CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-360

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	5/18/09
From	Joel Schiffenbauer
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	22-360 N-000
Applicant Name	GlaxoSmithKline
Date of Submission	7/18/08
PDUFA Goal Date	5/18/09
Proprietary Name / Established (USAN) Name	Nicorette/Nicotine Polacrilex
Dosage Forms / Strength	Lozenge
Proposed Indication(s)	1. reduces withdrawal symptoms including nicotine craving associated with quitting smoking
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Priscilla Callahan-Lyon/Daiva Shetty
Statistical Review	
Pharmacology Toxicology Review	Cindy Li/Wafa Harrouk
CMC Review/OBP Review	Yubing Tang/Shulin Ding
Microbiology Review	
Clinical Pharmacology Review	Ping Li/Suresh Doddapaneni
DDMAC /DMEPA	Zachary Oleszczuk
DSI	Xikui Chen
CDTL Review	
OSE/DMETS	
OSE/DDRE	
OSE/DSRCS	
Other Peds	Amy Taylor

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

NDA 22-360 was submitted by GlaxoSmithKline (GSK). The applicant seeks approval of a smaller version of Nicotine Polacrilex Lozenges, 2 mg and 4 mg (——— for the new version v' ——— for the original version), currently marketed by GlaxoSmithKline (GSK) under an approved NDA 21-330 as Commit lozenge. b(4)
The indication is identical to the currently approved Commit Lozenge: "reduces withdrawal symptoms, including nicotine craving associated with quitting smoking."

The sponsor conducted two *in vivo* bioequivalence studies comparing the new product to the current Commit lozenge. These two studies, S3010445 and S3010446 and an additional bioequivalence study (S3010567) form the basis of this submission.

This review will cover the bioequivalence studies and the updated safety information provided by the applicant, and address the issue of topical safety related to the oral cavity.

2. Background

GlaxoSmithKline (GSK) is submitting a New Drug Application, seeking approval of a smaller version of the currently available nicotine polacrilex lozenge, the Commit product. The new lozenges, Nicorette 2 mg and 4 mg, are considered by GSK to be a line extension of the currently marketed Commit Lozenges which are available in the same strengths and contain the same active ingredient, nicotine polacrilex.

Nicotine Polacrilex Lozenges (CommitLozenges), 2 and 4 mg, (NDA 21-330), was originally developed by GlaxoSmithKline (GSK) for the indication of reducing withdrawal symptoms, including nicotine craving associated with quitting smoking. The Commit Mini Lozenges, the subject of this NDA (NDA 22-360), have been designed, according to the applicant, to overcome the disadvantages associated with the large size of the currently marketed Commit Nicotine Polacrilex Lozenges under the approved NDA 21-330. The applicant's rationale for developing the mini lozenge is that at ——— Commit lozenge is quite large, takes some time to dissolve, and is therefore somewhat less than discreet for some individuals who use the product throughout the day in a public setting. On the other hand, the mini lozenges weigh ——— b(4) b(4)

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3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months under the labeled storage conditions. There are no outstanding issues.

The applicant made a cross-reference to their previously approved NDA 21-330 for Commit lozenges, which used the same drug substance (nicotine polacrilex USP) and similar manufacturing process. The main difference is the change in size and the formulation with different excipients.

However, at the time of this writing, the drug substance facility is pending an "acceptable" recommendation from the Office of Compliance.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Three separate bioequivalence studies were conducted to establish the bioequivalence of the Commit Mini Lozenge to the currently marketed lozenge formulation, Commit Nicotine Polacrilex Lozenges. Studies S3010445 and S3010466 (pilot studies) were 2-period cross-over studies to compare the nicotine PK profiles between the two products at 2 mg and 4 mg, respectively. Study S3010567 (pivotal BE study) was a single dose, 4-period cross-over study to compare the nicotine PK profiles between the two products at both 2 mg and 4 mg dosage strength.

The results of the BE studies is that bioequivalence criteria were met.

However, according to a DSI review of the pivotal BE study (S3010567), two concerns were raised: 1) the quality control samples (3.00, 30.0 and 150 ng/mL) and calibration range (1.00 to 200 ng/mL) for nicotine used in the study were not representative of the nicotine plasma concentrations observed in study plasma samples; 2) the LC/MS/MS assay (LLOQ=1.00 ng/mL) did not have sufficient sensitivity to measure nicotine levels for at least three half lives in the study of 2 mg lozenges.

