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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Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable. Chemistry

SECTION VII. COMPONENTS AND COMPOSITION STATEMENTS

2. **Composition**

- Composition Statements
- The following is the Composition Statement for our Nicotine Polacrilex Gum, 2 mg

Ingredient	mg/piece
Nicotine Polacrilex Glycerinated	
Sorbitol,	
Sodium Carbonate,	
Gum Base	
Glycerin	
Gum Flavor,	
ble) Oil	
Talc	
Total Gum Piece Weight:	960.00

*Quantity based on % active assay and includes an % overage. Please refer to Section VI, Page 456 for an explanation of the overage.

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

SECTION VII. COMPONENTS AND COMPOSITION STATEMENTS

2. Composition

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

Ingredient	mg/piece
Nicotine Polacrilex Glycerinated	
Sorbitol,	
Sodium Carbonate.	
Gum Base	
Flavor	
(Butylated Hydroxytoluene)	
Blend,	
Carnauba Wax,	
Talc #	
JSP	
TOTAL GUM PIECE WEIGHT:	**960.00**

* 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. FDA	cc: Dr. M. Theodorakis	
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. Theordorakis need any further information, please contact me.

Sincerely,

/S/

Barbara Guntner

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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 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 ie 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 xposure 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 ‹e flavoring. The 4 mg proposed generic product differs from the approved products in both its sweeteners (it contains as well as sorbitol) and flavorings (it is lavored). 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

Apur

ODE III
5/24/96