

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20475-S021

Trade Name: RETIN-A-MICRO

Generic Name: tretinoin

Sponsor: Valeant International

Approval Date: January 28, 2014

Indications: Topical treatment of acne vulgaris

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20475-S021

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 20475-S021

APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020475/S-021

SUPPLEMENT APPROVAL

Valeant International Bermuda
c/o Keller & Heckman, LLP
Attention: John B. Dubeck
US Agent
1001 G Street, NW, Suite 500 W
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your Supplemental New Drug Application (sNDA) dated October 3, 2012, received October 4, 2012 under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Retin-A Micro[®] (tretinoin) Gel microsphere, 0.04%, 0.08% and 0.1%.

We acknowledge receipt of your amendments dated December 4, 2012, January 4, February 1, and 28, March 8, May 3, and September 23, 2013, and January 23, 2014.

The September 23, 2013, submission constituted a complete response to our April 19, 2013, action letter.

This "Prior Approval" supplemental new drug application provides for an intermediary strength, 0.08%, and revision of the Retin-A Micro full prescribing information to meet the labeling content and format requirements for human prescription drug and biological products according to 21 CFR 201.56(d) and 201.57.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending "Changes Being

Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels **and** carton and immediate-container labels submitted on January 23, 2014, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 020475/S-021.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, MD, FAAD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Carton and Container Labeling

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

/s/

SUSAN J WALKER
01/28/2014



NDA 020475/S-021

COMPLETE RESPONSE

Valeant Pharmaceuticals North America LLC
Attention: Charity Abelardo, RAC
Acting Senior Director, Regulatory Affairs
700 Route 202/206 North
Bridgewater, NJ 08807

Dear Ms. Abelardo:

Please refer to your Supplemental New Drug Application (sNDA) dated October 3, 2012, received October 4, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Retin-A MICRO[®] (tretinoin gel) Microsphere, 0.1% and 0.04%.

We acknowledge receipt of your amendments dated December 4, 2012; January 7, February 1, and 28, and March 8, 2013.

This supplemental new drug application proposes an intermediary strength of 0.08% tretinoin gel.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

DEFICIENCY

Your proposed formulation (b) (4) is not documented for Retin-A Micro gel

INFORMATION NEEDED TO RESOLVE DEFICIENCY

1. Revise the formulation composition table for the 0.08% gel (b) (4).
2. Revise the Master Batch Record for the 0.08% gel (b) (4)
3. Revise the drug product specification table for the 0.08% gel (b) (4)

4. Provide release and 3 months of stability data from a batch of 0.08% gel that is manufactured using the revised formulation [REDACTED] (b) (4).

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

Under 21 CFR 314.70 (c) (7), products manufactured with the changes proposed in this supplement can no longer be distributed until this supplement is approved.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, MD, FAAD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

SUSAN J WALKER
04/19/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 20475-S021

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RETIN-A MICRO® safely and effectively. See full prescribing information for RETIN-A MICRO®.

Retin-A Micro (tretinoin) Gel microsphere 0.1%, 0.08% and 0.04% for topical use

Initial U.S. Approval: 1997

INDICATIONS AND USAGE

Retin-A Micro (tretinoin) Gel microsphere, 0.1%, 0.08% and 0.04%, is a retinoid, indicated for topical treatment of acne vulgaris. (1)

DOSAGE AND ADMINISTRATION

- Apply a thin layer of Retin-A Micro once daily, before bedtime, to skin where lesions occur. Keep away from eyes, mouth, nasal creases, and mucous membranes. (2)
- Not for oral, ophthalmic, or intravaginal use. (2)

DOSAGE FORMS AND STRENGTHS

Gel, 0.04%, 0.08% and 0.1% (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Retin-A Micro should not be used on eczematous or sunburned skin due to potential for severe irritation. (5.1)
- Avoid unprotected exposure to sunlight including sunlamps (UV light), when using Retin-A Micro due to potential for increased photosensitization. Use sunscreen of at least SPF 15 and protective clothing during exposure. (5.2)
- Avoid use of Retin-A Micro with weather extremes, such as wind or cold due to potential for increased irritation. (5.2)

ADVERSE REACTIONS

Most common adverse reactions are skin pain, pruritus, skin irritation/subcutaneous irritation, pharyngitis, and erythema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS

- Retin-A Micro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There are no adequate and well-controlled studies in pregnant and nursing women. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 01/2014

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Retin-A Micro[®] (tretinoin) Gel microsphere, 0.1%, 0.08% and 0.04%, is a retinoid indicated for topical application in the treatment of acne vulgaris.

2 DOSAGE AND ADMINISTRATION

For topical use only. Not for ophthalmic, oral, or intravaginal use.

Retin-A Micro (tretinoin) Gel microsphere, 0.1%, 0.08% and 0.04%, should be applied once a day, in the evening, to the skin where acne lesions appear, using enough to cover the entire affected area in a thin layer. Areas to be treated should be cleansed thoroughly before the medication is applied. If medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur. A transitory feeling of warmth or slight stinging may be noted on application. In cases where it has been necessary to temporarily discontinue therapy or to reduce the frequency of application, therapy may be resumed or the frequency of application increased as the patient becomes able to tolerate the treatment. Frequency of application should be closely monitored by careful observation of the clinical therapeutic response and skin tolerance. Efficacy has not been established for less than once daily dosing frequencies.

During the early weeks of therapy, an apparent exacerbation of inflammatory lesions may occur. If tolerated, this should not be considered a reason to discontinue therapy [see *Adverse Reactions* (6.1)].

Therapeutic results may be noticed after two weeks, but more than seven weeks of therapy are required before consistent beneficial effects are observed.

Retin-A Micro (tretinoin) el microsphere, 0.1%, 0.08% and 0.04%, should be kept away from the eyes, the mouth, paranasal creases of the nose, and mucous membranes.

Patients treated with Retin-A Micro (tretinoin) gel microsphere, 0.1%, 0.08% and 0.04% may use cosmetics.

Concomitant topical medication, medicated or abrasive soaps and cleansers, products that have a strong drying effect, products with high concentrations of alcohol, astringents, or spices should be used with caution because of possible interaction with tretinoin. Avoid contact with the peel of limes. Particular caution should be exercised with the concomitant use of topical over-the-counter acne preparations containing benzoyl peroxide, sulfur, resorcinol, or salicylic acid with Retin-A Micro (tretinoin) Gel microsphere, 0.1% and 0.04%. It also is advisable to allow the effects of such preparations to subside before use of Retin-A Micro (tretinoin) Gel microsphere, 0.1% and 0.04%, is begun.

3 DOSAGE FORMS AND STRENGTHS

Retin-A Micro is a white to very pale yellow opaque gel. Retin-A Micro is available in three strengths: 0.04%, 0.08% and 0.1%.

Each gram of Retin-A Micro Gel 0.1% contains 1 mg of tretinoin.

Each gram of Retin-A Micro Gel 0.08% contains 0.8 mg of tretinoin.

Each gram of Retin-A Micro Gel 0.04% contains 0.4 mg of tretinoin.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Local Irritation

The skin of certain individuals may become excessively dry, red, swollen, or blistered.

Tretinoin has been reported to cause severe irritation on eczematous skin and should be used with utmost caution in patients with this condition.

If the degree of irritation warrants, patients should be directed to temporarily reduce the amount or frequency of application of the medication, discontinue use temporarily, or discontinue use all together. Efficacy at reduced frequencies of application has not been established. If a reaction suggesting sensitivity occurs, use of the medication should be discontinued.

To help limit skin irritation, patients must

- wash the treated skin gently, using a mild, non-medicated soap, and pat it dry, and
- avoid washing the treated skin too often or scrubbing it hard when washing.

Patients should apply a topical moisturizer if dryness is bothersome.

5.2 Exposure to Ultraviolet Light or Weather Extremes

Unprotected exposure to sunlight, including sunlamps (UV light) should be avoided or minimized during the use of Retin-A Micro (tretinoin) Gel microsphere, 0.1%, 0.08% and 0.04%, and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight as a result of the use of tretinoin. Patients who may be required to have extended periods of UV exposure (e.g., due to occupation or sports), or those with inherent sensitivity to the sun, or those using medications that cause photosensitivity, should exercise particular caution. Use of sunscreen products (SPF15 or higher and protective clothing over treated areas are recommended when exposure cannot be avoided [see *Nonclinical Toxicology* (13.1)]).

Weather extremes, such as wind or cold, also may be irritating to tretinoin-treated skin.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials in Subjects with Acne

In separate clinical trials for each concentration, acne subjects treated with Retin-A Micro (tretinoin) Gel microsphere 0.1% or 0.04%, over the twelve week period showed that cutaneous irritation scores for erythema, peeling, dryness, burning/stinging, or itching peaked during the initial two weeks of therapy, decreasing thereafter.

Approximately half of the subjects treated with Retin-A Micro 0.04% had cutaneous irritation at Week 2. Of those subjects who did experience cutaneous side effects, most had signs or symptoms that were mild in severity (severity was ranked on a 4-point ordinal scale: 0=none, 1=mild, 2=moderate, and 3=severe). Less than 10% of patients experienced moderate cutaneous irritation and there was no severe irritation at Week 2.

In trials of Retin-A Micro (tretinoin) Gel microsphere 0.04%, throughout the treatment period the majority of subjects experienced some degree of irritation (mild, moderate, or severe) with 1% (2/225) of subjects having scores indicative of a severe irritation; 1.3% (3/225) of subjects treated with Retin-A Micro (tretinoin) Gel microsphere, 0.04%, discontinued treatment due to irritation, which included dryness in one patient and peeling and urticaria in another.

In studies of Retin-A Micro (tretinoin) Gel microsphere 0.1%, no more than 3% of subjects had cutaneous irritation scores indicative of severe irritation; 6% (14/224) of subjects treated with Retin-A Micro (tretinoin) Gel microsphere, 0.1% discontinued treatment due to irritation. Of these 14 subjects, four had severe irritation after 3 to 5 days of treatment, with blistering in one subject.

In a double-blind trial with 156 acne subjects comparing 12 weeks of treatment with Retin-A-Micro (tretinoin) Gel 0.04% or 0.1% (78 subjects each group), the most frequently-reported adverse events affected the skin and subcutaneous tissue (15.4% in the 0.04% group, and 20.5% in the 0.1% group). The most prevalent of the dermatologic adverse events in the 0.04% group was skin irritation (6.4%); and in the 0.1% group skin burning (7.7%), erythema (5.1%), skin irritation (3.8%), and dermatitis (3.8%). Most adverse events were of mild intensity (63.4%), and 34.4% were moderate. One subject in each group had adverse events characterized as severe, neither were dermatologic findings and neither was characterized as related to drug by the investigator.

