CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-714

ADMINISTRATIVE DOCUMENTS

CSO Review of Labeling

NDA 20-714

Drug: Nicotrol Inhaler (nicotine inhalation system) 10 mg/cartridge, 4 mg delivered
Sponsor: Pharmacia & Upjohn Company

Materials Reviewed:
Draft labeling submitted with the NDA application on May 1, 1996; labeling amendments of November 13, 1996, March 20, March 26, April 24, April 28, April 29, May 1 and May 2, 1997.

Review: The labels are in conformity with labeling regulations (21 CFR 201.1, 201.5, 201.10, 201.15, 201.17, 201.18, 201.50, 201.51, 201.55, and 201.100).

Conclusions:

Draft versions of the container labeling was submitted on May 1, 1996 and March 26, 1997. Requests were made verbally to the sponsor which resulted in the sponsor's submitted faxes of May 1 and May 2, 1997 promising to label the containers with a warning that they are not child resistant and with the actual nicotine content in the cartridge along with the amount delivered. We await submission of the agreed upon labels.

Draft versions of the patient package insert were submitted on May 1, 1996 and March 26. The agency made requests for changes and the sponsor submitted further changes on April 24 and May 1, 1997. The approved version is a marked-up insert provided by the agency on May 2, 1997.

The physician's package insert went through many versions. The sponsor submitted draft labeling on May1, 1996. The agency edited this version which became a November 4, 1996 version. The agency made more changes on November 8 and the sponsor resubmitted the draft on November 13, 1996. The agency edited this version and submitted a November 15, 1996 version to the Drug Abuse Advisory Committee. The sponsor submitted a March 20, 1997 version. This went through a number of editings by the division and was returned to the sponsor on April 8, 1997. The sponsor resubmitted labeling on April 24, 1997. With back and forth discussions with the sponsor from April 28 through May 1, the approved draft labeling was finalized by the agency on May 1, 1997.

Concur:

Corinne P. Moody
Chief, Project Management Staff

Bonnie McNeal
Project Manager

5/7/97

PATENT LISTING FILED PURSUANT TO 21 U.S.C. 355(b)(1)(F)

This Patent Information Statement is submitted in NDA No. 20-714 directed to a nicotine inhalation system, filed May 1, 1996, pursuant to the provisions of 21 U.S.C. 355(b)(1)(F). The listed patents claim the drug product for which Applicant submitted the NDA or else claim a method of using such drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug product.

Applicant, through it its parent Pharmacia AB, has exclusive rights to the patents listed below. A copy of each patent is attached.

PATENT NO.	ISSUE DATE	EXPIRATION DATE	TYPE OF CLAIM
5,167,242	12 DEC 92	01 DEC 2009	Nicotine inhalation delivery system.
5,400,808	28 MAR 95	01 DEC 2009	Nicotine inhalation delivery system.
4,917,120	17 APR 90	17 APR 2007	Nicotine inhaler.
4,800,903	31 JAN 89	31 JAN 2006	Tobacco free nicotine dispensers
4,793,366	27 DEC 88	27 DEC 2005	Nicotine inhalation dispensing system
4,284,089	18 AUG 81	18 AUG 98	Nicotine dispensing system.

Respectfully submitted,

Patricia A. Coburn

Patricia A. Coburn
Assistant General Counsel

PEDIATRIC PAGE
(Complete for all original applications and all efficacy supplements)

NDA # 20-714 Supplement # NA Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-170 Trade and generic names/dosage form: Nicotrol Inhaler, 4 mg (nicotine inhalation system)
Action: (AP) AE NA

Applicant: Pharmacia & Upjohn Co. Therapeutic Class: Nicotine replacement product
Indication(s) previously approved: NA
Pediatric information in labeling of approved indication(s) (is adequate) inadequate

Indication in this application: As an aid to smoking cessation
(For supplements, answer the following questions in relation to the proposed indication.)

