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

June 15, 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 May 5, 1993 submitted pursuant to Section 526 of the Federal Food, Drug, and Cosmetic Act (FFDCA) for the designation of buprenorphine hydrochloride as an orphan drug (application [redacted]). We also refer to your amendment dated November 15, 1993.

We have completed the review of this application, as amended, and have determined that buprenorphine 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 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 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 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:
GCF-1/J.Cohen
HFD-85/M.A.Holovac
HFD-007
HF-35/OP File[redacted]
HF-35/B.Steeves
HF-35/chron
HF-35/P.Vaccari 6/15/94 dsg.752

6/15/94

Review of a Request for Orphan Drug Designation

Date of submission: May 5, 1993
Received by reviewer: May 6, 1993
Review initiated: June 1, 1993
Review completed: June 25, 1993
Date Supplement Received: November 17, 1993
Date Further Supplement Received: February 7, 1994
Date Review Completed: June 14, 1994

Designation [redacted]

Drug Name:
code name:
generic name: buprenorphine hydrochloride
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 substance and finished dosage form is manufactured by:

[redacted]

Proposed Designation:
For use in treatment-seeking opiate users 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.. Both the injectable and the sublingual are marketed in numerous countries outside of the U.S. as an analgesic.

Evaluation and Recommendation:
Prior review of the sponsor's application found that there is adequate clinical evidence to support the designation of buprenorphine, but identified a substantial concern with this application because of the size of the intended population. Most sources estimate the number of opioid addicts at 1,000,000 to 1,500,000. The sponsor stated that approximately 120,000 of these addicts are presently on drug therapy, and this represented the size of the population likely to use a pharmacologic agent. Without specific characteristics of the drug which would limit it's use, OPD would not accept such a limitation on a population and concluded that it was reasonable to assume that if there are 1,000,000 opioid addicts then this is also the prevalence of the disease or condition which this drug is intended to treat. 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 fluctuating number.

In addition, the prior application did not specify how many patients are in treatment, since the sponsor makes no attempt to provide a number for the patients which are treated in programs that are not a part of the methadone clinics.

The sponsor received an incomplete letter stating these deficiencies and was informed that:

> It is unclear from your application how many addicts are "treatment-seeking" since you do not provide the number of patients in treatment programs other than methadone maintenance clinics. It is also unclear why "treatment seeking" should be considered a medically plausible subset as defined by the recently published regulations, since there does not seem to be any characteristic of the drug which would preclude its use in any opiate addicted patient.
>
> As an alternative to justifying a designation by limiting the number of addicts available for treatment, you may wish to consider requesting designation because it is unlikely that the sales of buprenorphine in the United States will be adequate to recover the preclinical and clinical development cost within 7 years of approval. As you may be aware congress provided for drugs which may be "orphans" for reasons other than the size of the population they are intended to treat, by allowing this office to designate drugs based on their expected lack of profitability. This approach has not been used since the amendments to the Orphan Drug Act were passed in 1985; however, it would seem that this product may be designatable under this portion of the statute. We are enclosing a copy of the pertinent regulations, and should you have any questions relating to the process of applying for designation because of an expected lack of profitability, you may wish to contact Mr. Robert Steeves J.D. of this office.

The sponsor has responded to these deficiencies and issues by providing additional information.

REVIEW OF SUPPLEMENTARY MATERIALS AND RECOMMENDATIONS:

Prior review of the sponsor's application resulted in a determination that the patient prevalence for opiate addiction easily exceeded the 200,000 patient figure established by law as the upper limit for orphan designation. The Office indicated its intention to reject the argument that since the number of treatment slots available under state and federal antiaddiction programs has been steady at 104,000, that that figure should be assumed to be the potential treatable addict population. A series of meetings with the sponsor, and representative of the National Institutes on Drug Abuse ensued over several months because NIDA wished to have a Cooperative Research and Development Agreement with the sponsor for the development of this addiction treatment, and the sponsor was unwilling to proceed without the exclusivity that orphan designation would provide under the circumstances.

Without relinquishing the right to pursue or challenge the population/prevalence arguments, the sponsor submitted a supplemental request for designation under Section 526(a)(2)(B) on the basis that "there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug."

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 reviewer consulted with AICPA on the nature and content of the report anticipated by its Statement and concluded that the [redacted] letter and attachments dated 11 November 1993 meets the requirement set forth in the orphan drug regulations, 21 CFR s 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 with its supplemental request excerpts from the CRADA with NIDA for the development of this drug which showed that in addition to the [redacted] future costs the sponsor was agreeing to expend on behalf of the CRADA, it had or would incur another [redacted] in expenses related to the development of buprenorphine. 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 of [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]ast 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 acknowledge that marketing approval is at least two or more years away. Chart 2 projects that the unrecovered costs 7 years after marketing would be a [redacted]

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] and Chart 4A projects [redacted] with a 2-year delay in NDA approval).

Charts 6 and 6A address price. The assumption in all prior calculations is that at th[redacted] per 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 by [redacted] In this case, ---and the patient estimates were doubled. Under these circumstances, Chart 6 shows a [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 o[redacted] per year (which is the figure used in all the above charts and analyses), and compares that wit[redacted]or LAAM an[redacted]for 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.

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.

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This reviewer concludes that the patient population estimates and market shares submitted by the sponsor are reasonable and fair, and that projections verify that the statutory requirement that there is no reasonable expectation that the development costs will recovered in the first 7 years of marketing has been satisfied.

The data from the charts are shown in graph form, per the attached.

It is recommended that buprenorphine hydrochloride be designated an orphan product for the treatment of opiate addiction in opiate users under Section 526(a)(2)(B).

Robert F. Steeves, R.Ph., LL.M.
Office of Orphan Products Development

Concur: ______ Date: 14 June '94

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

cc:
HF-35/Designation File [redacted]
HF-35/Chron File
HF-35/Jmccormick
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