

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-070

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Coria Laboratories, Ltd Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>	Form Approved: OMB No. 0910-0513 Expiration Date: 2-21-96 Patent Information See OMB Statement on Page 3.
	NDA NUMBER 22,070 NAME OF APPLICANT / NDA HOLDER Coria Laboratories, Ltd.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME) Atralin™ Gel, 0.05%	
ACTIVE INGREDIENT(S) Tretinoin	STRENGTH(S) 0.05% w/w
DOSAGE FORM Topical Gel	

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number 5,670,547	b. Issue Date of Patent 09/23/1997	c. Expiration Date of Patent 09/23/2014
d. Name of Patent Owner Dow Pharmaceutical Sciences, Inc.	Address (of Patent Owner)	
	City/State Petaluma, CA	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
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4.2a. If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
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5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

Corixa Laboratories, Ltd

NDA 22-070 Patent Information

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Mike Bernstein

Date Signed

08/31/2006

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

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The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

1.3.5.2 Patent Certification

In "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book), two patents are listed for NDA # 20-475 Retin-A MICRO 0.1% and 0.04% Gel (the NDA for which some investigations will be relied upon by the Sponsor for approval of this application and were not conducted by or for the Coria and for which a right of reference or use from the person by or for whom the investigations were conducted has not been obtained):

- Patent No. 4,690,825, Expired October 4, 2005
- Patent No. 5,955,109, Expires September 21, 2016

Patent No. 4,690,825, Paragraph II Certification

I, Michael Bernstein, certify that Patent No. 4,690,825 has expired as of this date.

Patent No. 5,955,109, Paragraph IV Certification

I, Michael Bernstein, certify that Patent No. 5,955,109 will not be infringed by the manufacture, use, or sale of Tretinoin Gel, 0.05%, for which this application is submitted.

Coria Laboratories, Ltd. will provide to the holders listed in Patent No. 5,955,109 notice of this certification in compliance with the regulations at 21 CFR 314.52.



Michael Bernstein, MPH
Vice-President, Regulatory Affairs
Coria Laboratories, Ltd.



United States Patent [19]

[11] Patent Number: **5,670,547**

Milstein et al.

[45] Date of Patent: **Sep. 23, 1997**

[54] **MOISTURIZING VEHICLE FOR TOPICAL APPLICATION OF VITAMIN A ACID**

[75] Inventors: Elliott A. Milstein, West Bloomfield; Nathan Milstein, Hazel Park, both of Mich.

[73] Assignee: Dow Pharmaceutical Sciences, Petaluma, Calif.

[21] Appl. No.: 430,154

[22] Filed: Apr. 26, 1995

Related U.S. Application Data

[63] Continuation of Ser. No. 296,083, Aug. 25, 1994, abandoned, which is a continuation of Ser. No. 951,938, Sep. 25, 1992, abandoned, which is a continuation of Ser. No. 697,527, Apr. 29, 1991, abandoned, which is a continuation of Ser. No. 335,144, Apr. 17, 1989, abandoned.

[51] Int. Cl.⁶ A61K 31/07
[52] U.S. Cl. 514/725; 514/844; 514/847
[58] Field of Search 514/725, 844, 514/847

[56] References Cited

U.S. PATENT DOCUMENTS

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3,906,108	9/1975	Felty	514/560
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FOREIGN PATENT DOCUMENTS

0219208 4/1987 European Pat. Off.

OTHER PUBLICATIONS

Sales brochure and produce description of colladerm gel moisturizer manufactured by C & M Pharamacal, Inc., Hazel Park, Michigan, U.S.A.

Primary Examiner—Theodore J. Criares
Attorney, Agent, or Firm—Needle & Rosenberg, P.C.

[57] ABSTRACT

A formulation containing tretinoin, a gelling agent, proteinaceous material, and water is provided for the uniform topical application of tretinoin. The water-based formulation is oil- and fat-free, alcohol-free, and rich in proteinaceous material. The formulation is stable over time and is comedogenic and less irritating and drying to the skin.

22 Claims, No Drawings

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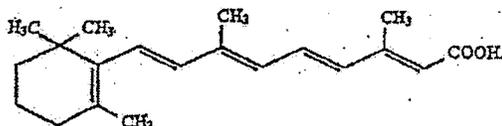
MOISTURIZING VEHICLE FOR TOPICAL APPLICATION OF VITAMIN A ACID

This application is a continuation of application Ser. No. 08/296,083, filed Aug. 25, 1994 now abandoned; which is a continuation of Ser. No. 07/951,938, filed Sep. 25, 1992, abandoned; which is a continuation of Ser. No. 07/697,527, filed Apr. 29, 1991, abandoned; which is a continuation of Ser. No. 07/335,144, filed Apr. 17, 1989, abandoned.

BACKGROUND OF THE INVENTION

The present invention relates to a topical dosage formulation of tretinoin in which the active ingredient tretinoin is contained in a stable, oil- and fat-free, alcohol-free, and potentially moisturizing vehicle. This product is particularly advantageous for treating such dermatological disorders as acne vulgaris, although it will be understood that this formulation is effective generally for treating dermatological conditions where tretinoin is indicated.

Tretinoin (Vitamin A acid) has been applied topically, (Beer, Yon P., "Untersuchungen über die Wirkung der Vitamin A-Säure," *Dermatological*, 124:192-195, March, 1962 and Stütgen, G., "Zur Lokalbehandlung von Keratosen mit Vitamin A-Säure," *Dermatological*, 124:65-80, February, 1962) in those hyperkeratotic disorders which are responsive to high oral doses of Vitamin A. Tretinoin, or all trans-retinoic acid, has the following chemical structure:



It has been previously demonstrated that prolonged topical application of Vitamin A acid is effective in the treatment of acne (Kligman, A. M., "Topical Vitamin A acid in Acne Vulgaris," *Arch Derm.*, 99:469-476 April 1969). U.S. Pat. No. 3,729,568 to Kligman utilizes a composition in which Vitamin A acid is dispersed in a water-miscible liquid carrier having high solvating action. The carrier used by Kligman consists of a combination of (A) from about 25 to about 75%, by weight, of ethyl alcohol or isopropyl alcohol, and (B) the balance essentially a liquid glycol above ethylene glycol or a liquid glycol above ethylene glycol and a liquid ethylene glycol mono methyl or mono ethyl ether. The topical application of this Vitamin A acid composition causes irritation of the skin in the treated areas.

More recently, it has been found that acne can be effectively treated with a cream formulation containing tretinoin, or Vitamin A acid. A cream formulation is generally more acceptable to patients than the liquid vehicle from the point of view of aesthetics and ease of application. Moreover, another important advantage of the cream form of tretinoin is that it reduces the side effects normally associated with topical application, such as erythema, stinging and itching. These side effects may be sufficient to cause the patient to discontinue the application of tretinoin before it can be fully effective upon the acne.

Notwithstanding these advantages, cream formulations containing tretinoin possess some undesirable attributes. One of these undesirable attributes is the difficulty in uniformly applying sufficient amounts of the active ingredient to the lesion of acne to be effective and at the same time avoid local excesses, surface spread or pooling into facial

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creases, the nasolabial folds and corners of the mouth where the cream may cause erythema, stinging and itching. Another undesirable attribute of cream formulations of tretinoin is their relative instability, often necessitating the use of refrigeration or special additives to maintain physical and chemical stability over time.

U.S. Pat. No. 3,906,108 to Felty discloses an improvement in stability over previous cream formulations of tretinoin by the addition of xanthan gum to the preparation. The cream consists essentially of a stabilized cream emulsion formulation generally comprising from about 0.005% to about 0.5% by weight of tretinoin; from about 0.1% to about 1.0% by weight of xanthan gum; from about 1% to about 10% by weight of an emulsifier, preferably a non-ionic emulsifier; from about 15% to about 50% by weight of a combination of at least one normally liquid and at least one normally solid hydrophobic material selected from the fatty acids, fatty alcohols and fatty acid esters wherein the fatty acid moiety has from about 12 to about 20 carbon atoms, and pharmaceutical grades of waxes and hydrocarbons (liquid and solid); between about 0.05% and 0.75% by weight of a preservative which prevents bacterial growth in the cream; and from about 0.01% to about 1.0% by weight of an antioxidant, the balance being water. Felty relies upon the use of various fats and oils to provide a carrier for the active ingredient tretinoin.

