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RESEARCH**

APPLICATION NUMBER:

18-612/S025

20-066/S007

PHARMACOLOGY REVIEW

41.1

NOV 10 1998

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Division of Anesthetic, Critical Care & Addiction Drug Products
HFD-170 / Harry M. Geyer, III Ph.D.

NDA #18-612 S-025

Sponsor: SmithKline Beecham
Parsippany, NJ 07054

Review Date: November 10, 1998

Drug Product: Nicorette 2mg

Related Drugs:
NDA 20-066 S-007- Nicorette 4mg.

Comments and Evaluation:

The drug product differs from the approved OTC product by use of mint flavoring and xylitol replacing sorbitol as the alcohol sugar. These substitutions were found reasonably safe. The product is safe from the pharmacology / toxicology perspective.

Conclusions and Recommendations:

From the pharmacology / toxicology perspective, this product is recommended for approval.

ISL

Pharmacologist: Harry M. Geyer III, Ph.D.

ISL *11/10/98*

Team Leader: Dou Huey Jean, Ph.D.

cc: Orig IND
HFD 170/Div File
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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-066/SE4-007, 18-612/SE4-025

Name: Nicorette® 2 & 4 mg

Sponsor: SmithKline Beecham Consumer Healthcare, 1500 Littleton Road, Parsipanny, NJ

Submission Type: Formulation Revision - Bioequivalency Study Report

Submission Date: May 15, 1998

Reviewer: Suresh Doddapaneni, Ph.D.

Introduction

Nicorette® 2 mg (NDA 18-612) and Nicorette® 4 mg (NDA 20-066) have received supplemental approval for OTC sale on 9 February, 1996. These two products are 'original' flavored. The current submission consists of a supplemental application seeking the approval of a mint flavored Nicorette® gum. An application for this product (and citrus flavored gum as well) was originally submitted on March 6, 1996 (supplement # 005). In the March 1996 submission, the sponsor submitted a bioequivalence study (93NNCG001) that demonstrated bioequivalence (for both 2 and 4 mg strengths) between original Nicorette® gum and mint Nicorette® gum and bioequivalence between original Nicorette® gum and citrus Nicorette® gum. The study also demonstrated dose-proportionality between the 2 and 4 mg strengths for all the three flavors. However, the March 1996 application was not approved based on inadequate data addressing the abuse liability of these products.

In the current submission, new information addressing the abuse potential of the mint Nicorette® gum has been submitted while the same bioequivalence study submitted in the March 1996 submission and reviewed by the Agency is resubmitted again. The sponsor has limited the current submission to mint flavor only in order to complete data generation and re-filing in the most expeditious manner. Review of the abuse liability data is deferred to reviewing Medical officer/Control Substance Evaluation Team. Since the bioequivalence study 93NNCG001 was already reviewed and bioequivalence was concluded between the original and mint flavored Nicorette® gum, this study will not be reviewed again (see Clinical Pharmacology and Biopharmaceutics review dated August 2, 1996 for a complete discussion of this study). However, this review will address the sponsor's response to four comments generated from the review of the bioequivalence study 93NNCG001 in the March 1996 submission. It should be noted that the Agency already concluded bioequivalence between original and mint flavored Nicorette® gum and between original and citrus flavored Nicorette® gum and these comments were meant to be applicable for future bioequivalence studies.

Discussion

The following were the comments sent to the sponsor in the August 2, 1996 review for the March 6, 1996 supplement;

1. It is recommended that the sponsor perform cotinine pharmacokinetic and statistical analysis in future submissions. While, the sponsor's explanation of

Recommendation

This submission (20-066/SE4-007, 18-612/SE4-025) can be approved from the viewpoint of Office of Clinical Pharmacology and Biopharmaceutics.

/S/ 11/25/98

Suresh Doddapaneni, Ph.D.
Clinical Pharmacologist,
Division of Pharmaceutical Evaluation II

FT initialed by Ramana Uppoor, Ph.D.

/S/
11/25/98

CC:

NDA 20-066/18-612, HFD-170 (Division Files, Kumar), HFD-850 (Lesko), HFD-870 (Doddapaneni, Mei-Ling Chen, Uppoor), CDR (Barbara Murphy).