Trials in Subjects Without Acne

In a half-face comparison trial conducted for up to 14 days in women with sensitive skin, but without acne, Retin-A Micro (tretinoin) Gel microsphere, 0.1% was statistically less irritating than tretinoin cream, 0.1%. In addition, a cumulative 21 day irritation evaluation in subjects with normal skin showed that Retin-A Micro (tretinoin) Gel microsphere, 0.1%, had a lower irritation profile than tretinoin cream, 0.1%. The clinical significance of these irritation studies for patients with acne is not established. Comparable effectiveness of Retin-A Micro (tretinoin) Gel

microsphere, 0.1% and tretinoin cream, 0.1%, has not been established. The lower irritancy of Retin-A Micro (tretinoin) Gel microsphere, 0.1% in subjects without acne may be attributable to the properties of its vehicle. The contribution of decreased irritancy by the MICROSPONGE System has not been established. No irritation trials have been performed to compare Retin-A Micro (tretinoin) Gel microsphere, 0.04%, with either Retin-A Micro (tretinoin) Gel microsphere, 0.1%, or tretinoin cream, 0.1%.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Retin A Micro Gel. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Temporary hyper- or hypopigmentation has been reported with repeated application of tretinoin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Retin-A Micro[®] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Thirty human cases of temporally associated congenital malformations have been reported during two decades of clinical use of Retin-A Micro[®] (tretinoin) Gel microsphere, 0.1% and 0.04%. Although no definite pattern of teratogenicity and no causal association has been established from these cases, five of the reports describe the rare birth defect category holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

For purposes of comparison of the animal exposure to systemic human exposure, the Maximum Recommended Human Dose (MRHD) applied topically is defined as 1 gram of Retin-A Micro[®] (tretinoin) Gel microsphere 0.1% applied daily to a 60 kg person (0.017 mg tretinoin/kg body weight).

Pregnant rats were treated with of Retin-A Micro (tretinoin) Gel microsphere, 0.1%, at daily dermal doses of 0.5 to 1 mg/kg/day on gestation days 6-15. Alterations were seen in vertebrae and ribs of offspring at 5 to 10 times the MRHD based on the body surface area (BSA) comparison.

Pregnant New Zealand White rabbits were treated with Retin-A Micro (tretinoin) Gel microsphere, 0.1%, at daily dermal doses of 0.2, 0.5, and 1.0 mg/kg/day tretinoin on gestation days 7-19. Doses were administered topically for 24 hours a day while wearing Elizabethan collars to prevent ingestion of the drug. Increased incidences of certain alterations, including domed head and hydrocephaly, typical of retinoid-induced fetal malformations in this species, were observed at 0.5 and 1.0 mg/kg/day. Similar malformations were not observed at 0.2 mg/kg/day, -4 times the MRHD based on BSA comparison Other pregnant rabbits exposed topically for six hours per day to 0.5 or 1.0 mg/kg/day tretinoin while restrained in stocks to

prevent ingestion, did not show any teratogenic effects at doses up to 19 times (1.0 mg/kg/day) the MRHD based on BSA comparison, but fetal resorptions were increased at 0.5 mg/kg (10 times the MRHD based on BSA comparison).

Oral tretinoin has been shown to be teratogenic in rats, mice, rabbits, hamsters, and nonhuman primates.

Tretinoin was teratogenic in Wistar rats when given orally in doses greater than 1 mg/kg/day (10 times the MRHD based on BSA comparison). In the cynomolgus monkey, fetal malformations were reported for doses of 10 mg/kg/day but none were observed at 5 mg/kg/day (95 times the MRHD based on BSA comparison), although increased skeletal variations were observed at all doses. Dose-related increases in embryoletality and abortion also were reported. Similar results have also been reported in pigtail macaques.

There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (10 times the maximum MRHD based on BSA comparison). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day was topically applied. Supernumerary ribs have been a consistent finding in rats when dams were treated topically or orally with retinoids.

In oral peri- and postnatal development studies in rats with tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (19 times the MRHD based on BSA comparison).

Nonteratogenic effects on fetus

Oral tretinoin has been shown to be fetotoxic when administered (in doses 24 times the MRHD based on BSA comparison).

Topical tretinoin has been shown to be fetotoxic in rabbits when administered in doses 10 times the MHRD based on BSA comparison.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Retin-A Micro (tretinoin) Gel microsphere, 0.1%, 0.08% or 0.04%, is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in children below the age of 12 have not been established.

8.5 Geriatric Use

Safety and effectiveness in a geriatric population have not been established. Clinical trials of Retin-A Micro[®] (tretinoin) Gel microsphere 0.1% and 0.04% did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects.

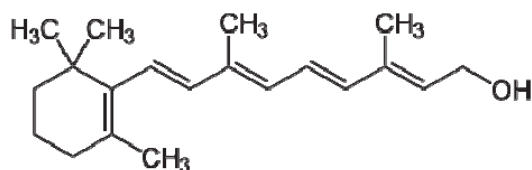
10 OVERDOSAGE

Oral ingestion of large amounts of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

11 DESCRIPTION

Retin-A Micro (tretinoin) Gel microsphere, 0.1%, 0.08% and 0.04%, is a white to very pale yellow opaque for topical treatment of acne vulgaris.

Chemically, tretinoin is all-trans-retinoic acid, also known as (all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid. It is a member of the retinoid class of compounds, and a metabolite of naturally occurring Vitamin A. Tretinoin has a molecular weight of 300.44, a molecular formula of $C_{20}H_{28}O_2$ and the following chemical structure:



Each gram of Retin-A Micro, Gel 0.1% contains 1 mg of tretinoin.

Each gram of Retin-A Micro, Gel 0.08% contains 0.8 mg of tretinoin.

Each gram of Retin-A Micro, Gel 0.04% contains 0.4 mg of tretinoin.

The formulation uses methyl methacrylate/glycol dimethacrylate crosspolymer porous microspheres (MICROSPONGE[®] System) to enable inclusion of the active ingredient, tretinoin, in an aqueous gel. Other components consist of benzyl alcohol, butylated hydroxytoluene, carbomer 934P, carbomer 974P, cyclomethicone, dimethicone copolyol, disodium EDTA, glycerin, PPG-20 methyl glucose ether distearate, propylene glycol, purified water, sorbic acid and trolamine.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Although tretinoin activates three members of the retinoic acid (RAR) nuclear receptors (RAR α , RAR β , and RAR γ) which may act to modify gene expression, subsequent protein synthesis, and epithelial cell growth and differentiation, it has not been established whether the clinical effects of tretinoin are mediated through activation of retinoic acid receptors and/or other mechanisms.

The exact mode of action of tretinoin is unknown. Current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells with decreased microcomedone formation. Additionally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells causing extrusion of the comedones.

12.3 Pharmacokinetics

Tretinoin is a metabolite of Vitamin A metabolism in man. Percutaneous absorption, as determined by the cumulative excretion of radiolabeled drug into urine and feces, was assessed in 44 healthy men and women after single and repeated daily applications of 500 mg of a 0.1% tretinoin gel formulation. Estimates of *in vivo* bioavailability, mean (SD)%, following both single and multiple daily applications, for a period of 28 days with the 0.1% gel, were 0.82 (0.11)% and 1.41 (0.54)%, respectively. The plasma concentrations of tretinoin and its metabolites, 13-*cis*-retinoic acid, all-*trans*-4-oxo-retinoic acid, and 13-*cis*-4-oxo-retinoic acid, generally ranged from 1 to 3 ng/mL and were essentially unaltered after either single or multiple daily applications of Retin-A Micro (tretinoin) Gel microsphere, 0.1%, relative to baseline levels. Clinical pharmacokinetic trials have not been performed with Retin-A Micro (tretinoin) Gel microsphere, 0.04% and 0.08%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dermal carcinogenicity testing has not been performed with Retin-A Micro (tretinoin) gel microsphere, 0.1%, 0.08%, or 0.04%.

In a 91-week dermal study in which CD-1 mice were administered 0.017% and 0.035% formulations of tretinoin, cutaneous squamous cell carcinomas and papillomas in the treatment area were observed in some female mice. These concentrations are near the tretinoin concentration of the 0.04% and 0.1% clinical formulations. A dose-related incidence of liver tumors in male mice was observed at those same doses. The maximum systemic doses associated with the administered 0.017% and 0.035% formulations are 0.5 and 1.0 mg/kg/day tretinoin, respectively. These doses are two and four times the MHRD based on BSA comparison.

The biological significance of these findings is not clear because they occurred at doses that exceeded the dermal maximally tolerated dose of tretinoin and because they were within the background natural occurrence rate for these tumors in this strain of mice.

There was no evidence of carcinogenic potential when 0.025 mg/kg/day of tretinoin was administered topically to mice (0.1 times the MHRD based on BSA comparison). Studies in hairless albino mice suggest that concurrent exposure to tretinoin may enhance the tumorigenic potential of carcinogenic doses of UVB and UVA light from a solar simulator. This effect has been confirmed in a later study in pigmented mice, and dark pigmentation did not overcome the enhancement of photocarcinogenesis by 0.05% tretinoin. Although the significance of these studies to humans is not clear, patients should minimize exposure to sunlight or artificial ultraviolet irradiation sources [see *Warnings and Precautions* (5.2)].

The genotoxic potential of tretinoin was evaluated in the Ames assay and in the *in vivo* mouse micronucleus assay, both of which were negative.

The components of the microspheres have shown potential for genetic toxicity and teratogenesis. EGDMA, a component of the excipient acrylates copolymer, was positive for induction of structural chromosomal aberrations in the *in vitro* chromosomal aberration assay in mammalian

cells in the absence of metabolic activation, and negative for genetic toxicity in the Ames assay, and the in vivo mouse micronucleus assay.

In oral fertility studies in rats with tretinoin, the no-observable effect level was 2 mg/kg/day (19 times the MHRD based on BSA comparison).

14 CLINICAL STUDIES

14.1 Retin-A Micro[®] (tretinoin) Gel microsphere, 0.1%

In two vehicle-controlled trials, Retin-A Micro[®] (tretinoin) Gel microsphere, 0.1%, applied once daily was significantly more effective than vehicle in reducing the acne lesion counts. The mean reductions in lesion counts from baseline after treatment for 12 weeks are shown in the following table:

Table 1: Mean Percent Reduction in Lesion Counts Retin-A Micro[®] (tretinoin) Gel microsphere, 0.1%

	Retin-A Micro [®] (tretinoin) Gel microsphere, 0.1%		Vehicle Gel	
	Study #1 72 pts	Study #2 71 pts	Study #1 72 pts	Study #2 67 pts
Non-inflammatory lesion counts	49%	32%	22%	3%
Inflammatory lesion counts	37%	29%	18%	24%
Total lesion counts	45%	32%	23%	16%

Retin-A Micro[®] (tretinoin) Gel microsphere, 0.1% was also significantly superior to the vehicle in the investigator's global evaluation of the clinical response. In Study #1, thirty-five percent (35%) of subjects using Retin-A Micro[®] (tretinoin) Gel microsphere, 0.1%, achieved an excellent result, as compared to eleven percent (11%) of subjects on the vehicle control. In Study #2, twenty-eight percent (28%) of patients using Retin-A Micro[®] (tretinoin) Gel microsphere, 0.1%, achieved an excellent result, as compared to nine percent (9%) of the subjects on the vehicle control.

