CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-360

CHEMISTRY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: May 15, 2009

From: Yubing Tang, Ph.D.
Review Chemist, ONDQA
Premarketing Assessment Division II
ONDQA

Through: Moo-Jhong Rhee, Ph. D.
Chief, Branch III
Premarketing Assessment Division II
ONDQA

To: NDA 22-360, CMC Review #1

Subject: Establishment Evaluation

CMC Review #1 was DFS'd on April 07, 2009 with a recommendation of Not Approval due to pending Establishment Evaluation. On May 15, 2009, the Office of Compliance issued an overall acceptable recommendation for all the facilities involved in the manufacture and testing of the drug substance and drug product. Thus, this application is recommended for Approval from the perspective of Chemistry, Manufacturing and Controls. This memorandum closes all pending issues for this NDA from the CMC perspective. The EER Summary Report is shown below:

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 22360/000
Org Code: 560
Priority: 5S
Stamp Date: 18-JUL-2008
PDUFA Date: 18-MAY-2009
Action Goal:
District Goal: 19-MAR-2009

Sponsor: GLAXOSMITHKLINE CONS
1500 LITTLETON RD.
PARSIPPANY, NJ, 07054-3884
Brand Name: NICOTINE POLACRILEX
MINI MINT LOZENGE
Estab. Name:
Generic Name: NICOTINE POLACRILEX
MINI MINT LOZENGE
Dosage Form: (TROCHE)
Strength: 2 MG AND 4 MG

FDA Contacts: S. GOLDIE, Project Manager, 301-796-2055
Y. TANG, Review Chemist, 301-796-2457
S. DING, Team Leader, 301-796-1349

Overall Recommendation: ACCEPTABLE on 15-MAY-2009
by E. JOHNSON (HFD-320) 301-796-3334

Establishment: CFN: 1046838 FEI: 1046838
GLAXOSMITHKLINE CONSUMER HEALTHCARE;
DBA-GLAXOSMITHKLINE
65 WINDHAM BLVD
AIKEN, SC 298059384
DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: TTR OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-JAN-09
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 9610449 FEI: 3003723174
SBP IRVINE SMITHKLINE BEECHAM PHARMACEUTICALS
AYRSHIRE, SCOTLAND
IRVINE, UK
DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-MAY-09
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

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/s/

Yubing Tang
5/15/2009 03:33:27 PM
CHEMIST

Shulin, Please let Moo-Jhong know this since I cannot write any explanation to him.

Shulin Ding
5/15/2009 03:42:19 PM
CHEMIST
On behalf of Moo-Jhong.

CHEMISTRY REVIEW

NDA 22-360

Nicorette® Mini Mint Lozenge
(nicotine polacrilex) 2mg / 4mg lozenges

GlaxoSmithKline Consumer Healthcare, L.P.

Yubing Tang, Ph.D.

Branch III, Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

CMC Review of NDA 22,360
For the Division of Nonprescription Product

Table of Contents

Chemistry Review Data Sheet

1. NDA: 22-360

2. REVIEW: #1

3. REVIEW DATE : March 25, 2009

4. REVIEWER: Yubing Tang, Ph.D.

5. PREVIOUS DOCUMENTS:
Not applicable

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	July 22, 2008
Amendment[1]	September 09, 2008
Amendment[2]	October 21, 2008
Amendment[3]	January 13, 2009
Amendment[4]	February 09, 2009
Amendment[5]	February 13, 2009
Amendment[6]	March 27, 2009
Amendment[7]	April 02, 2009

1. Response to 74 day letter dated August 26, 2008
2. Response to IR letter dated September 29, 2008
3. Response to IR letter dated December 15, 2008
4. Response to IR letter dated December 19, 2008
5. Response to IR letter dated January 29, 2009
6. Response to IR letter dated March 11, 2009
7. Response to IR letter dated April 01, 2009

7. NAME & ADDRESS OF APPLICANT:

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Name: GlaxoSmithKline Consumer Healthcare, L.P.

Address: 1500 Little Road
Parsippany, NJ 07054-3884

Representative: Iris H. Shelton
Assistant Director, Regulatory Affairs
GlaxoSmithKline Consumer Healthcare, L.P.