In response to these issues the applicant reanalyzed all the pharmacokinetic plasma samples from the pivotal study S3010567. The reviewer notes that in the reanalysis, quality control samples were selected at concentrations of 0.60, 3.00 and 7.50 ng/mL, and calibration standards in the range of 0.20 to 10.0 ng/mL were utilized. The QC samples and calibration curve range in the reassay were found to be representative of the plasma nicotine concentrations generated in the study. The new LC/MS/MS assay (LLOQ = 0.20 ng/ml) was able to measure nicotine levels more than three half lives at both 2 and 4 mg doses.

Overall, the clinical pharmacology reviewer commented that the applicant adequately addressed the Clinical Pharmacology and Biopharmaceutics aspects of the NDA.

The results from the pivotal BE study are shown in tables 1 and 2 in the appendix.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

There were no clinical microbiology issues with this application.

7. Clinical/Statistical-Efficacy

There are no new efficacy data in this NDA submission. The efficacy of the marketed lozenge formulation was established in the pivotal safety and efficacy study (S1410043) in the approved original NDA 21-330. Study S3010567 indicated bioequivalence to the marketed Commit lozenge for both the 2 mg and 4 mg product.

8. Safety

Safety data to support this NDA comes from adverse event reports from the Phase I (S2300319, S2300339, and S2300320) and Phase II studies (S3010445, S3010466, and S3010567), and in addition, submitted postmarketing safety data. As part of the safety review, the medical officer also examined the data for the potential that the more rapid dissolution of the Nicorette lozenge may result in higher oral cavity nicotine levels and possibly increased side effects.

The medical reviewer notes that the Phase I pharmacokinetic studies were performed using a different formulation of the smaller lozenge. However, the active ingredient is the same (nicotine polacrilex) but the exact formulation is different from the proposed product. The information obtained from these studies was reviewed for adverse events, safety, and extent of exposure. Of the 233 subjects enrolled in the Phase I studies, 134 received lozenges. A total of 36 patients in the Phase I studies received a 2 mg lozenge and 6 (16.7%) had an adverse event considered to be treatment related. A total of 56 subjects in the Phase I studies received a 4 mg lozenge and 5 (9%) experienced a treatment related adverse event. There were also 42 patients in study S2300339 that received thirteen doses of the 1.5 mg lozenge and 43% had an event possibly or probably related to treatment. The subjects in the other studies only received single doses of the lozenge. The most common adverse events noted in the Phase I studies were gastrointestinal symptoms, dizziness, and headache. None of the adverse events were serious. Most of the adverse events reported in the Phase I studies were in Study S2300339 (the multi-dose study). Of note, there were no unexpected or unlabeled adverse events.

The medical reviewer further notes that a total of 248 patients were evaluated in the Phase II studies. There were 66 subjects treated with the 2 mg Nicorette lozenge and 4.5% of subjects reported at least one treatment related adverse event. There were 63 subjects treated with the 2 mg Commit lozenge and 6.3% of subjects reported at least one treatment related adverse event. There were 119 subjects that received the 4 mg dose (58 received Nicorette and 61 received Commit). Of these, 24.1% of subjects treated with the 4 mg Nicorette lozenge, and 14.8% of subjects treated with the 4 mg Commit lozenge reported at least one treatment related adverse event.

The most commonly reported treatment related adverse events (reported by >2 subjects) in the 4 mg Nicorette lozenge group were dizziness (3 subjects, 5.2%), headache (4 subjects, 6.9%), and nausea (6 subjects, 10.3%). None of the adverse events were considered serious. In the 4 mg Commit lozenge group, the most commonly reported adverse event was nausea (3 subjects, 4.9%).

The Nicorette lozenge had an incidence of adverse events similar to the Commit lozenge. The most common adverse events noted in the studies were nausea and gastrointestinal symptoms, headache, dizziness, and dry mouth and these events appeared to be dose related, i.e. occurring in greater frequency with the 4 mg dose than the 2 mg dose. Importantly, there were no unexpected or unlabeled adverse events.

The exposure for the nicotine polacrilex gum and lozenge has been extensive. As of 31 August 2007, GSK estimates exposure to nicotine gum at ——— patients. Exposure to the lozenge is even more extensive with estimates of ——— patients as of 31 August 2008. b(4)

Therefore, the GSK Worldwide Adverse Event Database was searched for all reports of adverse events. Once again, the nature of reported events is consistent with the product label. Gastrointestinal disorders were the most common followed by psychiatric disorders and respiratory, thoracic, and mediastinal disorders.The FDA AERS database was searched for all reports for Nicorette and Commit up to quarter 1 of 2008. The nature of the reported events was consistent with the product label.