14.2 Retin-A Micro[®] (tretinoin) Gel microsphere, 0.04%

In two vehicle-controlled clinical trials, Retin-A Micro[®] (tretinoin) Gel microsphere, 0.04%, applied once daily, was more effective ($p < 0.05$) than vehicle in reducing the acne lesion counts. The mean reductions in lesion counts from baseline after treatment for 12 weeks are shown in the following table:

Table 2: Mean Percent Reduction in Lesion Counts Retin-A Micro[®] (tretinoin) Gel microsphere, 0.04%

	Retin-A Micro [®] (tretinoin) Gel microsphere, 0.04%		Vehicle Gel	
	Study #1 108 pts	Study #2 111 pts	Study #1 110 pts	Study #2 103 pts
Non-inflammatory lesion counts	37%	29%	-2%*	14%
Inflammatory lesion counts	44%	41%	13%	30%
Total lesion counts	40%	35%	8%	20%
* - That is, a mean percent increase of 2%				

Retin-A Micro[®] (tretinoin) Gel microsphere, 0.04%, was also superior ($p < 0.05$) to the vehicle in the investigator's global evaluation of the clinical response. In Study #1, fourteen percent (14%) of subjects using Retin-A Micro[®] (tretinoin) Gel microsphere, 0.04%, achieved an excellent result compared to five percent (5%) of subjects on vehicle control. In Study #2, nineteen percent (19%) of subjects using Retin-A Micro[®] (tretinoin) Gel microsphere, 0.04%, achieved an excellent result compared to nine percent (9%) of subjects on vehicle control.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Retin-A Micro Gel is opaque and white to very pale yellow in color.

Retin-A Micro Gel, 0.1% is supplied in

20 gram tube (NDC 0187-5140-20),

45 gram tube (NDC 0187-5140-45) and

50 gram pump (NDC 0187-5140-50).

Retin-A Micro Gel, 0.08% is supplied in

50 gram pump (NDC 0187-5148-50).

Retin-A Micro Gel, 0.04% is supplied in

20 gram tube (NDC 0187-5144-20),

45 gram tube (NDC 0187-5144-45) and

50 gram pump (NDC 0187-5144-50).

16.2 Storage Conditions

Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F-86°F) [*see USP Controlled Room Temperature*].

Store pump upright.

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information)

The patient should be instructed to:

Cleanse the treatment area thoroughly, before treatment with a mild, non-medicated cleanser. Do not to use more than the recommended amount and not to apply Retin-A Micro more than once daily as this will not produce faster or better results, but may increase irritation.

Minimize exposure to sunlight, including sunlamps. Recommend the use of sunscreen products and protective apparel (e.g., hat) when exposure cannot be avoided

Manufactured by: Janssen Ortho LLC, Manati, Puerto Rico 00674

Distributed by: Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807

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MICROSPONGE® is a registered trademark of AMCOL International Corporation

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Patient Information

Retin-A Micro[®] (ret-in-A MY-kroe)

(tretinoin) Gel microsphere, 0.1%, 0.08% and 0.04%
for topical use

Important information: Retin-A Micro[®] is for use on skin only. Do not get Retin-A Micro[®] in your eyes, mouth, vagina or the corners of your nose.

What is Retin-A Micro[®]?

Retin-A Micro[®] is a prescription medicine used on the skin (topical) to treat acne. Acne is a condition in which the skin has blackheads, whiteheads, and other pimples.

It is not known if Retin-A Micro[®] is safe and effective in the treatment of other conditions.

It is not known if Retin-A Micro[®] is safe and effective in children under 12 years of age.

What should I tell my doctor before using Retin-A Micro[®]?

Before using Retin-A Micro[®], tell your doctor if you:

- have a skin condition called eczema
- have a sunburn. You should not use Retin-A Micro[®] until your skin has healed.
- have any other medical condition
- are pregnant or plan to become pregnant. It is not known if Retin-A Micro[®] will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Retin-A Micro[®] passes into your breast milk.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, herbal supplements, and any skin products that you use.

Especially tell your doctor if you use any other medicines to treat your acne, including medicated cleansers or soaps. Using other topical acne products may increase the irritation of your skin when used with Retin-A Micro[®].

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I use Retin-A Micro[®]?

- Use Retin-A Micro[®] exactly as your doctor tells you to use it.
- Your doctor may change your dose of Retin-A Micro[®] if you have skin irritation.
- Before you apply Retin-A Micro[®], gently wash the affected skin area with a mild, non-medicated soap. Rinse and pat your skin dry.
- Apply Retin-A Micro[®] 1 time a day in the evening, or as prescribed by your doctor.
- Do not use more Retin-A Micro[®] than you need to cover the affected area and do not apply Retin-A Micro[®] more than 1 time a day. Using too much Retin-A

Micro[®] or using it too often will not give you faster or better results and you may get skin redness, peeling, or discomfort.

- You may have a brief feeling of warmth or slight stinging after applying Retin-A Micro[®].
- You may use moisturizers and cosmetic.
- Early in your treatment, you may get new pimples. At this stage, it is important to continue using Retin-A Micro[®].
- Your acne may not get better right away. Use Retin-A Micro[®] even after your acne improves. Your acne may get better after two weeks of treatment, but more than seven weeks of Retin-A Micro[®] treatment are needed before you get the full benefit.

Applying Retin-A Micro[®]:

- Retin-A Micro[®] comes in a tube and a pump. If you have been prescribed the:

Tube: Squeeze the gel from the tube onto a fingertip. Apply a thin layer to cover the affected area, as prescribed by your doctor. Spread Retin-A Micro[®] evenly over the affected area.

Pump: Fully depress the pump twice to dispense Retin-A Micro[®] onto a fingertip. Apply a thin layer to cover the affected area, as prescribed by your doctor. Spread Retin-A Micro[®] evenly over the affected area.

- Wash your hands after applying Retin-A Micro[®].

What should I avoid while using Retin-A Micro[®]?

- Avoid washing your skin too often and scrubbing the affected skin area.
- You should avoid sunlamps, tanning beds, and ultraviolet light during treatment with Retin-A Micro[®].
- Minimize exposure to sunlight.
- If you have to be in the sunlight or are sensitive to sunlight, use a sunscreen with SPF (sun protection factor) of 15 or more and wear a wide-brimmed hat or other protective clothing to cover the treated areas.
- If you do get sunburned, stop using Retin-A Micro[®] until your skin has healed and is back to normal.
- Cold weather and wind may irritate skin treated with Retin-A Micro[®]. Talk to your doctor about ways to manage skin irritation.
- Avoid contact with the peels of limes.

What are the possible side effects of Retin-A Micro[®]?

Retin-A Micro[®] may cause serious side effects, including:

Skin irritation. Retin-A Micro[®] may cause skin dryness, redness, swelling, and blistering. If you develop these symptoms, your doctor may tell you to stop using Retin-A Micro[®] for a while, change your dose, decrease the number of times you apply Retin-A Micro[®], or completely stop treatment with Retin-A Micro[®]. It is not known if Retin-A Micro[®] is effective when used less than 1 time a day.

The most common side effects of Retin-A Micro® include skin burning and itching.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Retin-A Micro®. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Retin-A Micro®?

- Store Retin-A Micro® at room temperature between 68°F to 77°F (20°C to 25°C).
- Store Retin-A Micro® pump upright.

Keep Retin-A Micro® and all medicines out of the reach of children.

General information about the safe and effective use of Retin-A Micro®.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Retin-A Micro® for a condition for which it was not prescribed. Do not give Retin-A Micro® to other people, even if they have the same symptoms you have. It may harm them.

If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Retin-A Micro® that is written for health professionals.

For more information, go to www.retinamicro.com or call 1-800-321-4576.

What are the ingredients of Retin-A Micro®?

Active ingredient: tretinoin

Inactive ingredients: benzyl alcohol, butylated hydroxytoluene, carbomer 934P, carbomer 974P, cyclomethicone, dimethicone copolyol, disodium EDTA, glycerin, PPG-20 methyl glucose ether distearate, propylene glycol, purified water, sorbic acid and trolamine

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured by: Janssen Ortho LLC, Manati, Puerto Rico 00674

Distributed by: Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807

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Revised: January 2014

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 20475-S021

MEDICAL REVIEW(S)

Medical Officer's Review
NDA 20-475/ S021

SDN: 452
CDER Stamp date: 9/23/13
Sponsor: Valeant Pharm.
Drug: Retin A Micro, 0.08%
Route of Administration: Topical
Clinical Team: Woitach/ Kettl
Project Manager: Williams/ Gould
Dosage Form: Topical gel

Active Ingredient(s): (all-E)-3,7,-
Dimethyl-9-(2,6,6-trimethyl-1-
cyclohexen-1-yl)-2,4,6,8-nontetraenoic
acid
Pharmacologic Category: Tretinoin/
Retinoic acid
Proposed Indication: Acne Vulgaris
Review start date: 1/21/14
Review revised: 1/21/14
In DARRTS: 1/21/14

Regulatory Background:

Retin A (tretinoin) Micro Gel 0.1% was approved on February 7, 1997; Retin A Micro Gel 0.04% was approved on May 10, 2002. Both are indicated for the treatment of acne vulgaris, and were approved under the same NDA, 20-475. The approved labeling for NDA 20-475 includes clinical data for both the 0.1% and 0.04% gel strengths.

This supplement provides for the addition of an intermediary 0.08% strength without providing any additional clinical data beyond that of referencing the currently approved 0.1% and 0.04% gel applications. Safety and efficacy of the new 0.08% concentration would be established by referencing data from the two bracketed concentrations, without additional clinical studies.

A COMPLETE RESPONSE action was taken on the initial submission of this supplement on April 19, 2013. The original submission was previously reviewed by this reviewer (see clinical review in DARRTS dated 1/30/13 and 4/17/13). The deficiencies identified in the original submission were as follows: 1- The determination that the 0.08% gel specifications shows an (b) (4) with the 0.1% gel specifications with regards to the allowable concentration range; 2- The proposed (b) (4) has been deemed to be unacceptable; 3- The overall Recommendation from Compliance for this supplement had been changed from Acceptable (b) (4) to Pending (b) (4). With this submission (SDN#452) the sponsor is responding to the deficiencies and requests communicated in the Agency's action letter and has proposed conversion of the label to conform with the physician labeling rule.

