CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-330

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-330

GlaxoSmithKline
1500 Littleton Road
Parsippany, NJ 07054-3884

Attention: David Schifkovitz
Director, Regulatory Affairs

Dear Mr. Schifkovitz:

Please refer to your new drug application (NDA) dated December 15, 2000, received December 20, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Commit™ (nicotine polacrilex lozenge), 2 mg and 4 mg.

We acknowledge receipt of your submissions dated December 18, 2000, January 30, February 8 and 16, April 23, May 7 and 14, June 6, July 5, August 24 (2), September 17, and October 1, 2001, February 26, March 11 and 12, May 1 and 30, June 3, July 1 and 8, August 30, September 6, October 15 and 25, 2002. We also acknowledge your fax dated October 26, 2002.

Your submission of May 1, 2002, constituted a complete response to our October 19, 2001, action letter.

This New Drug Application provides for the Over-the-Counter (OTC) marketing of Commit™ (nicotine polacrilex lozenge), 2 mg and 4 mg, for adults 18 years of age and older, to reduce withdrawal symptoms, including nicotine craving, associated with quitting smoking.

We completed our review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved, effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (User's Guide submitted August 30, 2002, blister pack and carton labels submitted August 30, 2002) and must be formatted in accordance with the requirements of 21 CFR 201.66. Marketing the product with FPL that is not identical to the approved labeling text and in "Drug Facts" format may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-330.**" Approval of this submission by FDA is not required before the labeling is used.

We remind you of your agreement as stated in your commitment letter dated October 25, 2002, to make the following revisions in your User's Guide and carton labels submitted August 30, 2002:

1. Carton back, under ***Directions***, bullet 11, place a period at the end of the second sentence.

2. User's Guide, Page 9, under the heading CUTTING BACK ON YOUR Commit™ LOZENGE USAGE, paragraph 1, bold the sentence that reads **"Stop Using Commit™ Lozenge at the end of week 12."**

After reviewing your proposed graphic specifications included in the October 25, 2002, commitment letter, we also recommend that you change the bullet sizes from 5.25 pt. to 5.0 in accordance with CFR 201.66(d)(4). We also suggest that the font size of the generic name on the principal display panel be at least 1/2 the font size of the brand name (21 CFR 201.61).

Please incorporate these recommendations at the time of next printing.

We remind you of your postmarketing study commitments in your submission dated February 26, 2002, and July 1, 2002. These commitments are listed below.

1. A study to be conducted in subjects with relative contraindications for use (underlying diseases such as diabetes mellitus or cardiovascular disease) who may be directed by their physician to use a nicotine product.

Protocol Submission:	Protocol submitted October 1, 2002, under IND 56,295.
Study Start:	May 2003
Final Report Submission:	February 2004

2. A study to solicit adverse event information.

Protocol Submission:	Protocol submitted September 13, 2002, under IND 56,295.
Study Start:	December 2002
Final Report Submission:	June 2003

Comments on the above protocols will be conveyed in a separate correspondence.

Submit all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol," "Postmarketing Study Final Report," or "Postmarketing Study Correspondence."

The text in italics below addresses the application of FDA's Pediatric Rule at [21 CFR 314.55/21 CFR 601.27] to this [NDA/BLA]. The Pediatric Rule has been challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. The government has not yet decided whether to seek a stay of the court's order. In addition, the government has not yet decided whether to appeal the decision; an appeal must be filed within 60 days. **Therefore, this letter contains a description of the pediatric studies that would be required under the Pediatric Rule, if the Pediatric Rule remained in effect and/or were upheld on appeal.** Please be aware that whether or not these pediatric studies will be required will depend upon the resolution of the litigation. FDA will notify you as soon as possible as to whether this application will be subject to the requirements of the Pediatric Rule as described below. In any event, we hope you will decide to conduct these pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (21 CFR 314.55).

Based on information submitted, we conclude the following:

For the marketing of Commit™ (nicotine polacrilex lozenge), to reduce withdrawal symptoms, including nicotine craving, associated with quitting smoking, we are deferring submission of pediatric studies for patients 10-17 years until October 31, 2007. We are waiving the pediatric study requirement for this application for patients under age 10.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request." FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

In addition, we request that you submit one copy of the introductory promotional material you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send the copy to the Division of Over-the-Counter Drug Products.

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

Oversight of this application is being transferred to the Division of Over-the-Counter Drug Products.

If you have any questions, call Ms. Laura Shay, M.S., Regulatory Project Manager at (301) 827-2274.

APPEARS THIS WAY
ON ORIGINAL

Sincerely,

Charles Ganley, M.D.

{See appended electronic signature page}

Director
Division of Over-The-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Bob Rappaport, M.D.