U.S. Pat. No. 4,247,547 to Marks discloses the use of the gelling agent hydroxypropyl cellulose as a carrier in a preparation containing tretinoin. Marks discloses a formulation for topical application comprising from about 0.01% to about 0.025% by weight of tretinoin and a vehicle system consisting essentially of (a) from about 84 to about 99% by weight of an organic solvent selected from the group consisting of ethanol, isopropanol, and propylene glycol; (b) an effective amount of a pharmaceutically acceptable antioxidant soluble in organic solvent to inhibit oxidation of tretinoin; and (c) an effective amount of hydroxypropyl cellulose to cause gelling. Marks retains the use of organic solvents in his vehicle and claims that the vehicle composition allows for more uniform and effective delivery of tretinoin to the skin with enhanced stability.

As discussed, these previous topical tretinoin formulations have employed a number of methods for the administration of tretinoin in a controlled fashion. Cream emulsion formulations were found to be generally more acceptable to patients than a liquid vehicle, but had the problem of uniformly applying sufficient amounts of the active ingredient to the lesion of acne without local excesses, surface spread or pooling into facial creases and folds, or pooling into the corners of the mouth. In addition, cream formulations contained various fats and oils that tended to form a physical barrier between the tretinoin and the skin surface, thus inhibiting ready absorption of the tretinoin. Methods of administration utilizing liquid solvents tended to be non-uniform in their application of the active ingredient in that they were found to be hard to control when applied to a vertical surface such as the face, i.e. the applied liquid would easily spill off the face, especially when applied liberally. Therefore, there exists a need for a formulation capable of uniformly delivering an effective amount of tretinoin to the surface of the skin in a way which allows for ready absorption by the skin.

Previous cream formulations of tretinoin have utilized hydrophobic materials consisting of various fats and oils to provide a carrier for the active ingredient tretinoin. These hydrophobic materials have included solid and liquid fatty acids, fatty alcohols, fatty acid esters and waxes.

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materials such as petrolatum, wax, lanolin and mineral oil. The fats and oils contained in these preparations have been found to be comedogenic over time, thereby having an adverse effect on the treatment of acne. This was found to be especially true when the preparations had been used over an extended period of time, which is frequently the clinical case. Therefore, there also exists a need for a formulation that is fat- and oil-free so as to be less comedogenic to the skin with use.

A number of alcohol-based preparations for the topical application of tretinoin have appeared, most of which have proved irritating to the skin at the site of application. This was especially found to be true of applications containing at least 0.025% of tretinoin, in which the astringent side effects of dryness and irritation had prompted discontinuation of use. Since many clinicians wanted the capability of delivering greater than 0.025% of tretinoin to the site of acne, the alcohol-based preparations presented a major obstacle in this regard. Therefore, there exists a further need for a formulation that is alcohol-free so as to be less drying and irritating to the skin with use.

Past cream formulations of tretinoin have encountered problems with physical and chemical stability over time, often requiring the addition of stabilizers or refrigeration. U.S. Pat. No. 3,906,108 to Felty describes the previous to the use of xanthan gum as a stabilizer. Therefore, there exists a further need for a formulation which possesses good physical and chemical stability over time.

One of the possible side effects of topical tretinoin use is the potential for skin drying and irritation. This effect may be severe enough to cause the patient to discontinue the application of tretinoin before it can be fully effective upon the acne, thereby eliminating the chance of any beneficial treatment plan. Therefore, there exists a further need for a formulation which contains a humectant so as to aid in moisturizing the skin and to thus avoid a potential side effect of tretinoin use.

Many of the organic solvents used in previous topical preparations of tretinoin are known to be drying and irritating to skin if applied frequently. The use of a water based preparation, on the other hand, would allow for maintenance of normal skin turgor and consistency by providing a moisturizing action. Therefore, there exists a still further need for a formulation which is water-based so as to avoid the harsh effects of irritating organic solvents.

SUMMARY OF THE INVENTION

The present invention relates to a semisolid dosage formulation used for the uniform topical application of tretinoin. The formulation comprises tretinoin, a gelling agent for uniformly delivering the tretinoin to the surface of the skin in a way which makes it readily absorbable, proteinaceous material for stabilizing the gelling agent, and water. Additional ingredients of the formulation may include, but are not limited to, an antioxidant, a preservative, a surfactant, and glycerin.

The formulation of the present invention provides for the uniform topical application of an effective amount of tretinoin to the skin in a semisolid vehicle which is non-irritating, non-drying and non-comedogenic. The tretinoin is accurately delivered to the surface of the skin and is readily absorbed. The formulation, being water-based and containing proteinaceous material, has a potential moisturizing effect which helps counter the drying side effects of tretinoin use. The formulation is stable over time and requires no additional stabilizers or refrigeration to maintain its chemi-

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cal and physical stability. The formulation is also oil- and fat-free and therefore less comedogenic than creams during heavy and prolonged use. The formulation of the present invention thus allows for greater amounts of tretinoin to be applied to the skin over time, since the side effects of the tretinoin and vehicle are minimized.

It is therefore the object of the present invention to provide a formulation capable of uniformly delivering an effective amount of tretinoin to the surface of the skin in a way that allows for ready absorption by the skin.

It is also the object of the present invention to provide a formulation that is fat-free and oil-free so as to be less comedogenic to the skin with use.

It is a further object to provide a formulation that is alcohol-free so as to be less drying and irritating to the skin with use.

It is another object of the present invention to provide a formulation which possesses good physical and chemical stability over time.

It is another object to provide a formulation which contains humectants so as to aid in moisturizing the skin and to thus avoid a potential side effect of tretinoin use.

It is still another object of the present invention to provide a formulation which is water-based so as to avoid the harsh effects of irritating organic solvents.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

A formulation of the present invention, in general, comprises tretinoin, a gelling agent for uniformly delivering the tretinoin to the surface of the skin in a way which makes it readily absorbable, proteinaceous material for stabilizing the gelling agent, and water. Additional ingredients of the formulation may include, but are not limited to, an antioxidant, a preservative, a surfactant, and glycerin.

The concentration of tretinoin in the formulations of the present invention preferably lies within a range of about 0.001% by weight to about 0.5% by weight, the range most likely to be encountered in clinical practice. The tretinoin may, however, be present in the formulation at any effective amount so long as the integrity of the other components of the formulation are not jeopardized.

The gelling agent employed in the formulations of the present invention should be water-soluble and acceptable for use in pharmaceutical preparations. The purpose of the gelling agent is to provide a semisolid formulation for the uniform delivery of tretinoin to the surface of the skin, thus making it readily absorbable. The gelling agent also needs to be of uniform consistency and proper viscosity, allowing the user to easily disperse the active ingredient evenly over acne-affected areas. Furthermore, the gelling agent must be water-soluble, since the use of harsh organic solvents (i.e. ethanol, isopropanol, propylene glycol) needed with non-water-based gelling agents has a detrimental effect on the skin. One such gelling agent that has been found to be extremely effective in the formulations of the present invention is an acidic carboxy polymer, such as Carbomer 940 or Carbopol 940 available from B.F. Goodrich Chemical Co., Cleveland, Ohio. This gelling agent is very stable and effective within a pH range of 5.2 to 5.5, and is used in the present invention with a neutralizing agent to maintain pH, since the viscosity of the acidic carboxy polymer drops off precipitously at a pH less than 5.2. Potential neutralizing agents include organic amines, such as triethanolamine.

The proteinaceous material which may be used in the present invention includes proteins, polypeptides, peptides.

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amino acids, mucopolysaccharides, or mixtures thereof. The protein is preferably collagen or elastin, although many other proteins well known in the art may be used. An acceptable mucopolysaccharide is sodium hyaluronate. The proteinaceous material in the present invention functions as (1) a stabilizer for the water-based gelling agent preventing breakdown of the gel structure over time and (2) a humectant for the skin countering the drying side effects of tretinoin. Proteins have the additional function of acting as protein-replenishing agents for damaged skin.

The use of water, preferably purified, in the formulations of the present invention is necessary to the functioning of the tretinoin vehicle. The water-based vehicle, containing no fats or oils, provides a formulation which is non-comedogenic and is actually moisturizing to potentially dry skin due to tretinoin use. In addition, the use of a water-based vehicle eliminates the necessity to completely solvate the tretinoin in a solvent to deliver it to the skin, as tretinoin is effectively delivered in a uniform fashion with the use of a water-based gel.