Review:

Deficiencies:

In this submission the sponsor has addressed the Agency's recommendations for the proposed 0.08% gel and revised the drug product specification for the (b) (4). The sponsor has submitted 3-month stability data from the batches made (u) (4) to support the modification. Dr. Tang, CMC reviewer has determined that the (b) (4) in the allowable ranges and finds the batch analysis and 3-month stability data from the batches made (b) (4) were adequate. Additionally, Dr. Tang finds the post-approval stability commitment to be adequate. See Dr. Tang's CMC review for a review of each deficiency.

(b) (4) the Office of Compliance has re-issued an overall ACCEPTABLE recommendation to the drug product facility.

Reviewer comment: This reviewer concurs that each topical tretinoin product should be distinct (b) (4) as per current standards. (u) (4) Therefore, this reviewer agrees with the CMC reviewer to recommend approval.

Labeling:

The applicant's proposed labeling was revised with the input of the review team. DMEPA searched the FDA Adverse Event Reporting System database for Retin A Micro gel medication error reports and concludes that the proposed labeling is acceptable.

The approach taken was to make labeling consistent with the approved Retin A Micro gel label. Also, the 0.8% strength was inserted, where applicable. The Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) also reviewed the applicant's proposed PPI for Retin A Micro gel. Labeling is currently in negotiations with the applicant. The finalized labeling which will be attached to the action letter will serve as a record of labeling agreed to by the clinical review team. See attached proposed labeling (appendix) which incorporates clinical recommendations. Pertinent changes in the Prescribing Information (PI) which require additional comment are discussed below.

6.2 Postmarketing Experience

The following standard paragraph was added:

The following adverse reactions have been identified during post-approval use of Retin A Micro gel. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

10 OVERDOSAGE

There are no human or appropriate animal overdosage data included in currently approved labeling that would be useful to the prescriber. Therefore, this section was deleted.

12.1 Mechanism of Action

Although the exact MOA is unknown, a search of the literature is supportive of the current description in the label. However, there is not enough data on hand to change the sentence to a more definitive conclusion. The decision to maintain the paragraph in this section was based on precedent paragraphs appearing in current topical tretinoin containing products such as Retin-A, Veltin, and Ziana.

Recommendation:

From a clinical standpoint, this application is recommended for APPROVAL based on the conclusions of the CMC review that the Complete Response deficiencies have been adequately addressed, and once agreement on labeling is reached with the sponsor.

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/s/

AMY S WOITACH
01/21/2014

DAVID L KETTL
01/21/2014

Medical Officer's
Clinical Addendum
NDA 20-475/ S021

SDN/ eCTD#: 422; 19
CDER Stamp date: 10/4/12
Sponsor: Valeant Pharm.
Drug: Retin A Micro, 0.08%
Route of Administration: Topical
Clinical Team: Woitach/ Kettl
Project Manager: Williams/ Gould
Dosage Form: Topical gel

Active Ingredient(s): (all-E)-3,7,-
Dimethyl-9-(2,6,6-trimethyl-1-
cyclohexen-1-yl)-2,4,6,8-nontetraenoic
acid
Pharmacologic Category: Tretinoin/
Retinoic acid
Proposed Indication: Acne Vulgaris
Review start date: 4/16/13
Review revised: 4/17/13
In DARRTS: 4/17/13

Regulatory Background:

Retin A (tretinoin) Micro Gel 0.1% was approved on February 7, 1997; Retin A Micro Gel 0.04% was approved on May 10, 2002. Both are indicated for the treatment of acne vulgaris, and were approved under the same NDA, 20-475. The approved labeling for NDA 20-475 includes clinical data for both the 0.1% and 0.04% gel strengths.

With this submission the sponsor is proposing the addition of an intermediary 0.08% strength without providing any additional clinical data beyond that of referencing the currently approved 0.1% and 0.04% gel applications. Safety and efficacy of the new 0.08% concentration would be established by referencing data from the two bracketed concentrations, without additional clinical studies.

Review:

This submission was previously reviewed by this reviewer (see clinical review in DARRTS dated 1/30/13). Since completion of the review, three additional issues have arisen. 1- The determination that the 0.08% gel specifications shows an (b) (4) with the 0.1% gel specifications with regards to the allowable concentration range; 2- The proposed (b) (4) has been deemed to be unacceptable; 3- The overall Recommendation from Compliance for this supplement had been changed from Acceptable (b) (4) to Pending (b) (4). These three issues necessitate this clinical addendum.

(b) (4) **Allowable Range for Assay**

An examination of the proposed assay acceptance criterion for the 0.08% gel shows an (b) (4) with the 0.1% gel with regards to the allowable range:

Label Claim	(b) (4)
0.1%	(b) (4)
0.08%	
0.04%	

supplement. The Office of Compliance has given an acceptable overall recommendation on (b) (4).

Recommendation:

From a clinical standpoint, this application is recommended for COMPLETE RESPONSE based on the conclusions of the ONDQA review. The clinical team concurs that the following deficiency and remedies should be communicated to the sponsor.

DEFICIENCY

Your proposed formulation (b) (4) is not documented for Retin-A Micro gel

INFORMATION NEEDED TO RESOLVE DEFICIENCY

1. Revise the formulation composition table for the 0.08% gel by (b) (4);
2. Revise Master Batch Record for the 0.08% gel by using the revised formulation without the (b) (4) for the commercial manufacture;
3. Revise drug product specification table for the 0.08% gel by (b) (4) of label claim;
4. Provide release and 3 months of stability data from a batch of 0.08% gel that is manufactured using the revised formulation (b) (4).

Amy S. Weitach, DO, MS
Medical Officer
CDER/ OND/ ODEIII/
Division of Dermatology and Dental Products

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/s/

AMY S WOITACH
04/17/2013

DAVID L KETTL
04/17/2013

Medical Officer's Review
NDA 20-475/ S021

SDN/ eCTD#: 422; 19
CDER Stamp date: 10/4/12
Sponsor: Valeant Pharm.
Drug: Retin A Micro, 0.08%
Route of Administration: Topical
Clinical Team: Woitach/ Kettl
Project Manager: Williams/ Gould
Dosage Form: Topical gel

Active Ingredient(s): (all-E)-3,7,-
Dimethyl-9-(2,6,6-trimethyl-1-
cyclohexen-1-yl)-2,4,6,8-nontetraenoic
acid
Pharmacologic Category: Tretinoin/
Retinoic acid
Proposed Indication: Acne Vulgaris
Review start date: 1/2/13
Review revised: 1/30/13
In DARRTS: 1/30/13

Regulatory Background:

Retin A (tretinoin) Micro Gel 0.1% was approved on February 7, 1997; Retin A Micro Gel 0.04% was approved on May 10, 2002. Both are indicated for the treatment of acne vulgaris, and were approved under the same NDA, 20-475. The approved labeling for NDA 20-475 includes clinical data for both the 0.1% and 0.04% gel strengths.

With this submission the sponsor is proposing the addition of an intermediary 0.08% strength without providing any additional clinical data beyond that of referencing the currently approved 0.1% and 0.04% gel applications. Safety and efficacy of the new 0.08% concentration would be established by referencing data from the two bracketed concentrations, without additional clinical studies. Prior to this submission the sponsor submitted a type C meeting package on 4/3/12 to obtain Agency feedback for the proposed plan for the introduction of the 0.08% strength and the Division consulted the Office of Regulatory Policy. Agency discussions on the regulatory implications for approving new strengths without clinical studies are ongoing, and no formal response to the sponsor meeting questions was conveyed to the applicant prior to submission of this supplement.

Review:

The sponsor of Retin A Micro Gel proposes to introduce a new, intermediate strength 0.08% gel concentration for the treatment of acne vulgaris. No new clinical studies would be conducted. Safety and efficacy would be bracketed by the currently approved 0.1% and 0.04% concentrations. Formulation of the 0.08% gel and excipients would be unchanged beyond the change in concentration of the active ingredient.

Reviewer comment: Although there is little concern regarding safety or efficacy related to the introduction of this intermediate strength, as the product should be at least as effective as the lower approved 0.04% concentration, and at least as safe as the approved

0.1% concentration. Approval of new concentrations without clinical trial data may have unintended or unforeseen consequences from a regulatory perspective. It is this reviewer's opinion that comparative claims to either approved product could not be substantiated in the absence of clinical data, and would not allow such claims in any marketing materials.

The Division consulted the Office of Regulatory Policy (ORP) for guidance on regulatory issues raised by the applicant's proposal. The questions posed by DDDP and the responses from Rachel Turow, JD, MPH (ORP) are as follows:

DDDP Question 1a: If this strategy is acceptable, could there be an infinite number of intermediate strengths allowable between the two approved concentrations?

ORP Response: Although it is theoretically possible, it probably would not make commercial sense for the sponsor to seek a multitude of different strengths. Since the sponsor has not indicated they are inclined to submit more than one intermediate strength, we do not believe this question poses a concern at this time. However, if DDDP receives a number of sNDAs for intermediate strengths for this product, we think it would be appropriate to revisit the issue.

(b) (4)



DDDP Question 2: Does the Agency have any authority to require that a proposed intermediate strength product offer a clinically meaningful addition to acne therapy?

ORP Response: It does not appear that this would be an issue for approval of the proposed additional strength of Retin A Micro. We would need more information from the division to understand the basis for which you might want to require a showing of clinical difference. We are aware that this issue has come up in the context of OTC switches, where section 503(b) of the Act prohibits the same drug product from being approved as both Rx and OTC. In that situation, sponsors may need to show there is a clinically meaningful difference between the Rx product and the product they intend to market as OTC.

Reviewer comment: A comparison study (n=156) of the two currently approved strengths, Retin-A Micro 0.1% and 0.04%, demonstrated the overall performance of both formulations to be similar with a subset of local cutaneous adverse reactions higher in the 0.1% treatment group. As expected, the higher concentration was more irritating, although the difference was marginal, and the size of the study limits any conclusions. It would be expected that any intermediary strength would perform similarly.

It is unclear to this reviewer on what basis the Agency could require an additional clinical trial(s) to support the safety and efficacy of the newly proposed 0.08% strength. The referenced, bracketed products should provide adequate evidence of safety and efficacy.

However, the prescribing information would not provide specific information for the new concentration. It is not clear on what basis a prescriber would choose this or any intermediary strength, other than on assumptions (without substantiation) of dose-dependent relative efficacy or irritancy potential for which labeling would provide no specific data .

