CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-360

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-360
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	July 18, 2008
PRODUCT:	Commit Mini Mint Lozenges*, 2mg and 4mg
INTENDED CLINICAL POPULATION:	Reduce withdrawal symptoms including nicotine craving associated with quitting smoking
APPLICANT:	GlaxoSmithKline Healthcare, L.P.
DOCUMENTS REVIEWED:	Vol. 1
REVIEW DIVISION:	Division of Nonprescription Clinical Evaluation (HFD-560)
PHARM/TOX REVIEWER:	Cindy Li, Ph.D.
PHARM/TOX SECONDARY REVIEWER:	Wafa Harrouk, Ph.D.
PHARM/TOX SUPERVISOR:	Paul Brown, Ph.D.
DIVISION DIRECTOR:	Andrea Leonard-Segal, M.D.
PROJECT MANAGER:	Mary Lewis, RPM

Date of review submission to Division File System (DFS): 3/26/2009

*Product Name was requested to be changed to Nicorette Lozenge on 2/10/20009

EXECUTIVE SUMMARY

A. Recommendation on approvability

This is a 505(b)(1) application. The sponsor is relying on data submitted under NDA 21-330, which was also submitted by this applicant. Based on the risk-benefit analysis and the experience of human use of nicotine polacrilex, NDA 22-360 can be approved from the nonclinical perspective.

B. Recommendation for nonclinical studies

There are no outstanding pharmacology/ toxicology issues.

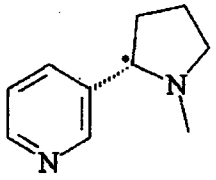
PHARMACOLOGY/TOXICOLOGY REVIEW

NDA number: 22-360
Review number: 1
Sequence number/date/type of submission: SN000/ 07/18/2008 /NDA
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: GlaxoSmithKline Healthcare, L.P.
Manufacturer for drug substance: GlaxoSmithKline Healthcare, L.P.

Reviewer name: Cindy Li, Ph.D.
Division name: DNCE, Office of Nonprescription Products (ONP)
HFD #: 560
Review completion date: 3/12/2009

Drug:

Trade name: Nicorette
Generic name: Nicotine® (Nicotine polacrilex) Mini Lozenges, 2mg and 4mg
Chemical name: 3-(1-methyl-2-pyrrolidinyl)pyridine
CAS registry number: 54-11-5
Molecular formula/molecular weight: C10H14N2, 162.234
Structure:



Relevant INDs/NDAs/DMFs:
IND: 56, 295 (Nicotine Polacrilex Lozenges)
NDA: 21-330 and supplements (Commit Nicotine Polacrilex Lozenges, 2mg and 4mg)
DMF:

DMF
DMF
DMF
DMF

b(4)

DMF

DMF

Drug class: Nicotine replacement therapy

Intended clinical population: Reduce withdrawal symptoms including nicotine craving associated with quitting smoking.
Clinical formulation: Nicotine Lozenges in oral dosage form

Route of administration: Oral Lozenges to be dissolved slowly in the mouth

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-360 are owned by GlaxoSmithKline Healthcare, L.P. or are data for which GlaxoSmithKline Healthcare, L.P. has obtained a written right of reference. Any information or data necessary for approval of NDA 22-360 that GlaxoSmithKline Healthcare, L.P. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that GlaxoSmithKline Healthcare, L.P. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-360.

Background:

The currently proposed product, Nicorette lozenges initially referred to as Commit Mini Mint Lozenges (Nicorette), 2mg and 4mg, are considered to be a line extension of the currently marketed Commit®, Nicotine Polacrilex Lozenges, 2mg and 4mg, by GlaxoSmithKline (GSK) (under approved NDA 21-330). Commit Lozenges (original, mint flavor, cherry flavor) are available in the same strengths, contain the same active ingredient, Nicotine Polacrilex and have the same indication. The proposed product is smaller in size and contains a different flavoring system. The smaller size is considered to be more discreet for individuals using the product in a public setting.

The intended clinical indication is to reduce withdrawal symptoms including nicotine craving associated with quitting smoking.