An antioxidant may be provided to retard oxidation and deterioration of the tretinoin, thus providing the formulation with increased long term stability. The antioxidant used must be safe for human topical use and non-reactive to the other components of the formulation. A preferred example of a suitable antioxidant is butylated hydroxytoluene (BHT).

A preservative may be included in the formulation of the present invention to prevent microorganism overgrowth with time. In the present formulations, sorbic acid and imidazolidinyl urea have been used, although any preservative known by those skilled in the art and not otherwise deleterious to the formulation may be used.

A surfactant may also be provided in the formulation of the present invention to allow good dispersion of the active ingredient and to enhance skin penetration. In general, non-ionic surfactants should be employed, although their choice is not critical. In the example below, octoxynol-9 (polyethylene glycol mono[p-(1,1,3,3-tetramethylbutyl)phenyl]ether) was utilized with effectiveness.

Other humectants, such as glycerin, may also be provided to enhance the moisturizing capability of the present formulation.

In one embodiment of the invention, the tretinoin is present from about 0.001 to about 1% by weight, the gelling agent is present from about 0.05 to about 15% by weight, the proteinaceous material is present from about 0.001 to about 50% by weight, and the water is present from about 35 to about 95% by weight. In another embodiment, an antioxidant is present from about 0.001 to about 0.5% by weight, a preservative is present from about 0.001 to about 15% by weight, a surfactant is present from about 0.001 to about 2% by weight, and glycerine is present from about 1.0% to about 50% percent by weight.

The following example is presented to further illustrate a formulation of the invention without thereby limiting the scope thereof:

EXAMPLE OF A 0.05% TRETINOIN FORMULATION

	% w/w
Glycerin	10.0
Soluble Animal Collagen	8.0

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-continued

	% w/w
Hydrolyzed Elastin	1.0
Triethanolamine	0.58
Carbomer 940	0.40
Imidazolidinyl Urea	0.364
Sorbic Acid	0.208
Octoxynol-9	0.115
Tretinoin USP	0.05
Butylate Hydroxytoluene (BHT)	0.0208
Sodium Hyaluronate	0.011
Purified Water	79.2

The formulations of the present invention are prepared by a number of procedures well known in the art. For instance, the formulation of the above Example was prepared by first adding small portions of Carbomer 940 to heated purified water under low shear agitation until solvation occurred. Sorbic acid, BHT and imidazolidinyl urea were then mixed with the Carbomer 940/water mixture until dispersed. Then the glycerin and octoxynol-9 were added and mixed to form a homogeneous solution. The solution was then allowed to cool to room temperature and tretinoin added. Sodium hyaluronate was first dissolved in purified water and then added to the solution containing tretinoin. The collagen and elastin were then added and mixed until homogeneous. Finally, the triethanolamine was slowly added while mixing until a gel formed and the proper consistency and pH were achieved.

To stabilize the acidic carboxy polymer Carbomer 940, the pH of the formulation must be maintained between approximately 5.2 and approximately 5.5. Since pH will change as the percentage of tretinoin changes with different formulations, it may be necessary to use a neutralizing agent to bring the pH within the desired range. For instance, in formulations similar to that of the above Example, pH may be adjusted by varying the amount of the neutralizing agent triethanolamine.

The resulting formulation, therefore, is a stable, oil- and fat-free, alcohol-free, and potentially moisturizing vehicle for tretinoin. The formulation may be employed in virtually all instances where topical application of tretinoin is desired.

What is claimed is:

1. A stable aqueous gel formulation comprising:

a) from about 0.001% to about 1% by weight tretinoin; b) from about 0.05% to about 15% by weight of a gelling agent for uniformly delivering said tretinoin to the surface of the skin in a way which makes it readily absorbable;

c) from about 0.001% to about 50% by weight of a proteinaceous material, wherein said proteinaceous material comprises a protein, polypeptide, amino acid, mucopolysaccharide, or a mixture thereof, wherein said proteinaceous material is in sufficient quantity to stabilize said gelling agent and tretinoin formulation; and

d) water; wherein said formulation is free of fat and oil and substantially free of alcohol as a carrier for the tretinoin, said weight percentages being based on 100 weight percent of the formulation, and wherein said formulation is a stable aqueous gel.

2. The formulation of claim 1, wherein said tretinoin is present from about 0.001% to about 0.5% by weight.

3. The formulation of claim 1, wherein said tretinoin is present at approximately 0.05% by weight.

4. The formulation of claim 1, wherein the gelling agent is an acidic carboxy polymer which is partially neutralized

5,670,547

7

8

with a neutralizing agent so as to maintain the pH of said formulation between approximately 5.2 and approximately 5.5.

5. The formulation of claim 1, and further comprising an antioxidant.

6. The formulation of claim 1, and further comprising a preservative.

7. The formulation of claim 1, and further comprising a surfactant.

8. The formulation of claim 1, and further comprising glycerin.

9. The formulation of claim 1, wherein said water is present from about 35 to about 95% by weight.

10. The formulation of claim 1, wherein the formulation comprises substantially no organic solvent so that the tretinoin remains substantially in suspension.

11. The formulation of claim 1, wherein the proteinaceous material comprises collagen, elastin, or sodium hyaluronate.

12. The formulation of claim 1, wherein the gelling agent is water soluble.

13. A stable aqueous gel formulation comprising:

- a) from about 0.001% to about 1% by weight tretinoin;
- b) from about 0.05% to about 15% by weight of an acidic carboxyl polymer gelling agent for uniformly delivering said tretinoin to the surface of the skin in a way which makes it readily absorbable;

- c) from about 0.001% to about 50% by weight of a proteinaceous material, wherein said proteinaceous material comprises a protein, polypeptide, amino acid, mucopolysaccharide, or a mixture thereof, wherein said proteinaceous material is in sufficient quantity to sta-

bilize said acidic carboxyl polymer and tretinoin formulation; and

d) water;

wherein the pH of said formulation is between approximately 5.2 and approximately 5.5 and wherein said formulation is free of fat and oil and substantially free of alcohol as a carrier for the tretinoin, said weight percentages being based on 100 weight percent of the formulation, and wherein said formulation is a stable aqueous gel.

14. The formulation of claim 13, wherein said tretinoin is present from about 0.001% to about 0.5% by weight.

15. The formulation of claim 13, wherein said tretinoin is present at approximately 0.05% by weight.

16. The formulation of claim 13, wherein said acidic carboxy polymer is partially neutralized with an organic amine.

17. The formulation of claim 13, and further comprising an antioxidant.

18. The formulation of claim 13, and further comprising a preservative.

19. The formulation of claim 13, and further comprising a surfactant.

20. The formulation of claim 17, and further comprising glycerin.

21. The formulation of claim 13, wherein the proteinaceous material comprises collagen, elastin, or sodium hyaluronate.

22. The formulation of claim 13, wherein said water is present from about 35 to about 95% by weight.

* * * * *

EXCLUSIVITY SUMMARY

NDA # 22-070

SUPPL # N/A

HFD # 540

Trade Name Atralin Gel 0.05%

Generic Name tretinoin

Applicant Name Coria Laboratories, Ltd

Approval Date, If Known July 26, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	20-400	Avita Gel 0.025%
	17-579	Retin A Gel 0.025%
NDA#	17-955	Retin A Gel 0.01%
NDA#	NDA 20-475	Retin A Micro Gel 0.1% and 0.04%

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

735.126.CL005/01, CL006/01, CL007/01, CL008/01, CL009/01,
20.CLIN.126.024 and 126.0418

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES NO

Investigation #2

YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES NO

Investigation #2

YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

735.126.CL005/01, CL006/01, CL007/01, CL008/01, CL009/01, 20.CLIN.126.024 and 126.0418

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 63,067 YES ! NO
! Explain:

Investigation #2
IND # 63,067 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Melinda Bauerlien

Title: Regulatory Project Manager

Date: July 12, 2007

Name of Office/Division Director signing form: Susan J. Walker, M.D.

Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Susan Walker
7/26/2007 03:11:14 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-070 Supplement Type (e.g. SE5): N/A Supplement Number:

Stamp Date: September 28, 2006 Action Date: July 28, 2007

HFD-540 Trade and generic names/dosage form: Atralin (tretinoin) Gel, 0.05%

Applicant: Coria Laboratories, Ltd Therapeutic Class: 3

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: topical treatment of acne vulgaris _____

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

XNo: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 12 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
 - Disease/condition does not exist in children
 - Too few children with disease to study
 - There are safety concerns
 - Adult studies ready for approval
 - Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. 12 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Melinda Bauerlien, M.S.
Regulatory Project Manager

cc: NDA 22-076
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

/s/

Melinda Bauerlien
7/25/2007 10:56:51 AM

David Kettl
7/25/2007 01:11:08 PM

Markham Luke
7/25/2007 06:22:16 PM
Concur with partial waiver of 0 to 12 year old patients.

Susan Walker
7/25/2007 09:57:45 PM

1.9.1 Request for Partial Waiver from Pediatric Research Equity Act

1. This partial waiver is requested under Section 505B(a)(4)(B) of the Act in order to exclude the requirement for conducting pediatric assessments in subjects under the age of 10 years. The two Phase III studies conducted as part of the clinical development plan for Tretinoin 0.05% Gel in the treatment of *acne vulgaris* (Protocols 735.126.CL009/01 and 20.CLN.126.0418) included subjects 10 years of age and older.
2. With regard to the age group for which this waiver is sought (pediatric subjects under the age of 10 years), the applicant asserts that studies within this age group are either impossible or highly impractical to conduct [see Section 505B(a)(4)(B)(i) of the Act]. The studied indication, *acne vulgaris*, has extremely limited applicability to pediatric patients under the age of 10 years because the disease is manifested predominantly during puberty with a typical age of onset of approximately 12-13 years (1); it has been estimated that 85% of all reported cases are in patients between 12 and 24 years of age (2).
3. Evidence that the statutory reasons for waiver of pediatric studies has been met is not required in relation to category 505B(a)(4)(B)(i) of the Act.
4. The applicant hereby certifies to the above stated reason for request of this waiver.



Mike Bernstein, MPH
Vice President, Regulatory Affairs

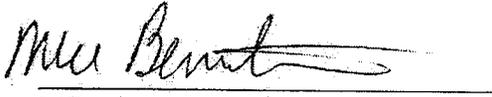
References

1. Gordon B. Neglected aspects in the management of acne. J R Soc Med. 1985;78(Suppl 10):10-14.
2. Pal S. 17 million persons have acne vulgaris. US Pharmacist.
www.uspharmacist.com/oldformat.asp?url=newlook/files/Tren/ACF76F.cfm&pub_id=8&article_id=315 (accessed July 6, 2006).

APPEARS THIS WAY ON ORIGINAL

1.3.3 Debarment Certification

Per Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act [21 USC 335a(k)(1)], Coria Laboratories, Ltd. hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under subsections (a) or (b) in connection with this application, NDA No. 22-070.


 Mike Bernstein, MPH
 Vice-President, Regulatory Affairs

The individuals listed on the following pages served as Investigators or Sub-Investigators in the Phase III clinical studies (Study 735.126.CL009/01 and Study 20.CLN.126.0418) included in this application. Please note, although Coyle Conway, DO, and Harold Farber, MD, are included in the list of Investigators for Study 20.CLN.126.0418, they did not screen or treat any patients. Dr. Farber is currently listed on the Agency's Totally Restricted Investigator's List as restricted from receiving study medication or performing clinical studies. Prior to initiation of Study 20.CLN.126.0418, Healthpoint, Ltd. followed the Agency's advice in not using this Investigator and discontinued him from the study.

Study 735.126.CL009/01

Principal Investigator Name and Address	Investigator Number	Sub-Investigator
Susan Barker, M.D. SFBC Fort Myers, Inc. 11406 North 56 th Street Temple Terrace, FL 33617	21	/
Karl Beutner, M.D. Solano Clinical Research 127 Hospital Drive, Suite 202 Vallejo, CA 94589	17	

b(4)

7 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Administrative- 1

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	(see attached list)	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Michael A. Patterson		TITLE Chief Financial Officer	
FIRM/ORGANIZATION Coria Laboratories, Ltd.			
SIGNATURE 		DATE 08/10/2006	

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

7 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Study Endpoints and Label Development (SEALD) Team Review of PLR Labeling

Application Number: NDA 22-070

Applicant: Coria Laboratories

Drug Names: Tretinoin

Receipt Date: September 28, 2006

SEALD Review Date: December 12, 2006

Project Manager: Shalini Jain

Review Division: Division of Dermatology and Dental Products

SEALD Reviewer(s): Jeanne M. Delasko, RN, MS/Label Initiatives Specialist

Concurrence(s): Laurie B. Burke, RPh, MPH/Director, SEALD

Executive Summary

This memo provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review of PLR labeling

Highlights:

- Because the drug names, dosage form, and route of administration appear at the beginning of the labeling, product identification information [i.e., Atralin (tretinoin) Gel [Coria Laboratories, Ltd.] is not needed as a header in Highlights and should be deleted.
- The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or rationale why pharmacologic class should be omitted from the Highlights.

- Under Dosage Forms and Strengths, please clarify “w/w”. The same applies to the FPI. Also, you indicate that Tretinoin is available in _____ gram and _____ gram tubes in the FPI but did not include this information in the Highlights under Dosage Forms and Strengths. Please include. **b(4)**
- Under Contraindications, it must state “None” not _____.” Please correct. The same applies to the Contraindications section in the FPI. [See 21 CFR 201.57(a)(9) and (c)(5)]
- The revision is missing from Highlights and will be the month/year that the application is approved. [See 21 CFR 201.57(a)(15)]

Full Prescribing Information (FPI): Contents:

- Under 8.1 Pregnancy, delete the phrases _____ since these are not subsection headings and should not be included in the Table of Contents.
- Section and subsection headings can only be numbered. Do not number headings within a subsection (e.g., 13.1.1 Carcinogenesis, 13.1.2 Mutagenesis, 13.1.3 Impairment of Fertility). Use headings without numbering (e.g., Carcinogenesis, Mutagenesis, Impairment of Fertility). Please correct in the FPI. [See 21 CFR 201.57(c)] Also, headings within a subsection must not be included in the Table of Contents. Delete all sub-subsection headings under Nonclinical Toxicology in the Contents.
- Delete “_____” and all headings that follow. This information should not be included in the Table of Contents. **b(4)**

Full Prescribing Information (FPI):

- Regarding Patient Counseling Information, FDA-approved patient labeling referenced in this section should read [*See FDA-Approved Patient Labeling (17.5)*], not ‘_____’ Please correct.
- Under 17.5 FDA-Approved Patient Labeling, delete “(on the following page).” It appears out of place since the labeling is one document.
- Delete the company website address (www.corialabs.com) at the end of the labeling.

Recommendations

After the comments are conveyed to the applicant and revised labeling is submitted,

please check to ensure that SEALD labeling comments have been addressed and incorporated into the labeling. At the first labeling meeting, use the applicant's updated (revised) draft labeling for review.

Appendix A: Applicant's Proposed Labeling

APPEARS THIS WAY ON ORIGINAL

13 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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this page is the manifestation of the electronic signature.**

/s/

Jeanne Delasko
12/14/2006 11:26:45 AM
CSO

Laurie Burke
12/14/2006 07:47:07 PM
INTERDISCIPLINARY



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 25, 2007

To: Amy Campbell	From: Melinda Bauerlien, M.S. Project Manager
Company: Healthpoint for Coria Laboratories	Division of Dermatology & Dental Products
Fax number: (817) 763-9948	Fax number: (301) 796-9895
Phone number: (817) 302-3901	Phone number: (301) 796-2110
Subject: NDA 20-070	

Total no. of pages including cover: 3

Comments: Phase 4 commitments

Please submit your agreement to conduct the Phase 4 commitments below.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2110. Thank you.

Phase 4 commitments for NDA 22-070

1. Description of Commitment:

A dermal safety study to assess cumulative irritancy from Atralin Gel 0.05%, using the final, to-be-marketed formulation

Protocol Submission: received 05/07

Study Start:

Final Report Submission: by 10/07

b(4)

2. Description of Commitment:

A dermal safety study to fully assess photoallergy and phototoxicity from Atralin Gel 0.05%, using the final, to-be-marketed formulation. This should include 50 evaluable subjects for the photoallergy and 30 evaluable subjects for the phototoxicity studies

Protocol Submission: by 10/07

Study Start: by 11/07

Final Report Submission: by 3/08



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III**

FACSIMILE TRANSMITTAL SHEET

DATE: July 24, 2007

To: Amy Campbell	From: Melinda Bauerlien, M.S. Project Manager
Company: Healthpoint for Coria Laboratories	Division of Dermatology & Dental Products
Fax number: (817) 763-9948	Fax number: (301) 796-9895
Phone number: (817) 302-3901	Phone number: (301) 796-2110

Subject: NDA 20-070

Total no. of pages including cover: 3

Comments: Phase 4 commitments

Please submit your agreement to conduct the Phase 4 commitment below.