DDDP Question 3: How would this product be labeled if clinical studies are not conducted?

ORP Response: Because the lower and higher strengths have identical labeling, we believe this product could also use the same labeling. The sections of the labeling pertaining to clinical studies would need to be footnoted to state that the clinical studies were not performed for the .08% strength.

(b) (4)

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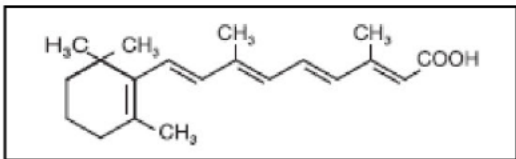
AMY S WOITACH
01/30/2013

DAVID L KETTL
01/30/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 20475-S021

CHEMISTRY REVIEW(S)

CHEMISTS REVIEW#4		1. ORGANIZATION	2. NDA NUMBER
		ONDQA Div II, Branch VI and HFD-540	20-475
3. NAME AND ADDRESS OF APPLICANT		4. COMMUNICATION, DATE	
Valeant International Bermuda		S-021; (PA) Letter Date: September 23, 2013 PDUFA Date: January 23, 2014	
5. PROPRIETARY NAME	6. NONPROPRIETARY NAME	7. AMENDMENTS, REPORT, DATE	
RETIN-A MICRO® (tretinoin gel) microsphere	All-Trans-Retinoic Acid, Retinoic Acid, Vitamin A Acid	N/A	
8. SUPPLEMENT PROVIDES FOR:			
addition of an intermediate strength of Retin-A- Micro (tretinoin gel) microsphere, 0.08%.			
9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF	
treatment of Acne Vulgaris	Rx	none	
12. DOSAGE FORM	13. POTENCY		
Gel	0.1% and 0.04%		
14. CHEMICAL NAME AND STRUCTURE			
<p>Tretinoin, USP (all-<i>E</i>)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nontetraenoic acid C₂₀H₂₈O₂, 300.44 g/mol CAS-302-79-4</p> 			
15. COMMENTS			
<p>This prior approval CMC supplement provides for the addition of an intermediate 0.08% strength without clinical data. This is the second cycle review. The first cycle review concluded with a COMPLETE RESPONSE (b) (4)</p> <p>In this submission, Valeant International Bermuda, represented by Valeant Pharmaceuticals North America LLC, accepted the Agency's recommendation of reformulating the 0.08% gel without the (b) (4). Accordingly, the drug product specification was (b) (4), and the BHT limit was adjusted to (U) (9). (U) (9) in the allowable ranges for assay described in CMC Review #3 of the first cycle review (see details on pp 4-6 of this review).</p> <p>Batch analysis and 3-month stability data from the batches made without the (b) (4) were also provided and found adequate. The Post-approval stability commitment was found adequate. The applicant's proposed 24 month expiration dating for the proposed new 0.08% strength is granted.</p>			

Labeling, in PLR format, that includes the proposed new intermediate 0.08% strength of RETIN-A MICRO® is submitted. From CMC perspective, this review made a few recommended changes for the proposed PI labeling.

(b) (4) the Office of Compliance has re-issued an overall ACCEPTABLE recommendation to the drug product facility (see Appendix for OC's recommendation summary).

16. CONCLUSION AND RECOMMENDATION

This supplement is recommended for **APPROVAL** after the applicant satisfactorily accepts all the labeling recommendations.

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Yubing Tang	See appended electronic signature sheet	January 14, 2014

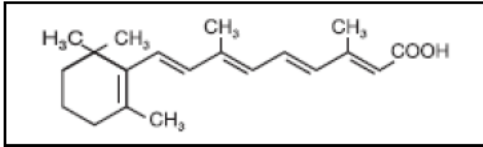
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/s/

YUBING TANG
01/14/2014

THOMAS F OLIVER
01/14/2014

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
#3	ONDQA Div II, Branch VI and HFD-540 (DDDP)	NDA 20-475
3. NAME AND ADDRESS OF APPLICANT		4. COMMUNICATION, DATE
Valeant Pharmaceuticals North America LLC 700 Route 202/206 North Bridgewater, NJ 08807		S-021 (PA CMC) Receipt Date: 10/4/12 User Fee Date: 2/4/13
5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
RETIN-A MICRO® (tretinoin gel) Microsphere	Tretinoin	Amendment dated Dec. 4, 2012 Amendment dated Jan. 4, 2013 Amendment dated March 11, 2013
8. COMMUNICATION PROVIDES FOR:		
The addition of an intermediate strength of 0.08%		
9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Indicated for topical application in the treatment of <i>acne vulgaris</i>	Rx only	
12. DOSAGE FORM	13. POTENCY	
Topical gel	0.1% and 0.04%	
14. CHEMICAL NAME AND STRUCTURE		
Tretinoin, USP (all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nontetraenoic acid C ₂₀ H ₂₈ O ₂ , 300.44 g/mol CAS-302-79-4		
		
15. COMMENTS		
This prior approval CMC supplement provides for the addition of an intermediate strength of 0.08% without clinical data. CMC Review #1 was signed off in DARTS on January 30, 2013 pending an overall recommendation from the Office of Compliance. CMC review #2 was signed off in DARRTS on Feb. 4, 2013 with a recommendation of Approval. As per review #3, CMC is recommending a Complete Response due to an unacceptable (b) (4). The Office of Compliance has given an acceptable recommendation on (b) (4).		
16. CONCLUSION AND RECOMMENDATION		
A Complete Response action is recommended for this supplement from the perspective of CMC.		
17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Shulin Ding	See appended electronic signature sheet	April 15, 2013
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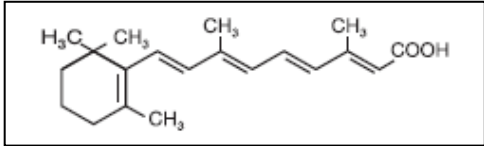
/s/

SHULIN DING

04/15/2013

THOMAS F OLIVER

04/16/2013

CHEMISTS REVIEW #2	1. ORGANIZATION ONDQA Div II, Branch VI and HFD-540 (DDDP)	2. NDA NUMBER NDA 20-475
3. NAME AND ADDRESS OF APPLICANT Valeant Pharmaceuticals North America LLC 700 Route 202/206 North Bridgewater, NJ 08807		4. COMMUNICATION, DATE S-021 (PA CMC) Receipt Date: 10/4/12 User Fee Date: 2/4/13
5. PROPRIETARY NAME RETIN-A MICRO® (tretinoin gel) Microsphere	6. NAME OF THE DRUG Tretinoin	7. AMENDMENTS, REPORT, DATE Amendment dated Dec. 4, 2012 Amendment dated Jan. 4, 2013
8. COMMUNICATION PROVIDES FOR:		
The addition of an intermediate strength of 0.08%		
9. PHARMACOLOGICAL CATEGORY Indicated for topical application in the treatment of <i>acne vulgaris</i>	10. HOW DISPENSED Rx only	11. RELATED IND, NDA, DMF
12. DOSAGE FORM Topical gel	13. POTENCY 0.1% and 0.04%	
14. CHEMICAL NAME AND STRUCTURE		
<p>Tretinoin, USP (all-<i>E</i>)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nontetraenoic acid C₂₀H₂₈O₂, 300.44 g/mol CAS-302-79-4</p> 		
15. COMMENTS		
<p>This prior approval CMC supplement provides for the addition of an intermediate strength of 0.08% without clinical data. CMC review #1 was signed off in DARRTS on Jan. 30, 2013 with pending cGMP compliance evaluation as the only remaining issue. All other CMC issues had been resolved.</p> <p>The Overall Compliance Recommendation was issued on (b) (4). The recommendation is Acceptable.</p>		
16. CONCLUSION AND RECOMMENDATION		
<p>All CMC issues have been resolved. The Overall Compliance Recommendation is Acceptable. Approval action is, therefore, recommended for this supplement. The Establishment Evaluation Summary report is attached to this review.</p>		
17. NAME Shulin Ding	18. REVIEWERS SIGNATURE See appended electronic signature sheet	19. DATE COMPLETED Jan. 30, 2013
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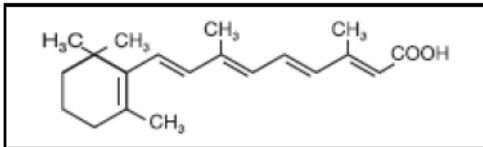
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/s/

SHULIN DING
02/04/2013

THOMAS F OLIVER
02/04/2013

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
#1	ONDQA Div II, Branch VI and HFD-540 (DDDP)	NDA 20-475
3. NAME AND ADDRESS OF APPLICANT		4. COMMUNICATION, DATE
Valeant Pharmaceuticals North America LLC 700 Route 202/206 North Bridgewater, NJ 08807		S-021 (PA CMC) Receipt Date: 10/4/12 User Fee Date: 2/4/13
5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
RETIN-A MICRO® (tretinoin gel) Microsphere	Tretinoin	Amendment dated Dec. 4, 2012 Amendment dated Jan. 4, 2013
8. COMMUNICATION PROVIDES FOR:		
The addition of an intermediate strength of 0.08%		
9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Indicated for topical application in the treatment of <i>acne vulgaris</i>	Rx only	
12. DOSAGE FORM	13. POTENCY	
Topical gel	0.1% and 0.04%	
14. CHEMICAL NAME AND STRUCTURE		
<p>Tretinoin, USP (all-<i>E</i>)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nontetraenoic acid C₂₀H₂₈O₂, 300.44 g/mol CAS-302-79-4</p> 		
15. COMMENTS		
<p>This prior approval CMC supplement provides for the addition of an intermediate strength of 0.08% without clinical data. For this new strength, the proposed trade size and packaging configuration is 50 g pump, and the physician sample is 2 g tube. The proposed drug product manufacturing site is Ortho Pharmaceutical at Manati, Puerto Rico. (b) (4)</p> <p>The CMC information provided to support this new strength includes formulation composition, establishment information, manufacturing process description, Executed Batch Records, drug product specification, container/closure system description, and 3 months of long term and accelerated stability data from one production scale batch for each packaging configuration. (b) (4)</p> <p>The proposed 0.08% gel is essentially the same as the approved 0.04% gel in formulation composition, establishments, manufacturing process, specification, and container/closure system. The 3 months long term and accelerated stability data show that the 0.08% gel is stable and remains well within the specification limits that were established through 0.04% and 0.1%. (b) (4)</p>		

(b) (4)		
<p>The proposed labels, package insert, and Patient Information leaflet for the 0.08% gel are essentially the same as the approved ones for 0.04% and 0.1%. The three strengths will share one Package Insert and Patient Information Leaflet. The carton/container labels are also identical except the difference in strength.</p> <p>GMP compliance is still being evaluated by Office of Compliance. The Overall Compliance Recommendation is pending.</p>		
16. CONCLUSION AND RECOMMENDATION		
<p>All CMC issues have been resolved except the pending inspection of (b) (4)</p> <p>(b) (4)</p> <p>CMC recommends no action be taken on this supplement until Office of Compliance issues Overall Compliance Recommendation.</p>		
17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Shulin Ding	See appended electronic signature sheet	Jan. 30, 2013
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/s/

SHULIN DING
01/30/2013

THOMAS F OLIVER
01/30/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 20475-S021

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA	020475 (S-021)	Submission Letter Date(s)	September 23, 2013
Product Name	Retin-A-Micro Microsphere (tretinoin gel), 0.04%, 0.08% and 0.1%		
Primary Reviewer	Chinmay Shukla, Ph.D.		
Team Leader	Doanh Tran, Ph.D.		
OCP Division	Division of Clinical Pharmacology 3		
OND Division	Division of Dermatology and Dental Products		
Sponsor	Valeant Pharmaceuticals North America LLC		
Submission Type	Resubmission after Complete Response Action and Physician Labeling Rule (PLR) Conversion		
Approved Indication	Retin-A-Micro Microsphere is indicated for the topical treatment of acne vulgaris.		