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

   a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

   b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

   c. The applicant has committed to doing such studies as will be required.
      (1) Studies are ongoing,
      (2) Protocols were submitted and approved.
      (3) Protocols were submitted and are under review.
      (4) If no protocol has been submitted, attach memo describing status of discussions.

   d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

(4.) PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed. See below.

5. If none of the above apply, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.
This product is inappropriate for use in children due to its physical characteristics.

B. McNeal / Project Manager
Signature of Preparer and Title Date: 4/22/97

cc: Orig NDA # 20-714
HFD-170 /Div File
NDA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised)

CERTIFICATION PURSUANT TO THE GENERIC DRUG ENFORCEMENT ACT OF 1992

Pursuant to 21 U.S.C. §335a (k)(1) Pharmacia Inc. ("Pharmacia") hereby certifies that to the best of its knowledge and belief it has not used in any capacity the services of any person debarred under subsections 21 U.S.C. § 335a(a) or (b) in connection with this Application and that it will not use in any capacity the services of any person debarred under 21 U.S.C. §335a(a) or (b) in connection with this Application.

Pharmacia has made a reasonable effort to list the convictions of all persons whose convictions are required to be listed under 21 U.S.C. §335a(k)(2) in connection with this Application. This effort included reviewing the Debarment List as published in the Federal Register and confirming that no employees of Pharmacia connected with this Application appear on that list. In addition, Pharmacia requires that all newly hired employees execute a certification concerning any convictions required to be listed. Finally, this effort included a requirement that all persons not employed by Pharmacia who provided significant services in connection with this Application certify to Pharmacia concerning any convictions of their organization or of any person employed by them. Relying in part on these certifications to Pharmacia, the following list of all convictions described in 21 U.S.C. §335a(a) or (b), which occurred in the previous five (5) years of Pharmacia and affiliated persons responsible for the development or submission of this Application is provided.

The listed convictions are: None.

Respectfully submitted,

By: Kenneth King
Kenneth F. King

Title: Senior Vice President, Regulatory and Scientific Affairs

Date: March 18, 1996

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

DACCAD HFD-170
Anesthetic, Critical Care
& Addiction Drug Products

Date: 4/14/97
From: Curtis Wright, Acting Director, HFD-170
To: NDA 20-714, "Nicotrol inhaler"

Subject: Division Director's Approval Memo

Summary- Nicotrol inhaler is a transmucosal dosage of nicotine for smoking cessation submitted for Rx approval. The product appears to have the same efficacy and safety as other self-titrated nicotine dosage forms. It is approvable with a Phase IV requirement to improve the child resistance of the packaging.

Background and Product Description: The group leader's memorandum is complete and accurate and the reader is directed to it.

Recommendation- Approval with the Phase IV requirement to improve the packaging to increase the child resistance. The present product is on a par with an ingested cigarette, and is acceptable, but modest attention to the packaging would improve the safety of the product.

Because of its physical characteristics (cigarette like), and the risk of abuse by heating the air stream, this product is not intrinsically suitable for pediatric use.

Curtis Wright
Acting Director,
Anesthetic, Critical Care,
& Addiction Drug Products Division

Team Leader Memo

From: E Douglas Kramer, MD
To: Curtis Wright, MD MPH

Subject: Nicotrol Inhaler Prescription NDA for Smoking Cessation
Recommendation: Approval
Date: April 28, 1997

Attached please find the action package for Pharmacia-McNeil's Nicotine Inhaler. This product consists of a cartridge containing 10mg of nicotine in a porous plug. The nicotine in the plug is released by inserting the cartridge into a mouthpiece which the patient uses to draw air through the plug. The nicotine that is released is deposited in the mouth and absorbed buccally. The quit rates seen are similar to those observed with other products in this class, with active drug being about twice as effective as placebo in promoting abstinence. This memo details some of the unique issues faced by the review team in their consideration of this product and their resolution.