The proposed use of the product is one lozenge every 1-2 hours each day for the first 6 weeks, one lozenge every 2-4 hours on Week 7-9, and one lozenge every 4-8 hours on Week 10-12, with a recommendation not to exceed a maximum dosage of 20 lozenges per day. The recommended duration of treatment is 12 weeks and [redacted] b(4)

The nonclinical section in Module 4 of this application cross-references the data provided under the approved nicorette (NDA 21-330) and supplements. The pharmacology and toxicology overview and summaries in Module 2 are provided with new information added to address [redacted] and pertinent literature data published since the previously approved submissions. b(4)

Pharmacology/Toxicology Review:

The components of the proposed product are presented in the below table:

Table 1
Quantitative Composition of Nicotine Mini Mint 4mg Lozenge

Name of Ingredients	Reference to Standard	Composition (mg/lozenge)	Function of Ingredient
Active substance			
Nicotine Polacrilex[1] (equivalent to Nicotine)	USP		Active
Excipients			
Mannitol[2]	USP		
	DMF		
Sodium Alginate[2]	NF		
	DMF		
	DMF		
Sodium Carbonate	NF		
Calcium Polycarbophil[2]	USP		
Magnesium Stearate	NF		
Xanthan Gum[2]	NF		
Acesulfame-k	EP		
Potassium Bicarbonate[2]	USP		
	USP		
Total lozenge weight	-		-

b(4)

b(4)

b(4)

1.
2.
3.

b(4)

Evaluation of Nicotine Polacrilex: The drug substance for this NDA, nicotine polacrilex USP, is the same as that used in the previously approved application for *Commit*® lozenges (NDA 21-330). It is (also called

b(4)

1) Review of

b(4)

b(4)

2) Review of the summary of recently published data on nicotine:

The in-depth review of toxicity studies of the active ingredient can be found in NDA 21-330 (Nicotine Polacrilex Lozenges) and its corresponding supplements.

A review of recently published pharmacology and toxicology studies (non-GLP) is provided below.

(1). Review of the recent scientific literature on the metabolism of nicotine concluded that a) studies of nicotine's potential to induce or inhibit cytochrome CYP2E1 showed that CYP2E1 regulatory mechanisms can vary and may be influenced by species, tissue, inducing agent and mode of administration; b). human CYP2A13 was an efficient enzyme in catalyzing the C-oxidation of nicotine to form cotinine *in vitro*; c) the relevance of these newly reported findings to the use of a nicotine replacement therapy is uncertain.

(2). CYP2A13 can efficiently metabolize nicotine, however, the observed in vitro results cannot be directly correlated to reactions that occur in vivo.

(3). A repeat-dose toxicity study that investigated the effects of nicotine on blood lipid levels, hepatic and renal function, arteriogenesis, angiogenesis and restenosis in a rabbit model showed that nicotine may promote angiogenesis and contribute to restenosis.

(4). A recently reported in vitro assay indicated that nicotine can be mutagenic and genotoxic to human cell cultures at 0.125 to 4 mM nicotine; however, the results of a mouse micronucleus study demonstrated the lack of an in vivo mutagenic effect by nicotine at 1-2 mg/kg/day.

(5). The effects of nicotine on the mitogenic, cell proliferating, angiogenic and tumor promoting potential were investigated. Nicotine can stimulate cell proliferation as a result of its mitogenic activity, which could contribute to the growth and progression of tumors. Nicotine may also induce cell proliferation by ß-arrestin–mediated activation of the Src and Rb–Raf-1 pathways; angiogenic effect of nicotine is mediated by β-FGF and induced through the nicotinic receptor, αvβ3 integrin, and MAPK.

(6). A reported toxicology study where adult male Wistar rats were administered 0.125 mg/kg nicotine by subcutaneous injection once daily for 90 days suggested that nicotine causes alterations in the secretory epithelium of the ventral prostate, which compromises its function and represents a risk factor for development of prostatic disease. The safety margin cannot be determined due to the different administration route.

(7). Results of the recently reported studies do not alter the conclusions regarding the reproductive and developmental toxicity of nicotine that were previously presented in NDA-21-330 and its corresponding supplements.

(8). The results of the recently published study of 0.25 mg /100g nicotine on the mucosa of rats indicated that epithelium of animals treated with nicotine demonstrated an altered phenotype characterized by a reduction in cellular area, cell membrane disorganization and tissue spoiling.