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1.	Executive Summary	*	*	*	*	*	*	*	*	1
1.1	Recommendations	*	*	*	*	*	*	*	*	1
1.2	Phase IV Commitments		*	*	*	*	*	*	*	1
1.3	Summary of Clinical Pharmacology and Biopharmaceutics Findings								*	1
2.	Question-Based Review		*	*	*	*	*	*	*	2
3.	Detailed Labeling Recommendations			*	*	*	*	*	*	2

1. Executive Summary: The original NDA was for the 0.1% strength and was approved on February 07, 1997 for the treatment of acne vulgaris. Subsequently, the 0.04% strength was approved on May 10, 2002 for the same indication. On October 4, 2012 the Sponsor submitted a supplement (S-021) to their approved NDA to include an intermediate strength of 0.08%. This application received a complete response on 04/19/2013 (see communication in DARRTS) with deficiencies identified by CMC. This application is a resubmission after complete response and the Sponsor has also submitted labeling in the PLR format.

1.1 Recommendations:

On review of the Sponsor's proposed changes to the format and the text of the PLR formatted label, the Office of Clinical Pharmacology has made recommended changes as specified in Section 3 of this review.

1.2 Phase IV Commitments:

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings:

With the original submission of this supplemental NDA application, Clinical Pharmacology determined that a pharmacokinetic (PK) trial with the intermediate strength 0.08% will not be needed (see Clinical Pharmacology review in DARRTS dated 01/16/2013). This review will focus on PLR conversion of the proposed labeling (label submitted on 09/23/2013).

2. Question Based Review:

Not Applicable.

3. Detailed Labeling Recommendations:

This section captures recommended revisions to the sponsor proposed label submitted on 09/23/2013, where Clinical Pharmacology provided input and recommendations. Deletions are indicated as “~~strikethroughs~~” and additions are indicated as “**bold underlined**”.

8.4 Pediatric Use

Safety and effectiveness in children below the age of 12 have not been established.

8.5 Geriatric Use

Safety and effectiveness in a geriatric population have not been established. Clinical **trials** studies of Retin-A Micro[®] (~~tretinoin gel~~) ~~microsphere 0.1% and 0.04%~~ did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

~~Tretinoin is a retinoid metabolite of Vitamin A that binds to intracellular receptors in the cytosol and nucleus, but cutaneous levels of tretinoin in excess of physiologic concentrations occur following application of a tretinoin-containing topical drug product.~~

~~Although tretinoin activates three members of the retinoic acid (RAR) nuclear receptors (RAR α , RAR β and RAR γ) which may act to modify gene expression, subsequent protein synthesis, and epithelial cell growth and differentiation, it has not been established whether the clinical effects of tretinoin are mediated through activation of retinoic acid receptors, other mechanisms, or both.~~

(b) (4)

Although tretinoin activates three members of the retinoic acid (RAR) nuclear receptors (RAR α , RAR β , and RAR γ) which may act to modify gene expression, subsequent protein synthesis, and epithelial cell growth and differentiation, it has not been established whether the clinical effects of tretinoin are mediated through activation of retinoic acid receptors and/or other mechanisms.

Although the exact mode of action of tretinoin is unknown, current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells with decreased microcomedone formation. Additionally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells causing extrusion of the comedones.

12.3 Pharmacokinetics

Tretinoin is a metabolite of Vitamin A metabolism in man. Percutaneous absorption, as determined by the cumulative excretion of radiolabeled drug into urine and feces, was assessed in 44 healthy men and women after single and repeated daily applications of 500 mg of a 0.1% tretinoin gel formulation. Estimates of *in vivo* bioavailability, mean (SD)%, following both single and multiple daily applications, for a period of 28 days with the 0.1% gel, were 0.82 (0.11)% and 1.41 (0.54)%, respectively. The plasma concentrations of tretinoin and its metabolites, 13-*cis*-retinoic acid, all-*trans*-4-oxo-retinoic acid, and 13-*cis*-4-oxo-retinoic acid, generally ranged from 1 to 3 ng/mL and were essentially unaltered after either single or multiple daily applications of Retin-A Micro (tretinoin gel) microsphere, 0.1%, relative to baseline levels. Clinical pharmacokinetic studies have not been performed with Retin-A Micro (tretinoin gel) microsphere, 0.04% and 0.08%.

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/s/

CHINMAY SHUKLA
11/22/2013

DOANH C TRAN
11/22/2013

CLINICAL PHARMACOLOGY REVIEW

NDA #: 020475/S-021
SD#: 422
Stamp Date: 10/04/2012
Product: Retin-A Micro[®] (tretinoin gel) Microsphere, 0.08%
Dosage Form: Gel
Sponsor: Valeant Pharmaceuticals North America LLC
Indication: Topical treatment of acne vulgaris
Type of Submission: Prior approval supplement
Primary Reviewer: Chinmay Shukla, Ph.D.
Team Leader: Doanh Tran, Ph.D.

Background: The original NDA was for the 0.1% strength and was approved on February 07, 1997 for the treatment of acne vulgaris. Subsequently, the 0.04% strength was approved on May 10, 2002 for the same indication. There were minor formulation changes between the 0.1% strength and the 0.04% strength (See Table 1), namely change in the (b) (4) (Carbomer 934P vs. Carbomer 974P) (b) (4) Sorbic acid (b) (4). No PK assessments were required for approval of the 0.04% strength.

Current submission: With this submission the Sponsor has proposed to introduce an intermediate strength of 0.08% for the same indication. Table 1 shows the composition comparison for the 3 strengths. (b) (4)

(see Table 1).

Table 1: Retin-A MICRO (tretinoin gel) microsphere – Composition Comparison
(Source: page 7 of meeting package for NDA 20475 submitted on 4/4/2012)

Ingredients	Grade	w/w %		
		0.1% LC*	0.08% LC*	0.04% LC*
Tretinoin (b) (4) in Microsponge® Polymer	n/a	(b) (4)		
Propylene Glycol	USP			
Carbomer 934P	NF			
Carbomer 974P	NF			
Glycerin	USP			
Butylated Hydroxytoluene (BHT)	NF			
Sorbic Acid	NF			
Edetate Disodium	USP			
PPG-20 Methyl Glucose Ether Distearate (Glucam P-20 Distearate)	n/a			
Cyclomethicone and Dimethicone Copolyol	n/a			
(b) (4)				
Benzyl Alcohol	NF			
Trolamine	NF			
Purified Water	USP			

* Label Claim

Proposed clinical trials: The Sponsor proposed that no clinical trials are needed to support this supplement to add the 0.08% strength.

Reviewer comments: The Sponsor has assessed systemic pharmacokinetics (PK) of the 0.1% strength and no PK assessment was conducted with the 0.04% strength. The PK trial with the 0.1% strength was not under maximal use conditions as it was conducted in healthy subjects following drug application to the face. The results indicated that the plasma tretinoin concentrations following single and multiple administrations were low and did not alter the endogenous (b) (4) (see Clinical Pharmacology review dated 12/05/1995 by Dr. Funmilayo O. Ajayi).

Furthermore, this reviewer checked via e-mail communication with the reviewing Medical Officer Dr. Amy Woitach regarding any systemic safety concerns reported with the 0.1% strength. On 01/11/2013, Dr. Woitach responded that the reported safety issues were mostly local reactions.

Because minimal systemic concentrations were observed following application of 0.1% strength and there are no systemic safety concerns raised with its clinical use since 1997, a maximal use PK trial will not be requested for the lower 0.08% strength.

Labeling: Retin-A-Micro[®] Microsphere label is not in the PLR format. The following changes are recommended in the Sponsor's proposed labeling. The **bold and underlined** text indicates insertion recommended by the reviewer and the ~~strikethrough~~ text indicates recommended deletion.

CLINICAL PHARMACOLOGY

Tretinoin is a retinoid metabolite of Vitamin A that binds to intracellular receptors in the cytosol and nucleus, but cutaneous levels of tretinoin in excess of physiologic concentrations occur following application of a tretinoin-containing topical drug product. Although tretinoin activates three members of the retinoid acid (RAR) nuclear receptors (RAR α , RAR β , and RAR γ) which may act to modify gene expression, subsequent protein synthesis, and epithelial cell growth and differentiation, it has not been established whether the clinical effects of tretinoin are mediated through activation of retinoic acid receptors, other mechanisms, or both.

Mode of Action

Although the exact mode of action of tretinoin is unknown, current evidence suggests that the effectiveness of tretinoin in acne is due primarily to its ability to modify abnormal follicular keratinization. Comedones form in follicles with an excess of keratinized epithelial cells. Tretinoin promotes detachment of cornified cells and the enhanced shedding of corneocytes from the follicle. By increasing the mitotic activity of follicular epithelia, tretinoin also increases the turnover rate of thin, loosely-adherent corneocytes. Through these actions, the comedo contents are extruded and the formation of the microcomedo, the precursor lesion of acne vulgaris, is reduced.

Additionally, tretinoin acts by modulating the proliferation and differentiation of epidermal cells. These effects are mediated by tretinoin's interaction with a family of nuclear retinoic receptors. Activation of these nuclear receptors causes changes in gene expression. The exact mechanisms whereby tretinoin-induced changes in gene expression regulate skin function are not understood.

Pharmacokinetics

Tretinoin is a metabolite of Vitamin A metabolism in man.

