

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-070

CHEMISTRY REVIEW(S)



CMC REVIEW OF NDA 22-070



Chemistry Review Data Sheet

NDA 20-070

Atralin (tretinoin) Gel, 0.05 %

Coria Laboratories, Ltd.

Tarun Mehta, M.Sc.

Review Chemist

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

**CMC REVIEW OF NDA 22-070
Division of Dermatology and Dental Products (HFD-540)**



CMC REVIEW OF NDA 22-070



Chemistry Review Data Sheet

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	6
I. Recommendations.....	6
A. Recommendation and Conclusion on Approvability	6
B. Recommendation on Phase 4 (Post-Marketing) Commitments.....	6
II. Summary of Chemistry Assessments	6
A. Description of the Drug Product and Drug substance.....	6
B. Description of How the Drug Product is Intended to be Used.....	7
C. Basis for approval recommendation:	8
III. Administrative	8
A. Reviewer's Signature:.....	8
B. Endorsement Block:.....	8
CMC Assessment.....	9
I. Review Of Common Technical Document-Quality (CTD-Q) Module 3.2:	9
Body Of Data.....	9
S DRUG SUBSTANCE [Tretinoin — Satisfactory	9
P DRUG PRODUCT: [Atralin (tretinoin) Gel, 0.05%]	17
A APPENDICES	62
R REGIONAL INFORMATION	63
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	63
A. Labeling & Package Insert.....	63
B. Claim of Categorical Exclusion Satisfactory.....	69

b(4)



CMC REVIEW OF NDA 22-070



Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA #: 22-070
2. REVIEW #: 1
3. REVIEW DATE: 16-Feb-2007
4. REVIEWER: Tarun Mehta

5. PREVIOUS DOCUMENTS:

6. SUBMISSION(S) BEING REVIEWS:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	September 27, 2006
Amendment 0001	January 5, 2007
Amendment 0004	March 30, 2007
Amendment 0008	June 20, 2007
Amendment 0010	July 3, 2007

7. NAME & ADDRESS OF THE APPLICANT:

Name: Coria Laboratories, Ltd.

Address: 3909 Hulen Street
Fort Worth, TX 76107

Representative: Mike Bernstein, MPH, VP, Regulatory Affairs

Telephone: 248-548-0900 X 433

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Atralin
- b) Non-Proprietary Name (USAN): Tretinoin
- c) Code Name/# (ONDQA only): _____
- d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL CATEGORY: Tretinoin is a metabolite of Vitamin A

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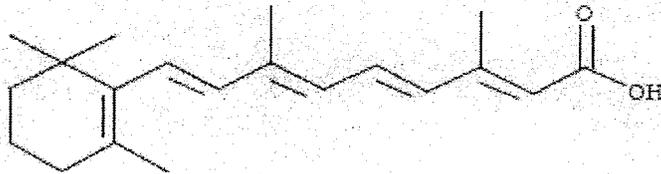
CMC REVIEW OF NDA 22-070

Chemistry Review Data Sheet

11. DOSAGE FORM: Gel
12. STRENGTH/POTENCY: 0.05% w/w
13. ROUTE OF ADMINISTRATION: Topical
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 Not a SPOTS product

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

Chemical Name: 2,4,6,8-Nonatetraenoic acid,3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl) (all E)



Chemical Structure:

Molecular weight: 300.4
Molecular formula: C₂₀H₂₈O₂

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE 1	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
5100	II	_____	_____	3	Adequate No changes made after last review	6/15/2004	Reviewed by Huang Liang Lii
_____	IV	_____	_____	4	adequate	6/14/07	Tarun Mehta
_____	IV	_____	_____	4	adequate	6/14/07	Tarun Mehta

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CMC REVIEW OF NDA 22-070



Chemistry Review Data Sheet

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	III			3	Adequate	9/25/2006	Reviewed by Jane Chang
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¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF is not review, 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)

18. STATUS:

ONDQA:

CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	Feb 23, 2007	S. Adams (HFD-322)

