CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-070

CROSS DISCIPLINE TEAM LEADER REVIEW

Team Leader Interdisciplinary Summary
NDA 22-070 Atralin (tretinoin) Gel, 0.05%

July 20, 2007

NDA 22-070 for Atralin (tretinoin) Gel, 0.05% is recommended to be approved for the treatment of acne vulgaris.

This is an 505(b)(2) application, with Retin-A Micro (tretinoin) Gel, 0.1% as the reference listed product. None of the currently marketed tretinoin gel products have 0.05% as the product strength. The gel formulation for Atralin is different from that of the other topical tretinoin products and is the basis for a New Drug Application.

Clinical Efficacy

The initial three-arm study failed to demonstrate comparable efficacy of Atralin Gel to Retin-A Micro Gel, 0.1%, however, Atralin Gel was superior to its own vehicle. The applicant then amended the development plan to conduct an additional study to evaluate superiority to vehicle. The results of the two studies comparing Atralin Gel to vehicle gel are as follows (from FDA Biostatistics reviewer, Dr. Kathy Fritch):

Efficacy Results at Week 12 in Studies 1 and 2

Study 1	**Atralin Gel N=375**	**Vehicle N=185**
Global Severity Score Success*	78 (21%)	23 (12%)
Non-Inflammatory Facial Lesions		
Mean Baseline Count	50.7	52.4
Mean Absolute Reduction	21.8	10.3
Mean Percent Reduction	43%	21%
Inflammatory Facial Lesions		
Mean Baseline Count	23.4	23.9
Mean Absolute Reduction	9.7	5.8
Mean Percent Reduction	41%	26%
Total Facial Lesions		
Mean Baseline Count	74.1	76.3
Mean Absolute Reduction	31.4	16.1
Mean Percent Reduction	43%	22%
Study 2	**Atralin Gel N=299**	**Vehicle N=302**
Global Severity Score Success**	69 (23%)	42 (14%)
Non-Inflammatory Facial Lesions		
Mean Baseline Count	51.9	52.7
Mean Absolute Reduction	18.7	10.8
Mean Percent Reduction	37%	20%
Inflammatory Facial Lesions		
Mean Baseline Count	22.9	23.4
Mean Absolute Reduction	7.0	4.0
Mean Percent Reduction	30%	17%
Total Facial Lesions		
Mean Baseline Count	74.8	76.1
Mean Absolute Reduction	25.7	14.7
Mean Percent Reduction	35%	19%

*Success was defined as 0 (clear) or 1 (very mild)
** Success was defined as 0 (clear) or 1 (very mild) with at least 2 grades reduction from baseline

The primary efficacy endpoints were evaluated at 12 weeks. No *a priori* evaluations were included for any other time points (e.g. 2 weeks or 8 weeks). The p-value (largest of three co-primaries) for tretinoin gel being superior to vehicle gel in Study 1 was <0.0022 and in study 2 was <0.0021 according the Biostatistics review.

The study included patients from 10 years old and up. Thus, no additional pediatric studies are needed as pediatric studies for below age 12 are generally waived for the acne indication.

Safety

The safety profile is as described in the agreed upon label. The majority of the safety events, as expected from a topical tretinoin drug product, are local, cutaneous events. These are identified in the table below:

Number of Subjects with Selected Adverse Reactions:

Event	Atralin Gel (n = 674)	Vehicle (n = 487)
Dry Skin	109 (16%)	8 (2%)
Peeling/Scaling/ Flaking Skin	78 (12%)	7 (1%)
Skin Burning Sensation	53 (8%)	8 (2%)
Erythema	47 (7%)	1 (<1%)
Pruritus	11 (2%)	3 (1%)
Pain of Skin	7 (1%)	0 (0%)
Sunburn	7 (1%)	3 (1%)

A post-marketing commitment is requested by the Pharmacology/Toxicology Reviewer and Supervisor to address carcinogenicity. This study was not submitted in the NDA submission, but for this product is acceptable as a post-marketing commitment as is described in the Pharm/Tox review. This was agreed upon at the pre-NDA meeting (June 1, 2006) in order to provide non-clinical data on long-term dermal exposure of Atralin Gel, 0.05%.

Fish Collagen Hydrolyzates and Sodium Hyaluronate

As per the CMC review, the product contains two excipients each identified by the applicant as being a "———". However, no substantiation of this claim has been reviewed and no labeling or claims should be allowed to be made for these excipients. The labeling for Atralin will contain the following statement in the Description section: "The contribution to efficacy of individual components of the vehicle has not been evaluated." This statement is common to other products where similar concerns are raised for individual excipients. b(4)

The fish collagen hydrolyzates (——— grams per 45 gram tube) also raise concerns regarding potential adverse interaction in patients with allergies to fish (see primary Clinical Review page 14, and consultation reply from the Division of Pulmonary and Allergy Drug Products Medical Officer, Dr. Susan Limb, dated June 20, 2007).