The new published information did not provide any scientific evidence that are strong enough to alter the conclusions regarding the toxicity of nicotine that were previously presented in NDA-21-330 and its corresponding supplements.

Conclusions: Some of the new published reports suggest that nicotine may contribute to prostate and cheek pouch toxicities. However, the risks associated with continued smoking would outweigh the risks associated with exposure to nicotine lozenges.

3. Evaluation of inactive ingredients:

The review of the toxicity profile of inactive ingredients is referred to NDA 21-330 and its corresponding supplements. The difference between the previously approved NDA (21-330) and the current NDA (22-360) is the new flavoring system which includes ——— b(4)

The ——— b(4)
——— NDA#21-330) or cherry flavor
(with ——— NDA#21-330 Supplement #4) that were approved for
Commit lozenge ——— DMFs ——— have been filed by the b(4)
manufacturers of these ———

Relevant DMFs on [redacted] b(4)

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE	COMMENTS
[redacted]					
[redacted]					b(4)
[redacted]					Reviewed under S004 of NDA 21-330 by Dr. Dan Mellon

The sponsor states the following:

"With the exception of the flavors and the sweetener, all of the excipients are approved pharmaceutical grade materials (US Pharmacopoeia or US National Formulary) and all are identical to those used in the currently marketed Commit Lozenges. Additionally, all of these excipients have a history of in-use safety in similar products of this type, and most of these ingredients are designated as substances that are generally recognized as safe (GRAS). All [redacted] of the flavor ingredients, consist of components which are designated as substances that are generally recognized as safe (GRAS), or are approved for use by a regulation of FDA. Additionally, each of the flavors complies with the Code of Practices of the International Organization for the Flavor Industry (IOFI). The sweetener, acesulfame potassium, is designated by FDA as a substance that may be safely used as a sweetening agent in food when used at a level not exceeding the amount reasonably required to accomplish the intended effect." b(4) b(4) b(4)

The CMC reviewer for NDA 22-360 noted that all three DMFs are adequate from the CMC's perspective.

The nonclinical safety assessment of acesulfame has been previously reviewed by Dr. Dan Mellon (Pharmacology/Toxicology reviewer) in an ONP consult on November 22, 2005 for NDA# 21-330 Supplement #4. He stated that acesulfame potassium is listed in the Inactive Ingredient Database for Approved Drug Products. In addition, CFR 21(172.800) indicates that Acesulfame K may be safely used as a sweetening agent in chewing gum with no limits on the maximum amount other than the amount should not exceed that reasonably required to accomplish the intended effect (as GRAS defined) . Dr. Mellon concluded that there are no preclinical concerns regarding this excipient.

The nonclinical safety assessment of [redacted] has been previously conducted by Dr. Dan Mellon in review of NDA#21-330 Supplement #4. He suggested that in consideration of the chemical composition of the flavoring agents and the designation of GRAS by the Flavor and Extract Manufacturers Association (FEMA), the flavoring agent[redacted] appear to be adequately qualified for safety in the drug product. b(4) b(4)

The other [redacted] flavors [redacted] consist of similar components a[redacted] which are either designated as substances that are generally recognized as safe [CFR 21 (182.10 and 20)], or have been evaluated by FEMA, or are approved by FDA. b(4)

As per the FDA's guidance document, Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients, the FDA will consider factors such as use in previously approved products or GRAS status as a direct food additive. The reviewer concurs that [redacted] flavors meet this standard from the nonclinical perspective. b(4)

Conclusion: there are no preclinical concerns regarding the flavoring agents in the proposed drug product.

4. Evaluation of degradation products and residual solvents profile:

Degradation products of Commit Mini Mint Lozenges (Nicorette), 2mg and 4mg, include cotinine, (1'R , 2'S)-nicotine-1'-N-oxide, (1'S,2'S)-nicotine-1'-N-oxide, myosmine, a complex of nornicotine and anatabine, and pseudooxynicotine.

