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APPLICATION NUMBER:

20-066/S010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUN 16 2000

Clinical Pharmacology/Biopharmaceutics Review

NDA:	18-612/SCF-028, 20-066/SCF-010	**Submission Date:**	02-22-00
Product:	Nicorette® (nicotine polacrilex) 2 & 4 mg Gum		
Sponsor:	SmithKline Beecham Consumer Healthcare Parsipany, NJ	**Reviewer:**	Abimbola Adebowale Ph.D.

Review of a Supplemental NDA

Synopsis

Nicorette ® 2 mg (NDA 18-612) and 4 mg (NDA 20-066) 'original flavored' were approved for prescription sale in 1984 and 1992 respectively, and then both approved for OTC sale on February 9, 1996. Nicorette® is a nicotine resin complex (nicotine polacrilex) that contains nicotine in a chewing gum base, currently indicated as an adjunct to smoking cessation programs (to reduce withdrawal symptoms including nicotine craving associated with quitting smoking).

This submission is a re-filing of a previous supplement for a new orange flavor of Nicorette® (nicotine polacrilex) 2mg and 4mg gum. Applications for both citrus and mint Nicorette were originally filed with the FDA (HFD-170) as NDA 18-612/S-023 for 2 mg and NDA 20-0666/S-005 for 4 mg on March 6, 1996. Non-approval for these SNDA submissions were issued on October 8, 1996 based on inadequate data addressing the abuse liability of these products.

Based on a meeting held on June 5, 1997 and, further discussions with the FDA, SmithKline Beecham conducted additional clinical trials and, submitted supplemental New Drug Applications NDA 18-612/S-025 and NDA 20-066/S-007 on May 15, 1998 for mint flavored Nicorette. The supplements were approved on December 23, 1998 along with a three-year period exclusivity that extends out to December 23, 2001.

A teleconference was held on June 29, 1999 with the FDA (HFD-560) to discuss the sponsor's development plan with regards to the resubmission of an SNDA for citrus flavored Nicorette. The applicant stated during this teleconference that the citrus Nicorette SNDA would be filed with only the previously submitted bioequivalence data comparing original, mint and citrus flavored Nicorette 2mg and 4 mg gum. The agency noted that while the current bioequivalence study is appropriate for the review of citrus, future flavor variants could be approved on the basis of in-vitro drug release.

The applicant has included in the human pharmacokinetic section of this submission a report for study 93NNC001 entitled "Bioequivalence of a fruit flavored 2 mg and 4 mg nicotine polacrilex gum relative to 2 mg and 4 mg Nicorette® gum and 2 mg and 4 mg Nicorette® mint gum"). The applicant stated that "fruit" "citrus" and "orange" are synonymous descriptions of the same product.

This study report was previously submitted to the agency as part of NDA 18-612/S-023 and NDA 20-066/S-005 on March 6, 1996and used for the approval of mint flavored Nicorette ® in NDA 18-612/SE-025 and NDA 20-066/SE4-007. The report was reviewed by Dr. S. Doddapaneni in both cases and, the conclusions of the biopharm review were that the

2mg and 4 mg strengths of the citrus and mint flavored gums were bioequivalent to the respective strengths of the already approved original flavored Nicorette® gum. Also the 2mg and 4mg strengths were found to be dose proportional within each flavor for all three flavored gums.

Since the bioeqivalence study 93NNC001 included in this submission was already reviewed and bioequivalence was concluded between the original and orange flavored Nicorette 2mg and 4mg gum and accepted by the Agency, this study will not be reviewed again.

The applicant stated that the formulation for "orange" flavored Nicorette 4 mg gum used in the bioequivalence differs from the intended commercial formulation only in colorant. The formulation used in the bioequivalence study contained E104 Quinoline Yellow Aluminum Lake and, the commercial formulation contains D&C Yellow # 10 Aluminium Lake as replacement. The Merck index (ed.12th) states that D& C yellow # 10 is a synonym for Quinoline Yellow. The Merck index also states that they are mixtures of monosulphonic and disulphonic acids of quinoline yellow spirit soluble which implies that they are similar and possibly interchangeable (confirmed with the chemistry review team leader, Dr. Mona Zarifa). The chemistry review by Dr. C. Yaciw stated that the [redacted] that contains the complete information on the components and composition of the drug product has been reviewed and found to be adequate. Following discussions with the chemistry review team leader and, based on the provisions of 21 CFR 320.22 (d)(4) this difference is acceptable provided the Office of New Drug Chemistry are in agreement.

Recommendation

Based on the information submitted in these supplemental applications, (NDA 18-612/S-028, 20-066/S-010), the applicant has met the requirements outlined in 21CFR 320 and their application is acceptable from a clinical pharmacology and biopharmaceutics perspective.

/S/ 06/16/00

Abimbola O. Adebowale Ph.D.
Office of Clinical Pharmacology /Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT signed by Dennis Bashaw, Pharm.D. /S/ 6/16/00