Document to be mailed: YES NO

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Phase 4 commitment for NDA 22-070

1. Description of Commitment:

~~_____~~

b(4)

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/s/

Melinda Bauerlien
7/24/2007 11:53:05 AM
CSO



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III**

FACSIMILE TRANSMITTAL SHEET

DATE: July 24, 2007

To: Amy Campbell	From: Melinda Bauerlien, M.S. Project Manager
Company: Healthpoint for Coria Laboratories	Division of Dermatology & Dental Products
Fax number: (817) 763-9948	Fax number: (301) 796-9895
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Phase 4 commitment for NDA 22-070

1. Description of Commitment:

A dermal safety study to fully assess photoallergy and phototoxicity from Atralin Gel 0.05%, using the final, to-be-marketed formulation. This should include 50 evaluable subjects for the photoallergy and 30 evaluable subjects for the phototoxicity studies

Protocol Submission: by / b(4)
Study Start: by /
Final Report Submission: by /

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Melinda Bauerlien
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HEALTHPOINT®

REGULATORY AFFAIRS

FACSIMILE

TO: MELINDA BAUERLIEN, MS **PHONE:** 301 796-2110
REGULATORY PROJECT **FAX:** 301 796-9895
MANAGER
FDA/CDER/DDDP **PAGES:** COVER + 0

FROM: AMY CAMPBELL **PHONE:** 817 302-3901
MANAGER
FAX: 817 763-9948

DATE: 23 JULY 2007

cc:

SUBJECT: NDA 22-070, PHASE 4 COMMITMENT - CARCINOGENICITY STUDY

Dear Melinda,
Coria Laboratories, Ltd. agrees to the Phase 4 Commitment below:

Mouse dermal carcinogenicity study

Protocol Submission: by 12/08
Study Start: by 08/09
Final Report Submission: by 08/12

If you have any questions concerning this Phase 4 Commitment, please contact me at (817) 302-3901 or at Amy.Campbell@healthpoint.com.

Thank you,



Amy Campbell
Regulatory Affairs Manager



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III**

FACSIMILE TRANSMITTAL SHEET

DATE: July 23, 2007

To: Amy Campbell	From: Melinda Bauerlien, M.S. Project Manager
Company: Healthpoint for Coria Laboratories	Division of Dermatology & Dental Products
Fax number: (817) 763-9948	Fax number: (301) 796-9895
Phone number: (817) 302-3901	Phone number: (301) 796-2110
Subject: NDA 20-070	

Total no. of pages including cover: 3

Comments: Phase 4 commitments

Please submit your agreement to conduct the Phase 4 commitment below.

Document to be mailed: YES NO

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Phase 4 commitment for NDA 22-070

1. Description of Commitment:

Mouse dermal carcinogenicity study

Protocol Submission: by 12/08

Study Start: by 08/09

Final Report Submission: by 08/12

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Melinda Bauerlien
7/23/2007 09:05:26 AM
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 16, 2007

To: Amy Campbell	From: Melinda Bauerlien, M.S. Project Manager
Company: Healthpoint for Coria Laboratories	Division of Dermatology & Dental Products
Fax number: (817) 763-9948	Fax number: (301) 796-9895
Phone number: (817) 302-3901	Phone number: (301) 796-2110
Subject: NDA 20-070	

Total no. of pages including cover: 3

Comments: Comments on carton/container

Document to be mailed: YES NO

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1. The established name appears less prominent than the proprietary name. Although the established name may be ½ the size of the proprietary name, it does not have a prominence commensurate with the proprietary name. Moreover, per 21 CFR 201.10(g)(2), “the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features”. Thus, we recommend increasing the prominence of the established name.
2. The font size and type (bold) of the manufacturer name competes with the prominence of the established name. Decrease the size and prominence of the manufacturer name so that it appears less prominent than the established name.
3. Increase the prominence of the product strength.
4. A graphic design in the form of a “wave” is present above and below the proprietary name. DMETS recommends deleting this graphic art as there should be no intervening matter between the proprietary and established names. Additionally, the graphics divert attention away from the proprietary and established names.
5. The net quantity is expressed in bold font and appears more prominent than the strength. Bolding of this statement draws attention to the net quantity rather than the strength. Unbold the net quantity expression ensuring that it is less prominent than the product strength to avoid confusion between the strength and the net quantity.
6. While the route of administration is present, it is inconsistently labeled in the labels and labeling. In some instances the route is referred to as, “For External Use Only”, while in other instances, the route is referred to as “For Topical Use Only” or “For Topical Dermatologic Use Only”. To be consistent with CDER terminology, revise the route of administration throughout the labels and labeling to read “For Topical Use Only” everywhere the route is referred to.

Tradename Comments

The tradename Atralin is acceptable. However be aware the name, Atralin, is a foreign drug that is an identical match in appearance and sound to Atralin. Atralin (sertraline) is available in Bangladesh for the treatment of depression.

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/s/

Melinda Bauerlien
7/16/2007 12:00:10 PM
CSO



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III**

FACSIMILE TRANSMITTAL SHEET

DATE: July 16, 2007

To: Amy Campbell	From: Melinda Bauerlien, M.S. Project Manager
Company: Healthpoint for Coria Laboratories	Division of Dermatology & Dental Products
Fax number: (817) 763-9948	Fax number: (301) 796-9895
Phone number: (817) 302-3901	Phone number: (301) 796-2110
Subject: NDA 20-070	

Total no. of pages including cover: 2

Comments: Phase 4 commitments

Please submit a timeline and the commitment to conduct the mouse dermal carcinogenicity study which was agreed to be conducted as a phase 4 study commitment. This should include dates of submission for the 90-day dose range-finding study report, study protocol submission, study start date and date of final report submission.

Document to be mailed: YES NO

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/s/

Melinda Bauerlien
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CSO



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: June 26, 2007

To: Amy Campbell	From: Melinda Bauerlien, M.S. Project Manager
Company: Healthpoint for Coria Laboratories	Division of Dermatology & Dental Products
Fax number: (817)-916-2300 763-9948	Fax number: (301) 796-9895
Phone number: (817) 302-3901	Phone number: (301) 796-2110

Subject: NDA 20-070 PK information request

Total no. of pages including cover: 2

Comments: Information Request. Please respond as soon as possible.

Please provide the batch/lot numbers of the purposed product used in the studies m735.126.CL008/01, 20.CLN.126.024 and 735.126.CL009/01 and the evidence that they are final to-be-marketed formulation.

Document to be mailed: YES NO

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/s/

Melinda Bauerlien
6/26/2007 11:46:39 AM
CSO



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: May 21, 2007

To: Amy Campbell	From: Melinda Bauerlien, M.S. Project Manager
Company: Healthpoint for Coria Laboratories	Division of Dermatology & Dental Products
Fax number: (817) 916-2300	Fax number: (301) 796-9895
Phone number: (817) 302-3901	Phone number: (301) 796-2110
Subject: NDA 20-070	

Total no. of pages including cover: 4

Comments: Information Request. Please respond as soon as possible.

Document to be mailed: YES NO

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 addressee, you are hereby notified that any review, disclosure, dissemination, copying, or
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 received this document in error, please notify us immediately by telephone at (301) 796-
 2110. Thank you.**

Clinical Information Request

Please address need for wording for proposed labeling with regard to patients who have fish allergies. One of your excipients has Pancogene Marin, a fish skin derivative.

Request for Revisions to the PI

Highlights:

- Because the drug names, dosage form, and route of administration appear at the beginning of the labeling, product identification information [i.e., Atralin (tretinoin) Gel [Coria Laboratories, Ltd.] is not needed as a header in Highlights and should be deleted.
- The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or rationale why pharmacologic class should be omitted from the Highlights.