Pharmacokinetics

Each inhaler cartridge contains 10mg of nicotine. About 4mg of this amount is delivered to the user as the product consumed. About half of this amount is bioavailable. The product is pharmacokinetically most similar to 4mg gum. Because the product is similar to the 4mg gum, the review team is recommending that the product be labeled a 4 mg inhaler rather than 10mg. This will give the physician better insight into the strength of the product. Such labeling is consistent with that used for the nicotine patches which are labeled for the amount of nicotine they deliver rather than their nicotine content.

Clinical Studies

The sponsor has conducted a total of 6 clinical studies using a prototype version of the mouthpiece the sponsor will market. Consultation with CDRH has assured the review team that changes to the mouthpiece will not affect the flow of air through the cartridge and that nicotine delivery of the 2 devices will be the same.

Two of these studies conducted at recommended doses of 4 to 20 inhalers per day were considered to clearly meet the substantial evidence standard. A third study conducted at the same dose was questioned by the medical reviewer since some of the subjects seemed to have stopped smoking prior to beginning treatment. Other studies which failed to show efficacy were at lower recommended doses. On the basis of this data, a dose of 6 to 16 inhalers per day is recommended in the labeling.

Safety

The safety profile of this product is similar to that of other nicotine replacement products. Irritant effects of nicotine were prominent among users, but seemed to be milder than for the nicotine nasal spray. Deaths occurring in this NDA were clearly unrelated to the treatment and included deaths following open heart surgery for valvular disease and CVA.

The pharmacokinetics of nicotine delivered via buccal absorption from unused (worst case) porous plugs retained in the mouth for 1 minute were examined in 7 healthy snuff users to estimate the pediatric exposure hazard. The average dose of nicotine based on the average amount of nicotine in the used plugs was 1.21mg (range mg). Uncorrected Cmax was 6.5ng/mL (range . Extrapolation suggests that nicotine concentrations in a 10kg child would be about higher. Buccal administration was not associated with significant changes in vital signs. The product does not appear to have an unusual ingestion hazard in the pediatric population.

Other safety concerns included improving the child-resistance of the cartridges (which the sponsor is undertaking as a phase 4 commitment per the recommendation of the reviewers and the advisory committee), and the possibility of bronchospasm induced from the irritant effects of nicotine in the inhaler (precautionary language has been added to the label).

The labeling for the adverse event section is based on event frequencies observed in the 2 trials considered to be pivotal. This decision was taken such that adverse event frequencies attributable to drug use would be based on trials in which patients actually used an amount of drug that enabled them to quit successfully.

Information on drug interactions has been updated to be more consistent with labels of OTC nicotine products and with the proposed revisions to the bupropion label to incorporate a smoking cessation indication. Specifically, the table listing several drug interactions has been replaced with a simple reminder to the physician that smoking cessation (rather than nicotine replacement) may alter the disposition of drugs such as theophylline and antidepressants.

Drug Abuse and Dependence

The reviewers had considerable concern that the inhaler device looks like a cigarette and is used in a similar way. However, the efficacy data for the product clearly show its usefulness as a smoking cessation product in a therapeutic setting, the pharmacokinetics of the product are quite different from cigarettes and the product is harder to puff on than a cigarette. Review of the clinical data

did reveal possible emergence of withdrawal symptoms when use of the active inhaler was discontinued, but these symptoms were clearly of a different nature from that encountered for the nicotine nasal spray (e.g. they were not clearly associated with dose escalation). Subjective effects of the inhaler were more than placebo but clearly less than cigarettes in single dose abuse liability testing. Data on the extent of prolonged use of the product and placebo are not available. The reviewers believe the available evidence supports a prescription approval for this product. This section of the label is similar to that for other products in the class except that it includes mention of the lack of an AV difference for this product as compared to cigarettes based on a pharmacokinetic study performed by the sponsor. This section of the label has been revised only slightly from the version presented to the DAAC.

E Douglas Kramer, MD
Medical Officer 11/24/97

Celia Winchell, MD
Medical Officer