**APPEARS THIS WAY
ON ORIGINAL**



Chemistry Assessment Section

The Chemistry Review for NDA 22-070

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the Chemistry, Manufacturing and Control standpoint, this NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug substance

(1) Drug Product

b(4)

Atralin (tretinoin) Gel, 0.05% w/w contains 0.5mg of tretinoin as an active ingredient. Atralin is the first aqueous based gel formulation of tretinoin. Final drug product contains _____ tretinoin, which is well dispersed in the gel. Appearance of gel is translucent, smooth, and yellow in color. Atralin Gel is indicated for topical treatment of acne vulgaris in patients of 10 years or older ages.

b(4)

Tretinoin is widely used in the marketed topical drug products and listed under USP monograph. Most excipients used in this gel formulation were of compendial grade except for sodium hyaluronate which has been used in the approved pharmaceutical topical products, and soluble collagen, which is a novel excipient derived from teleosts fish skin (non-bovine collagen) and preserved in an aqueous solution. Very low concentration (____ ppm) of collagen is used in this formulation; (its function is claimed to be _____). However, there is no data submitted to support this claim in this NDA. Adequate information is provided through the DMF for this NDA to assure the safety and quality of these excipients. All the raw materials are controlled by adequate specifications. The applicant has submitted soluble collagen's certificates of analysis from suppliers and drug product manufacturer.

Atralin Gel is a _____-phase gel system. Gel is formed with _____

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Chemistry Assessment Section

The manufacturing processes are adequately controlled. Important attribute such as particle size distribution was achieved in the active phase by _____
_____. Degradation of tretinoin in the drug product is minimized by the use of _____ during the process.

b(4)

The applicant's contract manufacturing site, DPT Laboratories has conducted product development, manufacturing of clinical supply and will manufacture the to-be-marketed drug product. Drug product composition for clinical supply and proposed commercial formulation are identical. A commercial size (_____g) batch at proposed scale-up site was successfully manufactured using the proposed manufacturing process and equipments.

b(4)

Various tests are listed in the specifications such as description, pH, viscosity, particle size distribution, tretinoin ID, assay, related substances, assay of preservative agents and microbial growth control. The specifications deemed satisfactory to control the quality of the drug product at the time of release and during the shelf life.

The proposed container/closure system for Atralin is _____

b(4)

Stability results derived from _____ 1k stability batches packaged in the proposed container/closure concluded that the drug product meets the stability specifications up to 36 months at 25°C/60% RH condition. Based on the real time 36 months stability data for 45g tube packaging at long-term storage condition, expiration date of 36 months is granted. There were not enough stability data to support _____g and _____g tube packaging. Therefore, the applicant agreed to receive the NDA approval of only 45g packaging.

b(4)

(2) Drug Substance

Tretinoin is a _____ material and manufactured by _____. The chemistry, manufacturing, and controls information on the drug substance is provided in _____, which is deemed adequate to support this application.

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

Atralin (tretinoin) gel, 0.05% applies once daily before bedtime to skin where acne lesions appear applying a thin layer to cover the entire affected skin areas.



Chemistry Assessment Section

C. Basis for approval recommendation:

CMC information submitted in this NDA adequately supports DPT Laboratories' capability to manufacture the drug product with consistent quality. In support of its robust manufacturing capability, the applicant has provided adequate manufacturing process and control data from the developmental stage to commercial bulk batches. Drug product quality will be monitored by the adequate specifications throughout the drug product life cycle. Marketed container/closure is a lined aluminum tube with a white polypropylene cap, which will protect the drug product from light. Adequate stability data support the expiry date and the quality of product during the shelf life.

The final recommendation from the Office of Compliance for the drug product and drug substance manufacturer is **ACCEPTABLE** (see Attachment).

The labeling/labels are satisfactory.

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Tarun Mehta, M.Sc.

B. Endorsement Block:

(See appended electronic signature page)

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

C. CC Block: entered electronically in DFS

Project Manager: Melinda Bauerlien

70 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Tarun Mehta
7/19/2007 03:35:19 PM
CHEMIST

Moo-Jhong Rhee
7/19/2007 03:53:56 PM
CHEMIST
Chief, Branch III