Telephone: 973-889-2167

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: *Nicorette*® mini mint lozenge
b) Non-Proprietary Name (USAN): nicotine polacrilex
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: nicotine replacement, smoking cessation aid

11. DOSAGE FORM: lozenge

12. STRENGTH/POTENCY: 2mg, 4mg, Maximum Daily Dose (MDD): 80mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: ___Rx _x_ OTC

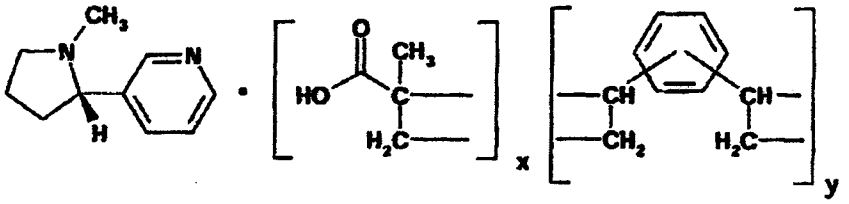
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name:	• Nicotine Polacrilex • 2 propenoic acid, 2-methyl-polymer with diethenylbenzene, complex with (S)-3-(1-methyl-2-pyrrolidinyl) pyridine

Structure Formula:	

Molecular Formula:	$C_{10}H_{14}N_2(C_4H_6O_2)_x(C_{10}H_{10})_y$

Molecular Weight:	162.23 + 86x +130y where: x = number of methacrylic acid units per NPA molecule y = number of divinylbenzene units per NPA molecule

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
					Adequate		Reviewed by Y. Tang
					Adequate		Reviewed by Y. Tang
					Adequate		
					Adequate	N/A	

b(4)

Chemistry Review Data Sheet

			Peppermint Flavor				
[					Adequate	N/A	Also reviewed under S004 of NDA 21-330.] b(4)
					Adequate	N/A	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
CMC Review #1, Aug. 19, 2002	NDA 21-330	Commit® Lozenge was approved under NDA 21-330, which uses the same drug substance and is sponsored by the same applicant. NDA 22-360 is cross-referenced to NDA 21-330.
CMC Review #2, Aug. 28, 2002	NDA 21-330	
CMC Review #3, Oct. 24, 2002	NDA 21-330	

18. CONSULTS/CMC-RELATED REVIEWS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending	April 1, 2009	
Pharm/Tox	Acceptable	March, 2009	Li, Cindy
Biopharm	N/A		
Division of Non-prescription products	N/A		

Chemistry Review Data Sheet

Methods Validation	N/A		
Labeling	N/A		
EA	Acceptable	Dec. 2008	Tang, Yubing
Microbiology	N/A		No consult needed.

The Chemistry Review for NDA 22-360

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. However, the final recommendation from Office of Compliance on the facility inspection is still pending. Therefore, from the CMC perspective, this NDA is not recommended for approval until cGMP issues are resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

II. Summary of Chemistry Assessments

This NDA is submitted for the nonprescription marketing of *Nicorette*® mini mint lozenges (nicotine polacrilex, 2 mg and 4 mg) for the treatment of smoking related withdrawal symptoms. 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 ——————————— b(4)

A. Description of the Drug Product(s) and Drug Substance(s)

1) Drug Product

The proposed drug product, *Nicorette*® mini lozenges (Nicotine Polacrilex USP, 2mg and 4mg lozenge), is a small, white to off-white, oval, mint flavored lozenge with convex surfaces, debossed M (2 mg lozenges) and F (4 mg lozenges) on one side. Each lozenge contains nicotine polacrilex equivalent to 2 mg or 4 mg of nicotine. The following are formulated as inactive ingredients: mannitol USP, ——————————— b(4)
sodium alginate NF ———————————
——————————, sodium carbonate ———— NF, calcium polycarbophil USP, magnesium stearate NF. xanthan gum NF, acesulfame-k EP, potassium bicarbonate USP, and ————————

The manufacturing process of *Nicorette*® mini mint lozenges and commercial batch size ———— are the same as those approved for *Commit*® lozenges under NDA 21-330. A b(4)

[redacted] b(4)

After the negotiation with the applicant regarding the dissolution method and the acceptance criteria, the proposal that the drug product specification for *Nicorette*® mini mint lozenges be the same as that approved under NDA 21-330/S-006 is acceptable. Supported with the registration stability results acquired under the bracket stability study design, the proposed 24 month expiration dating period is granted.

Nicorette® mini mint lozenges are proposed to be packaged in a child-resistant, [redacted] vial equipped with a flip-top closure [redacted] The vial [redacted] has an [redacted] There is a neck band served as the required tamper-evident feature. b(4)

Since this is an OTC product, the labeling review is deferred to the Division of Non-prescription Products for the content of the insert and the label.

2) Drug Substance

The drug substance for this New Drug Application, nicotine polacrilex USP, is the same as that used in the previously approved applications for *Commit*® lozenges (NDA 21-330). It is produced via a [redacted] (also called [redacted] supplied by [redacted] are referenced to DMF [redacted] respectively. Both DMFs have been reviewed and found to be adequate under the current NDA. The specification and the stability of nicotine polacrilex USP remain the same as those already approved *Commit*® lozenges under NDA 21-330. b(4)

B. Description of How the Drug Product is Intended to be Used

Nicorette® mini mint lozenges are small, white to off-white, oval shaped and mint flavored lozenges with convex surfaces. It is intended to be used to reduce withdrawal symptoms associated with quitting smoking. Each lozenge contains 2mg (or 4 mg) of nicotine and is formulated to be slowly dissolved (approximately 10 minutes) when placed into mouths. Users are instructed to occasionally move a lozenges from one side of the mouth to the other side to allow the dissolution of the lozenges to release nicotine. The dosing is symptom dependent with 20 x 4mg nicotine lozenges being the maximum daily dose.

