketing results. Where delays are included in the calculations, the year-dates remain unchanged in the charts. The delay period appear as "XX" or some variation in order to keep the marketing period results clear and comparable. Obviously, if the NDA is first approved in 1998, then the exclusivity period relevant for the statutory assessment begins in 1998 and ends 7 years later.

Chart 1 is a simple reconstruction of the sponsors spreadsheet which establishes the validity of the formulas and interrelationships of prevalence, sales, cost recovery, etc. It demonstrates that if the

product were approved and marketed in 1995, the excess of development costs in 2001 (7 years later) would be [redacted] (last column of line 19, Chart 1).

Chart 2 is the same data as used above, but adds an assumption that marketing approval is not forthcoming until two years later than shown in Chart 1. Since the IND's had just been submitted in May, 1994, the CRADA has just been formally agreed to with NIDA, and 1994 is half over, it seems reasonable to conclude that marketing approval is at least two or more years away. Chart 2 projects that the unrecovered costs 7 years after marketing would b[redacted] (line 19, Chart 2).

Chart 2A is a variation on the above two with the added assumption that the delay in marketing approval will be at least three years in the future. The projection here is that the first 7 years of marketing experience will produce[redacted]

Charts 3A and 3B test the effects of assuming the sponsor estimates of the patient population market obtained should be fifty percent higher in all phases of the project. Chart 3A used the 1995 marketing date assumption, Chart 3B assumes a two-year delay. These charts can also be considered surrogates for an assumption that the 104,000 patient treatment group should be increase by fifty percent (up to 156,000) but that the market share for buprenorphine (in %) remains as estimated by the sponsor. Chart 3A shows [redacted] whereas Chart 3B shows [redacted]

Charts 4 and 4A are similar to Charts 3A & 3B, except that the patient market is doubled (a 100% increase over the sponsor estimates). Chart 4 shows [redacted] nd Chart 4A projects a [redacted] (with a 2-year delay in NDA approval).

Charts 6 and 6A address price. The assumption in all prior calculations is that at the [redacted] er dose charge cannot be increased because of the unique characteristics of the market. However, these charts are a "what if" the price could be increased b[redacted] In this case, ---and the patient estimates were doubled. Under these circumstances, Chart 6 shows [redacted] and Chart 6A (with a 2-year delay) shows [redacted]

The sponsor maintains that the price competition between its product and methadone will effectively curtail any increases in price. The sponsor projects an annual patient cost of [redacted] er year (which is the figure used in all the above charts and analyses), and compares that with [redacted] or LAAM and [redacted] or methadone. Their theory is that since most of these products are purchased by treatment centers, governments, etc., rather than individuals, it is unlikely that buprenorphine will supplant any of the market for the cheaper products. This seems to be a reasonable conclusion. The sponsor also notes that the cost of manufacturing buprenorphine is much greater than for methadone, so that (a) buprenorphine profits will be slimmer and (b) methadone is and remain more cost competitive in the future. The sponsor notes that while the pricing has not been established for the product, they have already concluded that the competitive agents will not permit the usual and full markup it would ordinarily consider for a new indication. This obviously will limit further their ability to recoup the development costs.

Additionally, the sponsor states that any increase in the price charged would decrease the market penetration, so that an increase in price would not proportionally or necessarily increase total sales, or profits. This states the obvious, but unlike the lethargic relationship expected for increases in sales or market shares, the negative effect on market share reduction in the circumstances of drug treatment centers is likely to be much more dramatic and immediate.

All of the figures and documentation for this product were also submitted and reviewed as part of the designation [redacted] for the mono-drug product by the same sponsor. It is unlikely that both products will be marketed however, should that occur at some later date the a reasonable expectation would be that both would compete for a portion of the market projected for either alone. Furthermore, it seems reasonable to conclude that the recovery period for this combination product would be longer simply because there is the additional cost of a second ingredient that is ignored in the underlying calculations based upon the mono-drug product.

The sponsor maintains that the maximum number of treatment-seeking addicts that could be treated is limited to 104,000 since there are only 115,000 treatment slots for methadon, et al., in existing drug treatment facilities. This argument was considered and rejected as a rationale for designating this product on the basis of a prevalence of 200,000 or less; however, it is relevant in estimating the marketing potential for the product. It is not reasonable to posit that the drug abusing population will en masse switch to this product. It is reasonable to assume that there will be virtually no change in the treatment-seeking population, or that any positive shift will be incremental. Thus, over seven years, the additional patients on this product beyond those projected by the sponsor should be inconsequential economically on the results of this analysis.

Robert F. Steeves, R.Ph., LL.M.
Office of Orphan Products
Development (HF-35)

Concur/NonConcur John J. McCormick Date: 10/24/94
JJMcCormick, M.D.

Concur: Marlene E. Haffner Date: 10/25/94
Marlene E. Haffner, M.D., M.P.H.