Percutaneous absorption, as determined by the cumulative excretion of radiolabeled drug into urine and feces, was assessed in 44 healthy men and women. Estimates of *in vivo* bioavailability, mean (SD)%, following both single and multiple daily applications, for a period of 28 days with the 0.1% gel, were 0.82 (0.11)% and 1.41 (0.54)%, respectively. The plasma concentrations of tretinoin and its metabolites, 13-*cis*-retinoic acid, all-*trans*-4-oxo-retinoic acid, and 13-*cis*-4-oxo-retinoic acid, generally ranged from 1 to 3 ng/mL and were essentially unaltered after either single or multiple daily applications of Retin-A Micro[®] (tretinoin gel) microsphere, 0.1%, relative to baseline levels. Clinical

pharmacokinetic studies have not been performed with Retin-A Micro® (tretinoin gel) microsphere, 0.04% **and 0.08%**.

Recommendation: From a Clinical Pharmacology standpoint, this application is acceptable provided the labeling comments are adequately addressed by the Sponsor.

Post-Marketing Requirements/Commitments: None

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/s/

CHINMAY SHUKLA
01/16/2013

DOANH C TRAN
01/16/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 20475-S021

OTHER REVIEW(S)

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title¹	Retin-A Micro (tretinoin) Gel microsphere 0.1%, 0.08% and 0.04% for topical use
Applicant	Valeant International (b) (4) SRL
Application/Supplement Number	NDA 20475, supplement 021
Type of Application	PLR Conversion
Indication(s)	For topical treatment of acne vulgaris
Office/Division	ODE III/DDDP
Division Project Manager	Dawn Williams
Date FDA Received Application	September 23, 2013
Goal Date	January 23, 2014
Date PI Received by SEALD	January 23, 2014
SEALD Review Date	January 23, 2014
SEALD Labeling Reviewer	Jeanne M. Delasko
Acting SEALD Division Director	Sandra Kweder

¹ Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**not a deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *There isn't any white space before each major HL heading.*

- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Selected Requirements of Prescribing Information

Comment: For Dosage Forms and Strengths, the reference "(3)" is missing at the end of the information.

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: The name of the drug product (RETIN-A MICRO) should appear in UPPER CASE letters. Only the name of the drug product should be included in this statement, and not the nonproprietary name, dosage form, and strengths (i.e., 0.1%, 0.08%, and 0.04%).

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Selected Requirements of Prescribing Information

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

N/A

Selected Requirements of Prescribing Information

20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- NO** 25. The TOC should be in a two-column format.
***Comment:** The TOC is in one column. The TOC should be in a two-column format. Also, there is extra spacing between section/subsections. Please delete the extra spacing.*
- YES** 26. The following heading must appear at the beginning of the TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- NO** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
***Comment:** Subsection headings 14.1 and 14.2 in the TOC do not exactly match the subsection headings 14.1 and 14.2 in the FPI.*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

NO

32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: In the FPI, there is a "period" after section numbers 1, 2, 3, 4, 5, and 6. There should be no periods after the section numbers. See above.

YES

33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "[see Warnings and Precautions (5.2)]" or "[see Warnings and Precautions (5.2)]".

Selected Requirements of Prescribing Information

Comment:

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES

Selected Requirements of Prescribing Information

41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

NO

42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment: *The FDA-approved patient labeling (patient information) does not appear at the end of the PI. All FDA-approved patient labeling must appear at the end of the PI upon approval.*

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

JEANNE M DELASKO
01/23/2014

ERIC R BRODSKY
01/23/2014

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Division Director.

From: Williams, Dawn
Sent: Thursday, January 16, 2014 6:46 AM
To: 'Humphrey, Sean'
Cc: Gould, Barbara
Subject: FDA Labeling Proposal sNDA 020475/021 Retin-A Micro (tretinoin) gel microsphere, 0.04%, 0.08% and 0.1%

Good Morning Mr. Humphrey-

Attached is the FDA labeling proposal for sNDA 020475/021 Retin-A Micro (tretinoin) gel microsphere, 0.04%, 0.08% and 0.1%. Note that we have revised the name presentation. Please ensure that this change is reflected throughout the FPI, PPI and revise the carton and container labels accordingly. Provide your response to our labeling proposal by COB Monday, January 20, 2013. Thank you!

CDR Dawn Williams, BSN, USPHS
Division of Dermatology and Dental Products, Room 5168
Office of Drug Evaluation III
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
Tel. (301)796-5376
Fax (301)796-9894

28 page(s) of Draft labeling has been withheld in full as b4 (CCI/TS) immediately following this page

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/s/

DAWN WILLIAMS
01/16/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: December 13, 2013

To: Dawn Williams
Regulatory Health Project Manager,
Division of Dermatology and Dental Products (DDDP)

From: Celestina Arowosegbe, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 20475
Retin-A Micro® (tretinoin gel) microsphere 0.1%, 0.08% and 0.04%
For topical use
Package Insert (PI)

As requested in your consult dated November 20, 2013, OPDP has reviewed the draft PI for Retin-A Micro® (tretinoin gel) microsphere 0.1%, 0.08% and 0.04% for topical use. OPDP's comments are based on the proposed substantially complete, marked-up version of the PI received on November 22, 2013. OPDP's comments on the PI are provided directly on the attached copy of the labeling.

Please note that comments on the proposed patient labeling will be provided under a separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

If you have any questions about OPDP's comments, please contact Celestina Arowosegbe at 301-796-4661 or at Celestina.Arowosegbe@fda.hhs.gov

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/s/

CELESTINA O AROWOSEGBE
12/13/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: December 12, 2013

To: Susan Walker, MD
Director
Division of Dermatology and Dental Products (DDDP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nathan Caulk, MS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Celestina Arowosegbe, Pharm.D
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): Retin-A Micro (tretinoin gel)

Dosage Form and Route: microsphere 0.1%, 0.08% and 0.04% for topical use

Application Type/Number: NDA 20475

Supplement Number: S-021

Applicant: Valeant Pharmaceuticals North America LLC

1 INTRODUCTION

On September 23, 2013, Valeant Pharmaceuticals North America LLC submitted for the Agency's review Prior Approval Supplemental New Drug Application (NDA) 20475/S-021 for Retin-A Micro (tretinoin gel) microsphere. On October 3, 2012 Valeant submitted S-021 for the proposed introduction of an intermediate 0.08% product strength. On April 19, 2013, Valeant received a Complete Response action letter due to CMC deficiencies for S-021. On September 23, 2013, the Applicant resubmitted NDA 20475/S-021 in response to the Complete Response letter with updates to the Prescribing Information (PI). In addition, the Applicant submitted revised labeling to convert to the Physician Labeling Rule (PLR) format. Retin-A Micro (tretinoin gel) microsphere was originally approved on February 7, 1997 and is indicated for topical application in the treatment of acne vulgaris.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dental Products (DDDP) on November 22, 2013, for DMPP and OPDP to review the Applicant's proposed Package Insert (PPI) for Retin-A Micro (tretinoin gel) microsphere.

2 MATERIAL REVIEWED

- Draft Retin-A Micro (tretinoin gel) microsphere PPI received on September 23, 2013, and received by DMPP and OPDP on November 22, 2013.

Draft Retin-A Micro (tretinoin gel) microsphere Prescribing Information (PI) received on September 23, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 22, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

- rearranged information due to conversion of the PI to Physicians Labeling Rule (PLR) format
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

NATHAN P CAULK
12/12/2013

CELESTINA O AROWOSEGBE
12/12/2013

BARBARA A FULLER
12/13/2013

LASHAWN M GRIFFITHS
12/13/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling, and Packaging Review

Date: December 9, 2013

Reviewer: Carlos M Mena-Grillasca, RPh, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, MS, PharmD
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Retin-A Micro (Tretinoin Gel) Microsphere, 0.08%

Application Type/Number: NDA 020475

Submission Number: S-021

Applicant/sponsor: Valeant International

OSE RCM #: 2013-2677

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review responds to a consult from the Division of Dermatology and Dental Products to evaluate the proposed full prescribing information, container labels and carton labeling for Retin-A Micro NDA 020475/S-021 for areas of vulnerability that could lead to medication errors. The applicant is proposing to add 0.08% strength to the current product line and the conversion of the Full Prescribing Information (FPI) to the Physician Labeling Rule (PLR) format.

1.1 REGULATORY HISTORY

Retin-A Micro (Tretinoin gel) Microsphere, 0.04% and 0.1% was approved on February 7, 1997. The original submission for Supplement S-021 received a Complete Response (CR) letter on April 14, 2013. The applicant responded to the CR letter on September 23, 2013 and Supplement S-021 currently under a second review cycle.

1.2 PRODUCT INFORMATION

The following product information is provided in the September 23, 2013 submission.

- Active Ingredient: Tretinoin
- Indication of Use: Treatment of acne vulgaris.
- Route of Administration: Topical
- Dosage Form: Gel, microspheres
- Strength: 0.04%, 0.08%, and 0.1%
- Dose and Frequency: Apply once daily, in the evening, to the skin where the acne lesions appear.
- How Supplied: 0.04% and 0.1% in 2 gram sample tubes, 20 g and 45 g tubes, and 50 g pump; 0.08% in 2 g sample tubes and 50 g pump
- Storage: 20 °-25 °C (68 °-77 °F); excursions permitted from 15 °-30 °C (59 °-86 °F). Store pump upright.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Retin-A Micro medication error reports. We also reviewed the Retin-A Micro container labels, carton and Full Prescribing Information labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1.

Table 1: FAERS Search Strategy	
Date	December 5, 2013. Date limitation from January 9, 2013 (last FAERS search for OSE review 2012-2895, dated January 18, 2013).
Drug Names	Trade Name: Retin-A Micro
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database search did not identify any cases. We note that our previous FAERS search for Retin-A Micro performed on January 9, 2013 for OSE review 2012-2895 retrieved 2 cases that were not relevant to product labeling

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Revised container labels and carton labeling submitted September 23, 2013 (Appendix B)
- Proposed container labels and carton labeling submitted October 3, 2012 during the first review cycle (Appendix C)
- Currently marketed container labels and carton labeling from Annual Report submitted June 20, 2012 (Appendix D)
- Proposed Full Prescribing Information submitted September 23, 2013 (no image)
- OSE Review 2012-2895, dated January 18, 2013. DMEPA's recommendations to the container labels and carton labeling have been implemented.

3 MEDICATION ERROR RISK ASSESSMENT

The Applicant is proposing the addition of an intermediate strength of 0.08% for the same indication (i.e. acne vulgaris) and with the same dosing (i.e. application of a thin layer to the affected area once daily) to the currently marketed product line (i.e. 0.04% and 0.1% strengths). At this time, the Applicant is proposing to market a 50 gram pump package size; whereas the currently marketed strengths are available in 20 g and 45 g tubes, and 50 g pump package sizes. We consider the 50 g pump package size adequate as it keeps in line with the currently available packaging configuration. Our post marketing data did not retrieve any cases of medication errors with the 50 g pump currently marketed. In addition, we find the proposed color scheme of the labels and labeling for the new strength appears to be adequately differentiated from those of the currently marketed strengths. .