- Under Dosage Forms and Strengths, please clarify “w/w”. The same applies to the FPI. Also, you indicate that Tretinoin is available in ~~—~~gram and 45 gram tubes in the FPI but did not include this information in the Highlights under Dosage Forms and Strengths. Please include. b(4)
- Under Contraindications, it must state “None” not “~~_____~~ Please correct. The same applies to the Contraindications section in the FPI. [See 21 CFR 201.57(a)(9) and (c)(5)] b(4)
- The revision is missing from Highlights and will be the month/year that the application is approved. [See 21 CFR 201.57(a)(15)] Full Prescribing Information (FPI): Contents:
- Under 8.1 Pregnancy, delete the phrases ~~_____~~ since these are not subsection headings and should not be included in the Table of Contents.
- Section and subsection headings can only be numbered. Do not number headings within a subsection (e.g., 13.1.1 Carcinogenesis, 13.1.2 Mutagenesis, 13.1.3 Impairment of Fertility). Use headings without numbering (e.g., Carcinogenesis, Mutagenesis, Impairment of Fertility). Please correct in the FPI. [See 21 CFR 201.57(c)] Also,

headings within a subsection must not be included in the Table of Contents. Delete all sub-subsection headings under Nonclinical Toxicology in the Contents.

- Delete ‘ ~~_____~~ and all headings that follow. This information should not be included in the Table of Contents. Full Prescribing Information (FPI):
- Regarding Patient Counseling Information, FDA-approved patient labeling referenced in this section should read [*See FDA-Approved Patient Labeling (17.5)*], not ‘ ~~_____~~ ’ Please correct.
- Under 17.5 FDA-Approved Patient Labeling, delete “(on the following page).” It appears out of place since the labeling is one document.
- Delete the company website address (www.corialabs.com) at the end of the labeling.

b(4)

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/s/

Melinda Bauerlien
5/21/2007 01:31:03 PM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Dermatology and Dental
Products

FACSIMILE TRANSMITTAL SHEET

DATE: 5/11/07

To: Amy Campbell	From: Shalini Jain
Company: Healthpoint	
Fax number: 817-916-2300	Fax number: 301-796-9894
Phone number: 817-302-3901	Phone number: 301-796-0692

Subject: IA for NDA 22070

Total no. of pages including cover: 3

Document to be mailed: YES NO

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Dear Ms. Campbell:

This memo provides a list of revisions for the proposed labeling you have submitted. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review of PLR labeling:

- Because the drug names, dosage form, and route of administration appear at the beginning of the labeling, product information [i.e., Atralin (tretinoin) Gel [Coria Laboratories, Ltd.] is not needed as a header in Highlights and should be deleted.
- The new rule [21 CFR 201,57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

Please propose a established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or rationale why pharmacologic class should be omitted from the Highlights.

- Under Dosage Forms and Strengths, please clarify “w/w”. The same applies to the FPI. Also, you indicate that Tretinoin is available in _____gram and 45 gram tubes in the FPI but did not include this information in the Highlights under Dosage Forms and Strengths. Please include.
- Under Contraindications, it must state “None” not “_____”
Please correct. The same applies to the Contraindications section in the FPI. [See 21 CFR 201.57(a)(9) and (c)(5)]
- The revision is missing from Highlights and will be the month/year that the application is approved [See 21 CFR 201.57(a)(15)]

Full Prescribing Information (FPI) Contents:

- Under 8.1 Pregnancy, delete the phrases _____
_____ since these are not subsection headings and should not be included in the Table of Contents.
- Section and subsection headings can only be numbered. Do not number headings within a subsection (e.g., 13.1.1 Carcinogenesis, 13.1.2 Mutagenesis, 13.1.3 Impairment of Fertility). Use headings without numbering (e.g., Carcinogenesis,

Mutagenesis, Impairment of Fertility). Please correct in the FPI. [See 21 CFR 201.57(c)] Also, heading within a subsection must not be included in the Table of Contents. Delete all sub-section headings under Nonclinical Toxicology in the Contents.

- Delete _____ and all headings that follow. This information should not be included in the Table of Contents.

Full Prescribing Information (FPI):

- Regarding Patient Counseling Information, FDA-approved patient labeling referenced in this section should read [*See FDA-Approved Patient Labeling (17.5)*], not "~~_____~~". Please correct. b(4)
- Under 17.5 FDA-approved Patient Labeling, delete "(on the following page)." It appears out of place since the labeling is one document
- Delete the company website address (www.corialabs.com) at the end of the labeling

Please submit the revised labeling with the labeling comments outlined in this memo to your NDA submission.

MEMORANDUM	Division of Medication Errors and Technical Support (DMETS) Office of Surveillance and Epidemiology WO22, Mail Stop 4447 Center for Drug Evaluation and Research
-------------------	---

TO: Susan Walker, M.D.
Director, Division of Dermatology and Dental Products

THROUGH: Todd D. Bridges, R.Ph., Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, WO22, Mail Stop 4447

FROM: Jinhee L. Jahng, Pharm.D., Safety Evaluator
Division of Medication Errors and Technical Support, WO22, Mail Stop 4447

DATE: May 30, 2007

SUBJECT: DMETS Label and Labeling Review
Drug: Atralin/ (Tretinoin Gel) 0.05% **b(4)**
NDA#: 22-070
Sponsor: Coria Laboratories Ltd.

PROJECT #: 2007-1163

This memorandum is in response to a May 21, 2007 request from the Division of Dermatology and Dental Products for a review of the container label, carton and insert labeling of Atralin/ In order to accommodate the Division's desired completion date for review of the labels and labeling, the assessment of the proprietary names, Atralin and , will follow in a separate OSE review. **b(4)**

Upon review of the labels and labeling for Atralin/ , DMETS has identified the following areas of improvement, in the interest of minimizing user error and maximizing patient safety.

A. CONTAINER LABEL - (-g and 45 g tubes) **b(4)**

1. The established name appears less prominent than the proprietary name. Although the established name may be 1/2 the size of the proprietary name, it does not have a prominence commensurate with the proprietary name. Moreover, per 21 CFR 201.10(g)(2), "the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features". Thus, we recommend increasing the prominence of the established name.
2. The font size and type (bold) of the manufacturer name competes with the prominence of the established name. Decrease the size and prominence of the manufacturer name so that it appears less prominent than the established name.
3. Increase the prominence of the product strength.

4. A graphic design in the form of a “wave” is present above and below the proprietary name. DMETS recommends deleting this graphic art as there should be no intervening matter between the proprietary and established names. Additionally, the graphics divert attention away from the proprietary and established names.
5. The net quantity is expressed in bold font and appears more prominent than the strength. Bolding of this statement draws attention to the net quantity rather than the strength. Unbold the net quantity expression ensuring that it is less prominent than the product strength to avoid confusion between the strength and the net quantity.
6. While the route of administration is present, it is inconsistently labeled in the labels and labeling. In some instances the route is referred to as, “For External Use Only”, while in other instances, the route is referred to as “For Topical Use Only” or “For Topical Dermatologic Use Only”. To be consistent with CDER terminology, revise the route of administration throughout the labels and labeling to read “For Topical Use Only” everywhere the route is referred to.
7. We note that in the WARNINGS and PRECAUTIONS section of the package insert, there is a subsection on “Fish Allergies”, section 5.3, that states that Atralin gel contains soluble fish proteins. Similarly, the Patient Labeling section of the package insert mentions that one’s physician should be aware of any sensitivity or allergies to fish. However, this information does not appear anywhere on the container label. This information is important for health care providers to be aware of so that they can determine if their patients are sensitive or allergic to fish. Thus, we request revision of the container labels and carton labeling to include a warning regarding use of this product in patients with known sensitivity or allergies to fish.

B. CONTAINER LABEL – (Physician Sample)

1. See comments A1 to A7.
2. The “Physician Sample” statement is difficult to identify. Relocate this statement to the top of the label so that it is more visible.

C. CARTON LABELING - (45 g tubes)

b(4)

See comments A1 and A3 – A7.

D. CARTON LABELING

b(4)

E. INSERT LABELING

1. See comment A6.

2. The sponsor has submitted container labels and carton labeling for 45 g and 45 g tubes. However, we note that in the annotated insert labeling, there is no mention of 45 g tubes. If the sponsor plans on marketing 45 g tubes in addition to 45 g tubes, include this information in the insert labeling. Otherwise, delete it from the HOW SUPPLIED/STORAGE AND HANDLING section because it is not a commercially available size.

b(4)

We recommend implementation of the above label and labeling recommendations. DMETS would appreciate feedback of the final outcome of this consult. Please copy DMETS on any correspondence to the sponsor pertaining to this issue. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Angela Robinson, OSE Project Manager, at 301-796-2284.