Labeling for the product includes the following advice:: "Use Atralin Gel with caution if allergic to fish due to potential for allergenicity to fish protein. Patients who develop pruritus or urticaria should contact their health care provider." This wording incorporates recommendations from the allergy consultant as well as from the applicant.

Clinical Pharmacology

The systemic exposure with this topical preparation of tretinoin is not different from that of other topical tretinoin preparations. See Clinical Biopharmaceutics review and relevant section of labeling.

With this in mind, a Pregnancy Category of C is recommended for Atralin Gel, mirroring that of the other topical tretinoin products. Historically, labeling regarding teratogenicity signals seen in the non-clinical studies with tretinoin are included. Sufficient information appears to be provided for systemic exposure to allow a bridge to that information for Atralin.

Tradename Issues

The tradename, Atralin, was reviewed by the Division of Medication Errors and Technical Support and signed off on July 13, 2007 as being acceptable for U.S. marketing. The primary noted concern that Atralin is the tradename for a sertraline product in Bangladesh. This was communicated to the sponsor who did not communicate concern to this regard.

In addition, the Division for Drug Marketing and Communication (DDMAC) has found Atralin acceptable from a promotional perspective.

Conclusion

In summary, the Clinical Team Leader recommends that Atralin (tretinoin) Gel, 0.05% be approved for the treatment of acne vulgaris with labeling as agreed upon with the applicant. A post-marketing commitment to conduct a carcinogenicity study as recommended by Pharm/Tox has been agreed to by the applicant.

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Lead Medical Officer, Dermatology

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/s/

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Team Leader Summary Review

Susan Walker
7/26/2007 05:31:32 PM
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Medical Officer Review of NDA 22-070
Clinical Review Addendum

NDA: 22-070	Correspondence Date: September 28, 2007
Serial Number: 000	CDER Stamp Date: September 29, 2007
RPM: Bauerlien	Review Date: July 26, 2007
	Clinical: Kettl/Luke

Sponsor: Coria Laboratories, Ltd.

Drug: Atralin (tretinoin gel) 0.05%

Pharmacologic Category: Retinoid

Indication: Acne vulgaris

Dosage Form and Route of Administration: Topical gel

Regulatory Summary:

The applicant has submitted a 0.05% gel formulation of tretinoin, Atralin Gel 0.05%, for daily topical application for the treatment of acne vulgaris. This review is an addendum to the clinical review dated July 15, 2007, and will elaborate on several issues which arose during the final review process prior to an action decision by the Division. The issues of the status of the 505(b)(2) clinical bridge and dermal safety studies will be discussed.

The applicant has submitted under section 505(b)(2) and has referenced Retin A Micro 0.1% Gel as the comparator reference product. There are currently no approved tretinoin gel products at the 0.05% concentration.

The sponsor's original development plan for tretinoin gel 0.05% in the treatment of acne vulgaris was to conduct one three-arm study to support a 505(b)(2) application with listed drug Retin-A Micro Gel (tretinoin) 0.1% (Study 009). The study demonstrated that tretinoin gel was superior to vehicle but could not demonstrate that tretinoin gel was non-inferior to Retin-A Micro Gel 0.1%.

After meeting with the Agency (December 2, 2004), the sponsor agreed to revise their development plan and conduct a second study so that the efficacy assessment could be based on two studies with vehicle control arms with the Retin-A Micro arm of the first study providing a bridge to the Agency's findings of safety for the listed product.

During the December 2, 2004 Guidance meeting, the applicant was informed that:

> If the sponsor submits a 505(b)(2) NDA with an adequate clinical bridge to Retin-A Micro Gel 0.1% then the Agency will be able to use its finding of safety for Retin-A Micro Gel 0.1% to help support the safety of the sponsor's product. In that case, no additional nonclinical studies would be recommended to support the active ingredient, tretinoin. However, adequate data to support the new excipients should be submitted.

The sponsor then completed a second phase 3 study which compared tretinoin gel 0.05% to vehicle and again confirmed superiority of the drug product to the vehicle. Thus efficacy was established with two adequate clinical phase 3 trials demonstrating efficacy to placebo.

The applicant has established a clinical bridge for both systemic and local safety with the reference comparator product, Retin A Micro Gel 0.1%.