Based on the available stability study data, the proposed 24 months expiration dating period is granted for both 2mg and 4mg lozenges under the labeled storage conditions (20° – 25°C (68° – 77°F)).

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

However, the drug substance facility is pending "acceptable" recommendation from the Office of Compliance.

III. Administrative

A. Reviewer's Signature: In DFS

Yubing Tang, Ph.D.
Chemist, Branch III/DPAII/ONDQA

B. Endorsement Block: In DFS

Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch III/DPAII/ONDQA

C. CC Block: In DFS

77 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Yubing Tang
4/7/2009 11:32:57 AM
CHEMIST

Moo-Jhong Rhee
4/7/2009 11:35:45 AM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Nonprescription Clinical Evaluation
NDA:	22-360
Applicant:.	GlaxoSmithKline Consumer Healthcare, L.P.
Stamp Date:	July 18, 2008
PDUFA Date	May 18, 2009
Trademark:	Commit® Mini™
Established Name:	Nicotine Polacrilex
Dosage Form:	Lozenges
Route of Administration:	Oral
Indication:	Reduction of withdrawal symptoms, including nicotine craving associated with quitting smoking
PAL:	Shulin Ding

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☒	☐

Summary and Critical Issues

A. Summary

This NDA is submitted by GlaxoSmithKline Consumer Healthcare under section 505(b)(1) of the Federal Food Drug and Cosmetic Act in support of the nonprescription marketing of Commit® Mini™ (nicotine polacrilex) lozenges 2 mg and 4 mg for the treatment of smoking related withdrawal symptoms. The NDA is a reformulation of Commit lozenges 2 mg and 4 mg, approved under NDA 21-330, to provide a smaller version of Commit lozenges. GlaxoSmithKline conducted one bioequivalence study to support the reformulation.

All CMC information of drug substance (nicotine polacrilex USP), and some CMC information of drug product are referenced to NDA 21-330. Since the holder of NDA 21-330 is also GlaxoSmithKline, no right-of-reference letter but a cross reference statement is provided in this NDA.

When compared with the approved, currently marketed standard lozenges, mini lozenges are smaller in size [redacted] mg. which is [redacted] of the standard lozenges by weight), and contains [redacted] and a new artificial sweetener (acesulfame-k NF). [redacted] b(4)

The reformulated products are white to off-white, oval, mint flavored lozenges with convex surfaces, debossed M (2 mg lozenges) and F (4 mg lozenges) on one side. Each lozenge contains nicotine polacrilex equivalent to 2 mg or 4 mg of nicotine, and the following inactive ingredients: mannitol USP. [redacted] sodium alginate NF. [redacted] b(4)

b(4)

[redacted], sodium carbonate [redacted] NF, b(4)
calcium polycarbophil USP, magnesium stearate NF, xanthan gum NF, acesulfame-k NF, potassium bicarbonate USP, and [redacted]

The manufacturing process and commercial batch size [redacted], of Commit Mini lozenges are the same as those approved for Commit standard lozenges under NDA 21-330 [redacted] b(4)

The proposed drug product specification for Commit Mini is the same as that approved under NDA 21-330/S-006 with one exception, which is dissolution method and acceptance criteria. For Commit Mini, the proposed dissolution method is a [redacted] test (instead of [redacted] approved under NDA 21-330), and the proposed acceptance criteria are [redacted] (instead of [redacted] approved under NDA 21-330). b(4)

Commit Mini lozenges are proposed to be packaged in a child-resistant [redacted] vial equipped with a flip-top closure [redacted] The vial [redacted] has an [redacted] is the smaller size to the vial previously approved under NDA 21-330/S-003 and S-004. A neck band is served as the required tamper-evident feature. The proposed lozenge counts per vial are unclear. It appears to be anywhere between [redacted] b(4) b(4)

The stability data supporting the proposed 24 month expiry period at the storage temperature of below 30°C include long term (25°C/60% RH) data of 3-36 months, 30°C/75% RH data of 3-6 months, and accelerated temperature (40°C/75% RH) data of 3-12 months from multiple pilot and production scale batches for each strength. Supporting stability data from five batches of 1.5 mg strength are also provided in the NDA. A categorical exclusion from the requirement to prepare an Environmental Assessment is claimed for this NDA.

