

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 74-707

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 3
2. ANDA # 74-707
3. NAME AND ADDRESS OF APPLICANT
Circa Pharmaceuticals, Inc.
Attention: Joyce Anne DelGaudio
33 Ralph Avenue
P.O. Box 30
Copiague, NY 11726-0030
4. LEGAL BASIS for ANDA SUBMISSION
Listed drug is Nicorette® (Marion Merrel Dow, NDA#18612)
Exclusivity for NCE expired 1/13/94 and for new product (NDA#
20066) expired 6/8/95. The firm has been asked to submit draft OTC
labeling for the product since the gum is already granted OTC
status. The product exclusivity for the OTC strength expires on
2/9/1999.
5. SUPPLEMENT(s) N/A
6. PROPRIETARY NAME None
7. NONPROPRIETARY NAME Nicotine Polacrilex Gum
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
9. AMENDMENTS AND OTHER DATES:
Firm:
7/6/95: Date of submission
11/3/95: Original amendment
3/28/96: Original amendment (bioequivalence)
8/14/97: Major amendment
9/2/98: Response/Major amendment
1.29.99: Telephone amendment
FDA:
8/17/95: RTF
3/11/96: Acceptable for filing
6/6/96: Label deficiencies
1/29/97: Chemistry & labeling deficiency letter
4/2/98: Bio request for a chew-out study
11/25/98: Label review acceptable
1/28/99: Telephone call by chemist
10. PHARMACOLOGICAL CATEGORY
Ganglionic Stimulating Agent
Use: Smoking deterrent
11. Rx or OTC
OTC
12. RELATED IND/NDA/DMF(s): See element #37 for list of DMFs
ANDA:74-507 (2 mg Gum) was granted Tentative Approval by the
Office.
13. DOSAGE FORM
Chewing Gum
14. POTENCY
4 mg

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Information and are not

releasable.

Chemistry

SECTION VII. COMPONENTS AND COMPOSITION STATEMENTS

2. **Composition**

- The following is the Composition Statement for our Nicotine Polacrilex Gum, 4 mg

<u>Ingredient</u>	<u>mg/piece</u>
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Nicotine Polacrilex Glycerinated	
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Sorbitol,	
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Sodium Carbonate.	
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Gum Base	
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Flavor	
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(Butylated Hydroxytoluene)	
----------------------------	--

Blend,	
--------	--

Carnauba Wax,	
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Talc #	
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JSP	
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TOTAL GUM PIECE WEIGHT:	960.00
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* Quantity based on active assay and includes an overage. Please refer to Section VI for an explanation of the overage.

**

Please refer to Section XI for a description of the manufacturing process.

**COPY FOR YOUR
INFORMATION**

TELEFAX

To: Mary I. Lambert , M.N., R.N., C.S. cc: Dr. M. Theodorakis
FDA

Fax No.: 301-443-7068

From: Manager, Regulatory Affairs

Tel. No. Fax No:

Date: March 29, 1996 Pages: 2 (including this page)

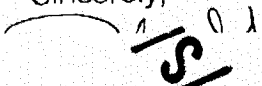
Subject: NICORETTE Chewing Gum

Dear Mary,

In response to Dr. Theodorakis' March 28, 1996 request, please find following a copy of the compositions for the OTC approved NICORETTE 2mg and 4 mg nicotine chewing gums. The following page was submitted to DMF April 1989.

Should you or Dr. Theodorakis need any further information, please contact me.

Sincerely,


Barbara Gunther

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Composition

CONSULT REVIEW

ANDA #: 74707
Drug: Nicotine Polacrilex Gum
Sponsor: Cira Pharmaceuticals
Submitted: 6/6/95; 11/3/95
Reviewer: E Douglas Kramer
Harry Geyer
Peer Reviewer: Curtis Wright
Anwar Goheer
CSO: Mary Lambert
Dates: 6/6/95; 11/3/95 Submitted (to FDA/OGD)
3/6/96 Consult Requested
5/2/96 Review Completed

Material received from OGD: ANDA Application (5 volumes, chemistry); FR notices on acesulfame

Purpose of consultation:

Cira Pharmaceuticals has produced a 2 and a 4mg generic nicotine gum. The ANDA application for the 4mg was refused for filing in OGD because one of its ingredients, _____, has not been approved for use in a drug product by the same route of administration. The sponsor is requesting a waiver of the requirement that the safety of _____ be demonstrated other than by showing that it has been previously approved for use in a drug product. OGD requests an evaluation of the safety of _____ in this consult.

Background on acesulfame:

_____ is a non-nutritive sweetener which is not metabolized and is approximately 200 times sweeter than sucrose (which is about twice as sweet as sorbitol). In July 1988 _____ was approved for use in sugar substitutes, chewing gum, dry bases for gelatins, puddings and pudding desserts, and dry bases for beverages, instant coffee and instant tea. The acceptable daily intake based on submitted safety studies was considered to be 15mg/kg and the 90th percentile of exposure to consumers was estimated to be 1.6mg/kg/day.

The sponsor of the ANDA lists the product as being used in Halls cough suppressant tablets under OTC monograph.

Exposure to

The proposed 4mg generic nicotine gum contains _____
smoker using the maximum recommended dose of the 4mg gum (24 pieces/day) would therefore have a daily _____ exposure of 62mg (<=1mg/kg/day)

Comparison of the proposed generic to the approved product

The composition of Nicorette and Nicorette DS and the proposed 2 and 4mg generic products are attached. The original products are sweetened with sorbitol and have a [redacted] flavoring. The 4 mg proposed generic product differs from the approved products in both its sweeteners (it contains [redacted] as well as sorbitol) and flavorings (it is [redacted] flavored). The flavor proposed for the 2mg generic is different from the flavor in the original product. No information about the relative palatability of either strength is provided.

Recommendations:

1. One of the biggest concerns in the OTC approval of Nicorette was that the product might become an entry to nicotine addiction if available in a more palatable formulation than the original product. For this reason we are planning to not approve a supplement to the Nicorette NDA's for _____ flavors in the absence of abuse liability testing, palatability testing, and comparative data on the extent of long-term use of the original and alternate proposed flavors. The formulations proposed in these applications are also potentially more palatable than the original product and should be nonapproved pending the same data.

Required clinical data includes, at a minimum, the following information: Formal placebo-controlled abuse liability testing of the original and proposed formulations of Nicorette in populations of heavy smokers, light smokers, nonsmokers, adolescent smokers and flavored smokeless tobacco users. Palatability should also be studied in these same groups. An assessment of the extent of long-term use of the different flavors of Nicorette when used for smoking cessation should also be considered.

We do not think these products are suitable for an ANDA until we know more about this issue. A more suitable route to approval would be a 505(B)2 application.

2. Concern about the safety of _____ is primarily based on the changes in palatability brought about by the use of an alternative sweetener. This concern can be addressed in the studies proposed above. No other pharmacologic or toxicologic safety issue is identified with this compound in the information reviewed.

 /S/ 5-2-96
E Douglas Kramer, MD
Medical Officer

 /S/
Harry Geyer, Ph.D.
Pharmacologist

 /S/
Curtis Wright, MD, MPH
Medical Officer

 /S/
Anwar Goheer, Ph.D.
Pharmacologist

Agree

ODE III
5/24/96