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

We reviewed the container labels and carton labeling and noted that the presentation of the established name [i.e. '(tretinoin gel) microsphere'] does not conform to current standards. We contacted CMC regarding this discrepancy during the first review cycle and they concurred with DMEPA; however, they recommended leaving it as is. DMEPA defers to CMC on this matter and will not make any recommendations to the Applicant.

4 CONCLUSIONS

DMEPA concludes that the proposed Full Prescribing Information, container labels and carton labeling are acceptable.

If you have further questions or need clarifications, please contact Janet Anderson, project manager, at 301-796-0675.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

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/s/

CARLOS M MENA-GRILLASCA
12/09/2013

LUBNA A MERCHANT
12/09/2013

Memorandum

Date: October 29, 2013

To: NDA 20475/S0021

Sponsor: Valeant International (b) (4) SRL

Trade name: Retin-A MICRO® (tretinoin gel) microsphere, 0.1%, 0.08% and 0.04%

Generic name: tretinoin gel 0.1%, 0.08%, and 0.04%

Indication: acne vulgaris

From: Jill C Merrill, PhD, reviewing toxicologist, DDDP

Through: Barbara Hill, PhD, Pharmacology/Toxicology Supervisor, DDDP

Re: PLR labeling

Background: The sponsor of Retin-A MICRO® microsphere submitted a labeling supplement (date: September 23, 2013; SDN 452) to the above referenced NDA that provides labeling for a new concentration, 0.08%, bracketed between the two previously approved tretinoin concentrations (*i.e.*, 0.1% and 0.04%). In addition, the entire label has been revised consistent with the physician's-labeling-rule (PLR) format.

Discussion: The portions of the PLR-formatted label that are supported by Pharmacology/Toxicology or pertain to nonclinical studies (sections 1, 8.1, 12.1, 12.2, and 13.1) contain the same information as in related sections of the previously approved (May 10, 2002) version of the drug label. However, in accordance with the 21st Century Review process, these sections have been modified to be consistent with respect to both format and terminology to comparable sections in different labels from drugs within the same established pharmacologic class (EPC). If the sponsor has not designated the EPC in the Indications and Usage statement (Section 1), Pharmacology/Toxicology proposes a scientifically valid and clinically useful PCE to be added to Section 1. In addition, the Agency's Maternal Health Team has requested that reference to the lack of studies in pregnant women and the risk/benefit statement concerning use of the drug during pregnancy be positioned at the top of Section 8.1. An average weight of 60 kg has been used to develop multiples of human exposure based on body surface area comparison. Accordingly Sections 1, 8.1, 12.1, 12.2, and 13.1 have been revised. It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the Retin-A Micro (tretinoin gel) microsphere label.

11 page(s) of Draft labeling has been withheld in full as b4 (CCI/TS) immediately following this page

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/s/

JILL C MERRILL
11/18/2013

BARBARA A HILL
11/18/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 20475-S021

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<h2 style="margin: 0;">REQUEST FOR CONSULTATION</h2>		
TO (Division/Office): Mail: OSE/DMEPA		FROM: Amy Weitach, Clinical Reviewer, DDDP; 6-4078 David Kettl, Clinical Team Leader, DDDP; 6-2105		
DATE November 22, 2013	IND NO.	NDA NO. 020475/021	TYPE OF DOCUMENT PLR Conversion	DATE OF DOCUMENT September 23, 2013
NAME OF DRUG Retin-A MICRO (tretinoin gel) Microsphere, 0.1%, 0.08% and 0.04%		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Acne Agent (4029041)	DESIRED COMPLETION DATE December 13, 2013
NAME OF FIRM: Valeant International (b) (4) SRL				
REASON FOR REQUEST				
I. GENERAL				
<div style="display: flex; justify-content: space-between;"> <div style="width: 30%;"> <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 </div> <div style="width: 30%;"> <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> CONTROL SUPPLEMENT </div> <div style="width: 30%;"> <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): </div> </div>				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH <input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		STATISTICAL APPLICATION BRANCH <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 IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV 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"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: <p>This supplement was originally a manufacturing supplement that provided for an intermediary strength of 0.08% (approved strengths are 0.1% and 0.04%) without clinical data to support. The safety and efficacy data have been extrapolated from the approved strengths (0.1% and 0.04%). A Complete Response was taken on this supplement on April 19, 2013. The sponsor submitted their complete response which included the label in PLR format. We are consulting DMEPA for recommendations related to the PLR conversion of the label. Thank you!</p> <p>Link to substantially complete label: http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofDermatologyandDentalProducts/0_3e95c </p> <p>Link to EDR submission: \\CDSESUB1\evsprod\NDA020475\020475.enx </p>				

SIGNATURE OF REQUESTER Dawn Williams, RPM	METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/s/

DAWN WILLIAMS
11/22/2013

From: Williams, Dawn
Sent: Tuesday, January 29, 2013 9:28 AM
To: Abelardo, Charity
Subject: Carton and Container Label Proposal sNDA 020475/021 Retin-A MICRO (tretinoin gel) Microsphere, 0.1% and 0.04%

Good Morning Charity-

The FDA has the following labeling proposal for your carton and container labels for the 0.08% proposed intermediary strength. Please let me know if this proposal is acceptable by tomorrow at noon, January 31, 2013. Thank you!

A. Proposed Container Label and Carton Labeling (50 g pump)

1. Delete the route of administration and Rx only statements from the side panel. As currently presented these statements are duplicative with statements on the principal display panel and the statements crowd information present on the side panel. The additional space gained from the deletion of these statements will allow for the implementation of the following recommendation.

2. Increase the prominence of the storage statements (i.e. 'Store at . . .' and 'Store pump upright') by providing white space before and after the statements and also by bolding the statements.

B. Proposed Container Label (50 g pump) and Carton Labeling (2 g tubes - 24 packer and 50 g pump)

Increase the prominence of the strength statement '0.08%' by relocating to a separate line immediately below the established name and dosage form statements. Also, increase the font size, and possibly consider other methods to increase the prominence of the strength to help further differentiate this strength and product from the other two market product strengths.

C. Proposed Carton Labeling (50 g pump)

Decrease the size of the Valeant name and logo on the principal display panel (PDP) or relocate to the side panel. As currently presented it is more prominent than more relevant information on the PDP such as the established name, dosage form and strength.

CDR Dawn Williams, BSN, USPHS
Division of Dermatology and Dental Products, Room 5164
Office of Drug Evaluation III
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
Tel. (301)796-5376
Fax (301)796-9894

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/s/

DAWN WILLIAMS
01/29/2013

Initial Quality Assessment and Triage

ONDQA Branch VI

OND Division: HFD-540 (DDDP)

NDA: 20-475

Supplement: S-021

DARRTS Document Number: SDN422 (amended via SDN426)

Applicant: Valeant

Letter Date: 10-03-2012

Stamp Date: 10-04-2012

ONDQA Receipt Date: delivered to CMC lead on 12-05-2012 (*9 weeks late!*)

ONDQA CMC Lead triage date: 12-06-2012

Application Type: electronic

Proprietary Name: RETIN-A MICRO® (tretinoin gel) microsphere, 0.08%

Established Name: tretinoin gel

Dosage Form: gel

Route of Administration: topical

Submission Type: Prior-approval supplement (PAS)

Recommended submission type: PAS*

- this application was submitted as PAS, but might be managed by OND. There is a clinical overview in QOS section 2.5.

***Note:** the ONDQA Pm contacted OND regarding management of this supplement. According to an E-mail from ONDQA PM, OND will allow ONDQA to manage the supplement because the proposed new strength is intermediate.*

The application provides a NEW STRENGTH for the drug product, 0.08%. Currently approved strengths are 0.1% and 0.04%.

Labeling is provided, covering the new strength.

The existing facility will have to be entered into EES to correlate the new strength with the existing facility.

This electronic PAS was submitted on 10-03-2012 and provides a new strength for the NDA 20-475 product, Retin-A-Micro® (tretinoin gel) microsphere. The existing (approved) strengths are 0.1% and 0.04%; this supplement provides an intermediate strength, 0.08%. The application includes a clinical overview (Module 2.5) and labeling, which will have to be reviewed by OND (and DMEPA).

The application was submitted on 10-03-2012, but the OND PM did not give the application to the CMC lead until 12-05-2012.

The ONDQA PM was requested to ask OND whether they will manage this application (request by E-Mail on 12-06-2012). OND does not have a problem with ONDQA managing the supplement because the new proposed strength is intermediate (between the lowest and highest approved strengths for NDA 20-475).

A meeting was requested by Valeant regarding the submission of an application for the new strength (see Module 1.6); OND PM should be asked about the outcome of this meeting.

The composition of the 0.08% strength gel is provided in Module 3.2.P.1, and is stated as being based on that for the 0.04% strength (qualitatively identical to that for the 0.04% strength except for the increased concentration of active ingredient and corresponding adjustment (down) of water content).

The original submission (10-03-2012) contained 1 month of stability data on one split batch (2GM7670-PE, filled into 50-gram pumps and 2-gram tubes). There is a stability submission in DARRTS (12-04-2012) that probably contains updated stability data.

The applicant provided updated manufacturing process sections corresponding to the manufacture of the 0.08% strength gel.

DMEPA will have to review the new labeling.

An EES entry will have to be made to cover the 0.08% strength at the existing facility.

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/s/

DAVID B LEWIS

01/04/2013

IQA, PAS, managed by ONDQA per OND

THOMAS F OLIVER

01/14/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Office/Division): OSE			FROM (Name, Office/Division, and Phone Number of Requestor): Cathy Tran-Zwanetz, ONDQA, 301-796-3877	
DATE 12-5-2012	IND NO.	NDA NO. 20475	TYPE OF DOCUMENT s-021	DATE OF DOCUMENT 10-3-2012
NAME OF DRUG Retin-A Micro		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE January 18, 2013
NAME OF FIRM: Valeant				
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 checked="" 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 checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input 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: This supplement provides for an intermediate strength, 0.08%. Electronic submission. PDUFA date: February 4, 2013.				
SIGNATURE OF REQUESTOR Cathy Tran-Zwanetz			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
PRINTED NAME AND SIGNATURE OF RECEIVER			PRINTED NAME AND SIGNATURE OF DELIVERER	

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/s/

CATHERINE A TRAN-ZWANETZ
12/05/2012