B. Critical issues for review

Drug Product Specification

- The applicant proposes to use a [redacted] dissolution specification to control the dissolution profile of the product. The acceptance criteria need to be carefully reviewed. Furthermore [redacted] are not adequate to describe a non-linear release profile. Normally, it needs at least [redacted] b(4)

- Identity test proposed covers [redacted] CMC reviews of NDA 21-330 indicate that the NDA was approved [redacted] On the other hand, it is noted that USP monograph on nicotine polacrilex gum include ID tests for both nicotine and polacrilex moieties. A critical review is necessary to determine if the absence of an ID on polacrilex is acceptable based on current regulatory thinking. b(4)

- Microbiological test is proposed to be performed for the first 5 batches using a method which can be any in-house method complying with USP<61>, and then one batch of each strength annually afterward. The reduced testing may be

acceptable but the microbiological method must be the one that has been validated for Commit Mini lozenges 2 mg and 4 mg. It can not be any method.

Drug Product Container/Closure Systems

- The applicant does not specify lozenge count per vial. A statement in Section 3.2.P.8.1 suggests that the count can be anywhere [redacted] The mock-up labels provided in Module 1 suggest that the counts could be 24 [redacted] and 108. CMC review can not be properly performed without an accurate understanding of the configurations sought for approval. b(4)

- The applicant does not describe in Module 3 what the tamper evident feature is and whether the same feature has been implemented for the approved Commit standard lozenges. Manufacturing information for tamper evident feature is not provided either.

Drug Product Post-approval Stability Protocol

- The proposed storage temperature for post-approval stability protocol is [redacted], which is unacceptable if the granted storage condition is below [redacted] as proposed by the applicant. b(4)

C. Comments for 74-Day Letter

The following comments are to be conveyed to the applicant in the 74-day letter:

1. Provide description and manufacturing information for tamper-evident feature.

2. Specify the exact lozenge counts per vial which you plan to market for the proposed Commit Mini lozenges 2 mg and 4 mg.

D. Comments/Recommendation

The following three filing issues and requests were conveyed to the applicant in the IR letter dated Aug. 26, 2008:

1. Provide formulation and manufacturing (date, site and batch size) information for each drug product clinical batch (including standard lozenges) used in the clinical BE study S3010567. We have noted discrepancies between Module 2 (p. 6 of 7, Section 2.3.P.2 Pharmaceutical Development) and Module 5 (pp. 15-16 of 166, clinical study report for study S3010567) regarding manufacturing site.

2. Provide method validation reports and data to support drug product methods C1925, C1926, C1927, and the three microbial methods included in drug product specification.

3. Provide a copy of the production scale master batch record for each proposed drug product.

An adequate response has been provided in the amendment dated Sep. 9, 2008 for each issue. This NDA is, therefore, **fileable** from chemistry, manufacturing and controls (CMC) perspective. The major review issues include container/closure system, and dissolution specification.

GMP inspections have been requested. The drug substance manufacturing site is in United Kingdom. The drug product manufacturing site is in U.S.

Shulin Ding
Pharmaceutical Assessment Lead, Branch III

Moo-Jhong Rhee
Chief, Branch III

Filing Checklists

A. Administrative Checklists

YES	NO		Comments
x		On its face, is the section organized adequately?	
x		Is the section indexed and paginated adequately?	
x		On its face, is the section legible?	
x		Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	
x		Has an environmental assessment report or categorical exclusion been provided?	

B. Technical Checklists

1. Drug Substance: Nicotine Polacrilex USP referenced to approved NDA 21-330

	x	Does the section contain synthetic scheme with in-process parameters?	
	x	Does the section contain structural elucidation data?	
	x	Does the section contain specifications?	
	x	Does the section contain information on impurities?	
	x	Does the section contain validation data for analytical methods?	
	x	Does the section contain container and closure information?	
	x	Does the section contain stability data?	

2. Drug Product

x		Does the section contain manufacturing process with in-process controls?	Missing Master batch record
x		Does the section contain quality controls of excipients?	
x		Does the section contain information on composition?	
x		Does the section contain specifications?	
x		Does the section contain information on degradation products?	
x		Does the section contain validation data for analytical methods?	
x		Does the section contain information on container and closure systems?	
x		Does the section contain stability data with a proposed expiration date?	
x		Does the section contain information on labels of container and cartons?	
x		Does the section contain tradename and established name?	

C. Review Issues

x		Has all information requested during the IND phases, and at the pre-NDA meetings been included?	
	x	Is a team review recommended?	

x		Are DMFs adequately referenced?	

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/s/

Shulin Ding
9/11/2008 03:21:51 PM
CHEMIST

Moo-Jhong Rhee
9/15/2008 01:20:06 PM
CHEMIST
Chief, Branch III