Cotinine, (1'R,2'S)-nicotine-1'-N-oxide, and (1'S,2'S)-nicotine-1'-N-oxide, each at a concentration of [redacted] of nicotine, results in a potential maximum daily exposure of [redacted] These degradation products are naturally-occurring metabolites of nicotine in humans, further qualification for their presence is not required (ICH Q3B(R2)). b(4)

Myosmine at a concentration of [redacted] of nicotine results in a potential maximum daily exposure of [redacted] ay). No significant adverse effects would be anticipated from the exposure to this degradation product from use of Mini Mint Nicotine Lozenges 2 mg and 4 mg. b(4)

A complex of nornicotine and anatabine, and Pseudooxynicotine at a concentration of [redacted] of nicotine, respectively, results in a potential maximum daily exposure of [redacted]. This exposure is below the qualification thresholds of 0.5% or 200 µg/day defined by ICH Topic Q3B and qualification of the presence of pseudooxynicotine in Mini Mint Nicotine Lozenges 2 mg and 4 mg on the basis of biological safety is therefore not required. b(4)

Conclusion: The presence of the degradation products, cotinine, (1'R , 2'S)-nicotine-1'-N-oxide, (1'S,2'S)-nicotine-1'-N-oxide, myosmine, a complex of nornicotine and anatabine, and pseudooxynicotine, at the specified amounts is not considered to be of toxicological concern in Nicotine Lozenges 2 mg and 4 mg.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:
On overview of the NDA application: there are no outstanding pharmacology/toxicology issues.

Unresolved toxicology issues (if any): None

Recommendations: NDA 22-360 can be approved from the nonclinical perspective.

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

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/s/

Xinguang Li
3/26/2009 05:14:59 PM
INTERDISCIPLINARY

Please review and sign off. Thanks!

Paul Brown
3/27/2009 11:09:34 AM
PHARMACOLOGIST

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-360 **Applicant:** GlaxoSmithKline Consumer Healthcare, L.P. **Stamp Date:** July 18, 2008

Drug Name: Commit® (nicotine polacrilex) Mini Mint 2mg and 4mg Lozenge **NDA Type:** 505(b)(1)

Background:
The Commit Mini Mint Lozenges, 2mg and 4mg, are considered to be a line extension of the currently marketed Commit® Lozenges, which are available in the same strengths, contain the same active ingredient (Nicotine Polacrilex), and have the same indication as "reduces withdrawal symptoms, including nicotine craving associated with quitting smoking". The currently proposed product is smaller in size and contains a different flavoring system.

The recommended use of the proposed product is one every 1-2 hours each day for the first 6 weeks, one lozenge every 2-4 hours on Week 7-9 and one lozenge every 4-8 hours on Week 10-12.

The present application cross-refers to the data provided in approved NDA 21-330, and supplements. Pharmacology and toxicology overview and summaries are provided with new information added to address the flavoring system and pertinent literature data published since the previously approved submissions.

On initial overview of the NDA application: There are no outstanding pharmacology/ toxicology issues since there are no additional studies for submission at this time in the pharmacology/toxicology section.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	Comment
1	On its face, is the pharmacology/toxicology section of the NDA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?	x		Yes- this is a 505(b)(1) application. The sponsor is relying on data submitted under NDA 21-330
2	Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner allowing substantive review to begin?			N/A
3	On its face, is the pharmacology/ toxicology section of the NDA legible so that substantive review can begin?			N/A
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility, juvenile studies, acute and repeat dose adult animal studies*, animal ADME studies, safety pharmacology, etc)?			N/A
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A
6	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?			N/A
7	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			N/A
8	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?			N/A

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?			N/A
10	If there are any impurities – etc. issues, have these been addressed? (New toxicity studies may not be needed.)			N/A
11	Has the sponsor addressed any abuse potential issues in the submission?			N/A
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?			The sponsor is relying on data submitted under NDA 21-330.
13	From a pharmacology/toxicology perspective, is the NDA fileable? If ``no`` please state below why it is not.	x		

Cindy Li — 12Nov08
Reviewing Pharmacologist — Date

Paul Brown — 12Nov08
Team Leader/Supervisor — Date

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/s/

Xinguang Li
11/12/2008 12:36:30 PM
INTERDISCIPLINARY

Paul Brown
11/25/2008 01:17:15 PM
PHARMACOLOGIST