The integrated safety review found no unexpected adverse events or unusual findings. Information provided regarding abuse, misuse and issues related to pregnancy, do not necessitate the need for any labeling changes. For details of these and other issues, and for the presentation of specific safety data, the reader is referred to the medical officer's review.

There were no specific studies to assess the more rapid dissolution time and the possibility of associated increased side effects. The sponsor states the Nicorette lozenge, as with the Commit lozenge, is intended to be moved around the mouth until completely dissolved. GSK believes that the movement around the mouth will disperse the nicotine and decrease the likelihood of an area of increased local concentration. In addition, the sponsor believes that if such an increase did have an impact on the tolerability of the new product this would likely be seen as reports of adverse events related to the mouth or throat or possibly the gastrointestinal tract (if swallowing of nicotine was an issue). However, a review of adverse events from the Phase II studies show relatively few issues related to the mouth or throat. Of events possibly related to swallowing of nicotine there was one report of hiccups for both the 2 mg and 4 mg Nicorette lozenge but none for either dose of Commit. Only for nausea was there any difference between the Nicorette lozenge and Commit; with 7 reports (about 12% of subjects) for 4 mg Nicorette lozenges and 3 reports (about 5% of subjects) for Commit.

No new adverse events unique to the Nicorette lozenge formulation were identified. The more rapid dissolution time does not appear to be of clinical concern, either locally or systemically (as bioequivalence was established).

9. Advisory Committee Meeting

There were no issues raised in this submission that required an advisory committee meeting.

10. Pediatrics

There were no changes in this submission that triggered PREA.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

The proposed name is acceptable. DMEPA comments that a warning should be placed on the PDP to inform consumers not to chew or swallow the lozenge whole, and to stop use of the lozenge at the end of 12 weeks. Both of these statements can already be found on the Drug Facts label and the Division has not required this of other sponsors, and therefore, I do not

agree with these recommendations. There do not appear to be any other significant labeling issues at this time.

13. Decision/Action/Risk Benefit Assessment

The proposed new formulation for nicotine polacrilex lozenges contains the same active ingredient as the currently marketed Commit lozenge, which has been shown to be safe and efficacious for smoking cessation. The new product is bioequivalent to Commit and there is no evidence that there are any new safety concerns, either locally, in the mouth, or systemically, identified during development of this product. Furthermore, no new efficacy or safety concerns were identified during the postmarketing safety review.

The recommended action is approval pending an "acceptable" recommendation from the Office of Compliance.

APPENDIX

Table 1: 2mg PK Parameters Based on Adjusted Concentrations

Parameter	(N) Mean[1] ± S.D.		*Ratio: Mini/Standard	
	Mini	Standard	Estimate	90% CI
C_{max} (ng/ml)	(38) 3.93 ± 1.14	(35) 4.18 ± 1.34	95.12%	[90.37%, 100.11%]
$AUC_{(0-t)}$ (ng·hr/ml)	(38) 14.02 ± 5.18	(35) 14.98 ± 5.97	94.09%	[90.22%, 98.12%]
$AUC_{(0-\infty)}$ (ng·hr/ml)	(38) 15.30 ± 5.74	(35) 16.32 ± 6.39	93.92%	[90.04%, 97.97%]

Table 2: 4mg PK Parameters Based on Adjusted Concentrations

Parameter	(N) Mean[1] ± S.D.		*Ratio: Mini/Standard	
	Mini	Standard	Estimate	90% CI
C_{max} (ng/ml)	(32) 6.28 ± 2.04	(35) 7.40 ± 2.77	85.40%	[80.35%, 90.78%]
$AUC_{(0-t)}$ (ng·hr/ml)	(32) 24.06 ± 9.14	(35) 27.32 ± 12.19	90.39%	[85.91%, 95.09%]
$AUC_{(0-\infty)}$ (ng·hr/ml)	(32) 25.72 ± 9.98	(34) 29.61 ± 13.11	90.57%	[86.21%, 95.15%]

Source: Table 9.2.2.2a

1 Unadjusted treatment means

* Ratio of geometric means

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/s/

Joel Schiffenbauer
5/18/2009 06:43:12 AM
MEDICAL OFFICER