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/s/

Jinhee Jahng
6/13/2007 02:44:07 PM
DRUG SAFETY OFFICE REVIEWER

Todd Bridges
6/13/2007 03:13:04 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/13/2007 03:47:06 PM
DRUG SAFETY OFFICE REVIEWER

REQUEST FOR CONSULTATION

TO (Office/Division): **DPAP**
Sandy Barnes, Supervisory Project Manager

FROM (Name, Office/Division, and Phone Number of Requestor): **Melinda Bauerlien, Project Manager**
Division of Dermatology and Dental Products

DATE
June 12, 2007

IND NO.

NDA NO.
22-070

TYPE OF DOCUMENT
NDA submission

DATE OF DOCUMENT
9/27/06

NAME OF DRUG
Tretinoin Gel 0.05%

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
July 1, 2007

NAME OF FIRM: **Coria**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END-OF-PHASE 2a MEETING
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY / EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|---|--|

II. BIOMETRICS

- | | |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

IV. DRUG SAFETY

- | | |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: DDDP has an NDA application under review for tretinoin 0.05% gel for the topical treatment of acne vulgaris. The formulation includes Pancogene Marin, described by the applicant as "soluble collagen". The origin of the collagen used is fish and is used in the tretinoin gel formulation as a r _____ at a concentration of ____%. Despite the low concentration of fish protein in the final formulation, we are concerned that there may be the potential risk of allergic reactions in patients with fish protein allergy. b(4)

This was not addressed in the clinical trials and study subjects were not questioned or excluded based on their history of fish allergy. Adverse events of tretinoin would typically include redness, burning, stinging, peeling, and itching and occur in formulations that do not include this excipient.

Please discuss any potential allergy concerns regarding the small amount of fish protein in the product when applied topically by a large number of patients. Please discuss any labeling recommendations, including adequacy of the proposed label. Please discuss any further study needs for this product.

The current draft labeling is attached as well as an article for your reference.

Please let me know if you need anything further.

SIGNATURE OF REQUESTOR

Melinda Bauerlien

METHOD OF DELIVERY (Check one)

DFS

EMAIL

MAIL

HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

7 Page(s) of
Copyright Material
have been Withheld from this
Portion of the Review.

8 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Melinda Bauerlien
6/12/2007 01:39:03 PM

MEMORANDUM

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

DATE: June 4, 2007

TO: Susan Walker, M.D., Director
Division of Dermatologic and Dental Products

VIA: Melinda Bauerlein, M.S., Regulatory Project Manager
Division of Dermatologic and Dental Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm.D., Deputy Director
Division of Surveillance, Research, and Communication Support

SUBJECT: OSE/DSRCS Review of Patient Labeling for (tretinoin) Gel, 0.05%
NDA 22-070

Background and Summary

Coria Laboratories, LTD. submitted an NDA for (tretinoin) Gel, 0.05% NDA 22-070, on September 28, 2006 for treatment of acne vulgaris.

Submitted labeling include Full Prescribing Information (FPI) and patient labeling in the form of a patient package insert (PPI).

OSE/DSRCS was consulted to review the revised patient information.

Comments and Recommendations

See the attached marked and clean copies of the PPI for our recommended revisions. We have made the patient information consistent with the FPI and removed unnecessary information. The sponsor did submit a PPI written in consumer friendly language with a reading level of 7.4 (Flesch-Kincaid). Our revisions lowered the reading level to 6.8. To enhance comprehension, patient information should be written at or below an 8th grade reading level.

Comments to the review division are **bolded, italicized, and underlined**. Please call us if you have any questions.

6 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Jeanine Best
6/4/2007 04:00:12 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
6/4/2007 04:31:56 PM
DRUG SAFETY OFFICE REVIEWER

REQUEST FOR CONSULTATION

TO (Division/Office): Director,
Division of Drug Risk Evaluation (DDRE),
HFD-430, W022, RM

FROM: Melinda Bauerlien, Project Manager, DDDP

David Kettl, Medical Officer, DDDP

DATE 5/21/07

IND NO.

NDA NO. 22-070

TYPE OF DOCUMENT
Original NDA

DATE OF DOCUMENT
(/28/06

NAME OF DRUG

Tretinoin Gel (0.05%)

PRIORITY CONSIDERATION

S

CLASSIFICATION OF DRUG

3

DESIRED COMPLETION DATE

Labeling due date June 18, 2007,
PDUFA due date July 29, 2007

NAME OF FIRM: Coria Laboratories Ltd.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER: Labels (PPI) review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review and comment on the patient package insert.

Draft label attached. Will send word copy as soon as I receive it from the sponsor by the end of the week.

If you have any questions, please feel free to contact me at 301-796-0906

PDUFA DATE: 07/29/07

Re: Draft Package Insert, Container and Carton Labels

CC: NDA 22-070

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/s/

Melinda Bauerlien
5/23/2007 07:54:55 AM

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; HFD-420)**

DATE RECEIVED: May 23, 2007	DESIRED COMPLETION DATE: July 29, 2007	OSE CONSULT #: 2007-1163
DATE OF DOCUMENT: September 27, 2006	PDUFA DATE: July 29, 2007	

TO: Susan Walker, M.D.
Director, Division of Dermatology and Dental Products

THROUGH: Todd Bridges, R.Ph., Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

FROM: Jinhee Jahng Lee, Pharm.D., Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME: Atralin (Tretinoin Gel) 0.05%	NDA SPONSOR: Coria Laboratories Ltd.
NDA #: 22-070	

RECOMMENDATIONS:

1. DMETS has not identified any sound or look-alike names in the U.S. market. However, DMETS has identified an exact match to this product in Bangladesh, containing an entirely different active ingredient, sertraline. Under the stipulation that we are evaluating names in the U.S. market only, this name would be considered acceptable. Nevertheless, the sponsor should be made aware of the potential for confusion and subsequent error that may result from having identical names marketed domestically and abroad based on postmarketing evidence of this type (see section IIC).

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before the NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

2. We refer you to container labels, carton labeling, and insert labeling comments contained in DMETS review #2007-1163, dated June 13, 2007.

3. DDMAC finds the proprietary name, Atralin, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. Please copy DMETS on any correspondence to the sponsor pertaining to this review. We would be willing to meet with the Division for further discussion if needed. If you have further questions or need clarifications, please contact Angela Robinson, OSE Project Manager, at 301-796-2284.

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/s/

Melinda Bauerlien
5/23/2007 08:04:57 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-070

Coria Laboratories, Ltd.
Attention: Mike Bernstein, M.P.H.
Vice President, Regulatory Affairs
3909 Hulen Street
Fort Worth, TX 76107

Dear Mr. Bernstein:

Please refer to your September 27, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tretinoin gel 0.05% for use in acne vulgaris.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 27, 2006 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential filing review issues, and are requesting the following information:

Chemistry and Manufacturing Controls:

1. The stability data to support the fill sizes of ~ 3 and ~ 6 mg are inadequate in that only one stability batch for each of these two sizes has been submitted to the NDA. Submit the additional stability data for the fill sizes of ~ 3 and ~ 6 to the NDA.

b(4)

Biostatistics:

1. Submit draft labeling in WORD format.
2. Only Amendment 4 of Protocol 735.126.CL009/01 has been submitted.
 - Submit any versions of Protocol 735.126.CL009/01 that were in effect while subjects were enrolled in the study (e.g., original issue and amendments 1-3)
3. Additional information regarding the presentation of the global severity scale in the CRF for Study 735.126.CL009/01 is needed. The following table below displays how the global severity scale appeared in the CRF:

Acne Severity Acne Grade (refer to scale)	
Clear	0 <input type="checkbox"/> ¹
Very Mild	1 <input type="checkbox"/> ²
Mild	2 <input type="checkbox"/> ³
Mildly - Moderate	3 <input type="checkbox"/> ⁴
Moderate	4 <input type="checkbox"/> ⁵
Severe	5 <input type="checkbox"/> ⁶

Each checkbox has two numbers associated with it: the larger numbers to the left associated with the levels (0-5) and the smaller numbers to the right (1-6). Clarify:

- Why two different sets of numbers are associated with the global severity scale
- How the numbers were used for data entry
- How you ensured that coding errors did not occur due to mixing of the two sets of numbers

We are providing the above comments to give you preliminary notice potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Shalini Jain, Regulatory Project Manager, at (301) 796-0692.