{See appended electronic signature page}

Acting Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bob Rappaport
10/30/02 06:03:41 PM

Charles Ganley
10/31/02 09:25:33 AM

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

(A)

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

5 pages

(A)

DRAFT
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Dear Mr. Schifkovitz:

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We acknowledge receipt of your submissions dated December 18, 2000, February 16, April 23, May 7, May 14, June 6, July 5, August 24, September 17, and October 1, 2001.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. You have provided evidence of efficacy for your product when used according to the directions *tested in the clinical trial.* However, the directions for use proposed in your labeling are not supported by the efficacy data. Your single efficacy study evaluated a dosing regimen of one lozenge every 1 to 2 hours daily (up to 20 lozenges/day) during the first six weeks of therapy, whereas your proposed labeling includes a dosing regime[redacted] to 2 hours daily during the first six weeks with a maximum of [redacted] s/day. In your study, the dosing regimen for nicotine lozenge clearly provided a significant improvement in smoking cessation rates compared to placebo. Subjects in your study self-titrated their lozenge use based on the dosing recommendations provided. Changing the dosing frequency and/or recommended maximum dose is likely to change user behavior in unpredictable ways. It cannot be assumed that consumers would use as much of the product under the modified directions as they did during the trial, even those who did not approach the maximum dosage or minimum dosing interval. Therefore, it also cannot be assumed efficacy would be preserved if the instructions differed from those tested. If you choose to pursue your proposed dosing regimen, you will have to provide efficacy data to support it.

   We note that users of nicotine gum or lozenge do not necessarily maintain steady state plasma levels. Few patients use the product at appropriate intervals to maintain steady state, and virtually none would use it round-the-clock. Therefore, the relevant comparison is the single-dose maximum concentrations (Cmax) from the two products. Because the single-dose pharmacokinetic studies reveal a 8-10% greater Cmax from the 4 mg lozenge compared to the gum, the safety of the 4 mg lozenge cannot be fully supported by our previous finding of safety of the gum.

The pharmacokinetic studies employed metronome-paced chewing, which is likely to produce higher Cmax than ad-lib chewing; therefore the difference between the two Cmax values in actual use may be underestimated by the pharmacokinetic studies.

We believe there is sufficient efficacy and safety information to support the use of the 2 mg nicotine lozenge at the tested regimen, including the data in the application and supported by the recognition that blood nicotine levels are less than those observed for 4 mg nicotine lozenge and gum. Safety data for the 4 mg nicotine lozenge, however, are deficient for the tested dosing regimen. The 4 mg nicotine lozenge delivers plasma levels of nicotine higher than any other currently marketed nicotine replacement therapy. This renders the safety experience with other nicotine replacement therapies inapplicable in supporting the safety of the 4 mg lozenge. As noted in our pre-NDA communications with you, we still have concerns about the limited number of subjects exposed through 12 weeks of therapy for this new 4 mg dosage form. The fact that the study randomized predominately Caucasian subjects (94% of subjects in study S1410043) who were generally healthy does not reassure us of the safety across all populations who may use this product. Additional exposure of 150 - 200 subjects at 12 weeks of treatment, including non-caucasians and subjects with underlying medical conditions who are likely to have this product recommended by their physician is needed.

2. The following comments pertain to the drug substance.

   a. Provide identification and qualification information for all impurities that are present in the drug substance at levels [redacted] Individual limits must be established for each impurity/degradation product [redacted] The regulatory specifications for acceptance of the drug substance must be revised accordingly. Provide a specification of [redacted] for any individual unspecified impurity.

   b. Clarify the term "labeled amount" in Table 4.A.1.g-1 (drug substance specifications).

   c. Provide information about the identity and source of the "artifactual peak" you observed at all time-points in the stability samples of the drug substance.

3. The following comments pertain to the drug product.

   a. Provide information as to how the [redacted] .. An in-process specification may be appropriate.

   b. Revise the regulatory specifications for acceptance of the drug product to include reporting of each specified degradation product, both identified and unidentified, that is [redacted] Provide a specification of less than [redacted] for any individual unspecified impurity.

   c. Provide identification for all degradation products that are present at levels of [redacted] mg of total daily intake (TDI), whichever is lower.

d. Provide information on the safety qualification for all degradation products that are present at levels of [redacted] whichever is lower.

e. The stability data for the drug product stored at 25°C/60% RH, showed that the limits for [redacted] and the sum of all impurities could be reduced further. Tighten the acceptance criteria for these degradation products.

f. Provide information about the limit of detection (LOD) and limit of quantitation (LOQ) for each identified degradation product.

g. Provide data justifying the [redacted] for the "sum of all impurities" included in the drug product's shelf-life (stability) specifications.

4. The following comments pertain to the specification for dissolution.

a. Provide acceptance criteria as follows:

1 hour: minimum and maximum
3 hours: minimum and maximum
6 hours: minimum

b. Provide acceptance criteria in the USP Chapter <711> or Chapter <724> format.

c. Provide data and analysis to support the proposed acceptance criteria.

5. Tighten the acceptance criteria for water content in the drug product.

6. Explain the meaning of "Check Specification," as reported in your stability data tables.

7. Provide updated drug product stability data including statistical analysis (e.g., assay, degradation products, water, dissolution, etc.).

8. Provide the usual three-point post-approval stability agreement.

9. Deficiency letters have been sent to [redacted]

10. Incorporate the following pregnancy warning into the labeling.

"**If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider.** Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known."
This warning should be the first warning under the Warnings heading in the Drug Facts labeling. Use this warning in lieu of general pregnancy warning and breast-feeding warning in 21 CFR 201.63 (a) and the warning currently on OTC NRT drug products. Any other proposed warning must be supported by data. The User's guide and other self-help materials