Sincerely,

{See appended electronic signature page}

Susan Walker, M.D.
 Division Director
 Division of Dermatology and Dental
 Products
 Office of Drug Evaluation III
 Center for Drug Evaluation and Research

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/s/

Susan Walker
12/11/2006 12:17:27 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-070

Coria Laboratories
Attention: Mike Bernstein, MPH
Vice-President, Regulatory Affairs
3909 Hulen Street
Forth Worth, TX 76107

Dear Mr. Bernstein:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Tretinoin Gel, 0.05%

Review Priority Classification: S

Date of Application: September 27, 2006

Date of Receipt: September 28, 2006

Our Reference Number: NDA 22-070

The application will be filed on November 27, 2006, in accordance with 21 CFR 314.101(a). The user fee goal date will be July 28, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

NDA 22-070

Page 2

Center for Drug Evaluation and Research
Division of Dermatology & Dental Products
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Shalini Jain, Regulatory Project Manager, at (301) 796-2110.

Sincerely,

{See appended electronic signature page}

Mary Jean Kozma-Fornaro
Supervisor, Project Management
Division of Dermatology & Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Maria Walsh
10/14/2006 04:14:33 PM
Signed for Mary Jean Kozma-Fornaro

Coria Laboratories, Ltd

NDA:22-070 User Fee Cover Sheet

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION** **PRESCRIPTION DRUG USER FEE COVERSHEET**

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website:
<http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

CORIA LABORATORIES LTD
Amy Campbell
3909 Hulen St.
Fort Worth TX 76107
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

22-070

2. TELEPHONE NUMBER
817-302-3901

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME
Atralin (Tretinoin Gel, 0.05%)

6. USER FEE I.D. NUMBER
PD3006721

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

Coria Laboratories, Ltd

NDA:22-070 User Fee Cover Sheet

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive,
Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

TITLE

DATE

M.H. Bennett

VP Regulatory Affairs 5 Sept. 06

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
\$767,400.00

Form FDA 3397 (12/03)

(BE PRMT CLOSE G) (Print Cover sheet)

3909 HULEN STREET
FORT WORTH, TEXAS 76107
817 900 4000
800 441 9227
CUSTOMER CARE FAX 817 700 4100

August 1/, 2006

CDER Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

Re: IND 63,067
Tretinoin Gel, 0.05%

Dear Sir or Madam,

Healthpoint, Ltd. hereby authorizes the Food and Drug administration to refer to and incorporate by reference, the information contained in the above-specific Investigational New Drug (IND) Application on behalf of:

Coria Laboratories, Ltd.
3909 Hulen Street
Fort Worth, TX 76107

This authorization is given in support of all their NDA, ANDA, and IND applications involving the above-mentioned product. If you have any further questions or concerns, please feel free to contact me at (817) 916-2294 or Mike.Bernstein@DFB.com.

Sincerely,



Mike Bernstein, MPH
Vice-President, Regulatory Affairs



DECLARATION of Joseph C. Famulare

I, Joseph C. Famulare, declare the following:

- 1) I am Director, Division of Manufacturing and Product Quality, Office of Compliance, Center for Drug Evaluation and Research, the United States Food and Drug Administration.
- 2) In this capacity, I issue Certificates of Pharmaceutical Products to foreign governments for export purpose concerning the manufacture, preparation, and marketing of drugs in the United States and the GMP status of the plant which produces them.
- 3) The manufacturing facility, registered as DPT Laboratories, LTD, located at 307 East Josephine Street, San Antonio, Texas 78215, is subject to periodic inspections by the FDA. The latest inspection showed that the plant, at this time, is in substantial compliance with current Good Manufacturing Practices (cGMPs) as required by the Federal Food, Drug, and Cosmetic Act and as recommended by the World Health Organization.
- 4) The registration number for the above facility is: 1628114.
- 5) Pursuant to 28 U.S.C. § 1746, I declare under a penalty of perjury that the foregoing is true and correct.

Joseph C. Famulare, Director
Division of Manufacturing and
Product Quality
Office of Compliance
Center for Drug Evaluation and Research.

State of Maryland) ss

Subscribed and sworn to before me this 5th day of DECEMBER 2005.

Notary Public

Concepcion Cruz
NOTARY PUBLIC

Montgomery County, Maryland

My Commission Expires 12/03/2008



February 12, 2007

CDER Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

NDA No.: NDA 22-070
Product: Tretinoin Gel, 0.05%
Amendment 0002 in eCTD Format
Re: 4-month Safety Update

Dear Sir or Madam:

Coria Laboratories, Ltd (a wholly-owned subsidiary of Healthpoint, Ltd.) is submitting Amendment 0002 to it's NDA for Tretinoin Gel, 0.05% in the eCTD format. This submission includes:

- 4-month Safety Update: There is no new safety information to submit to this application. No new studies have been initiated since the submission of this application.

Per the FDA Industry Guidance "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications", the Dallas District Office will be notified in a separate letter of this submission in the eCTD format.

If you have any questions concerning this application, please contact:

Amy Campbell
Regulatory Affairs Manager
Healthpoint, Ltd,
(817) 302-3901
Amy.Campbell@healthpoint.com

or

Bobbi Drais, MS
Sr. Director, Regulatory Affairs
Healthpoint, Ltd.
(817) 302-3904
Bobbi.Drais@healthpoint.com

Sincerely,

A handwritten signature in black ink that reads "Mike Bernstein".

Mike Bernstein, MPH
Vice-President, Regulatory Affairs

Enclosure

ACTION PACKAGE CHECKLIST

Application Information		
BLA # NDA # 22-070	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Atralin Established Name: tretinoin gel Dosage Form: 0.05%		Applicant: Coria Laboratories, Ltd
RPM: Melinda Bauerlien		Division: DDDP Phone # 301-796-2110
<p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>20-475 Retin-A MICRO 0.1% and 0.04% Gel</p> <p>Provide a brief explanation of how this product is different from the listed drug. Different strength</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</p> <p><input checked="" type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date: July 12, 2007</p>
❖ User Fee Goal Date		July 28, 2007
❖ Action Goal Date (if different)		
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (<i>specify type and date for each action taken</i>)		<input checked="" type="checkbox"/> None
❖ Advertising (<i>approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (<i>indicate dates of reviews</i>)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 3	
NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation	
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies
NDAs and NDA Supplements: <input type="checkbox"/> OTC drug	
Other: N/A	
Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> • Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) • OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input checked="" type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Press Office notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</p> <p>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</p>	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	July 26, 2007
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	N/A
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	July 24, 2007
• Original applicant-proposed labeling	September 26, 2006
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	July 24, 2007
• Original applicant-proposed labeling	September 26, 2006
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	N/A
• Original applicant-proposed labeling	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (full color carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	N/A
• Most recent applicant-proposed labeling	July 24, 2007
❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)	<input checked="" type="checkbox"/> DMETS June 13 and July 13, 2007 <input checked="" type="checkbox"/> DSRCS June 6, 2007 <input checked="" type="checkbox"/> DDMAC June 21, 2007 <input checked="" type="checkbox"/> SEALD December 14, 2006 <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	July 26, 2007
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	N/A
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) 	July 16, 2007
<ul style="list-style-type: none"> Incoming submission documenting commitment 	July 23, 2007
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	yes
❖ Internal memoranda, telecons, email, etc.	yes
❖ Minutes of Meetings	
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) 	May 29, 2007
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date</i>) 	<input type="checkbox"/> No mtg June 1, 2006
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date</i>) 	<input type="checkbox"/> No mtg October 21, 2001
<ul style="list-style-type: none"> Other (e.g., EOP2a, CMC pilot programs) 	N/A
❖ Advisory Committee Meeting	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date of Meeting 48-hour alert or minutes, if available 	
❖ <u>Federal Register</u> Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
CMC/Product Quality Information	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	July 19, 2007
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) 	July 19, 2007
<ul style="list-style-type: none"> <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) 	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> NDAs: Facilities inspections (include EER printout) 	Date completed: February 27, 2007 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	June 28, 2007
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	N/A
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	July 26, 2007 and July 27, 2007
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	July 27, 2007
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None Allergy 6/26/07
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	July 27, 2007
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
• Clinical Studies	
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None June 19, 2007
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None July 16, 2007

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.