Systemic safety was demonstrated in two head-to-head studies that investigated the systemic exposure under maximal use conditions for Atralin Gel 0.05% versus Retin-A Micro 0.1%. These phase 2 studies, 735.126.CL008, and 20.CLN.126.024, included 12 and 16 subjects, respectively. The two phase 2 studies included subjects with severe acne vulgaris and were performed to assess the systemic exposure of tretinoin and its metabolites following maximal topical application of the drug product. These pharmacokinetic studies were similar in design and compared tretinoin (Atralin) gel, 0.05% to tretinoin gel microsphere 0.1% (Retin-A Micro). There were no significant differences identified between treatment groups in serum level changes from baseline to day 14 for tretinoin or either of its metabolites. The clinical pharmacology review concluded that the systemic exposure of tretinoin and its two metabolites are comparable for the two tretinoin formulations, and the systemic safety of the proposed Atralin product is expected to be no worse than Retin A Micro Gel 0.1%.

Baseline and final plasma levels for tretinoin and metabolites

Compound	**735.126.CL008/01**				**20.CLN.126.024**			
	Tretinoin Gel, 0.05%		*RETIN-A Micro*		*Tretinoin Gel, 0.05%*		*RETIN-A Micro*	
	Baseline Conc (ng/ml)	Day 14 Conc (ng/ml)	Baseline Conc (ng/ml)	Day 14 Conc (ng/ml)	Baseline Conc (ng/ml)	Day 14 Conc (ng/ml)	Baseline Conc (ng/ml)	Day 14 Conc (ng/ml)
RA	0.9-1.6	0.7-1.7	0.7-1.6	0.7-1.7	0.7-1.5	0.7-2.9	0.8-1.8	0.7-3.3
13-cis	0.8-1.0	0.6-1.2	0.7-1.8	0.5-1.2	0.7-1.5	0.6-2.3	0.8-1.5	0.5-3.2
4-oxo	0.8-2.3	0.6-2.4	1.6-3.6	1.0-3.1	1.7-5.9	1.5-7.0	1.0-3.3	0.6-6.2

Day-14 AUC for tretinoin and metabolites

		735.126.CL008/01			20.CLN.126.024		
		Tretinoin Gel, 0.05%	Retin A Micro	P-Value	Tretinoin Gel, 0.05%	Retin A Micro	P-Value
N		6	6		7	8	
Tretinoin	Mean	27.47	26.22	0.544	32.759	32.675	0.9724
	STD	3.80	3.05		4.234	4.945	
	Range	21.9 - 32.0	21.9 - 31.3		27.5 – 37.8	26.7 – 40.8	
13-cis Retinoic Acid	Mean	20.58	19.35	0.475	31.29	33.16	0.6591
	STD	1.94	3.54		5.82	9.43	
	Range	16.9 - 22.0	13.4 - 24.2		24.4 – 41.4	21.3 – 47.3	
4-oxo-13 cis Retinoic Acid	Mean	34.19	44.07	0.156	71.81	63.29	0.6207
	STD	11.78	10.47		33.01	33.35	
	Range	18.2 - 50.4	31.7 - 56.4		40.0–138.2	24.3–113.3	

Local safety was assessed throughout development by the assessment of adverse event data from three phase 1 trials, two phase 2 trials, and two phase 3 trials. 960 subjects were exposed to tretinoin gel 0.05% in the course of these trials. In the two phase 2 trials already referenced above, as well as the initial phase 3 trial which compared Atralin Gel 0.05% to its vehicle and to the reference product, Retin A Micro Gel 0.1%, local safety was assessed and compared.

Local safety adverse events were less than the comparator product. However, it should again be noted that the concentration of the Retin A Gel product in twice that of the proposed Atralin product. These results were not unexpected, but they again help to bridge the local safety to the comparator product in support of a 505(b)(2) application.

This reviewer concludes that the studies which included Retin A Micro Gel 0.1% have adequately established a clinical bridge for the application of Atralin Gel 0.05% and the systemic and local safety of the proposed Atralin gel is expected to be no worse than the profile of Retin A Micro Gel 0.1%.

Dermal Safety Studies:

The applicant conducted several dermal safety studies to support labeling.

Study 735.126.CL007/01 assessed the contact irritation potential of repeated applications of tretinoin 0.05% gel to the skin of healthy volunteer subjects. Nine occlusive test patches were applied containing approximately 0.1 ml of each test article over a 21 day period. Skin reactions were recorded approximately 48-72 hours after each induction application. 237 subjects were enrolled and 215 subjects completed the study. The

conclusion of the study was that tretinoin 0.05% gel is irritating under occlusive conditions. One subject developed contact sensitization during the challenge phase. One subject had a serious adverse event (cholelithiasis) which was considered by the applicant to be unrelated to the study drug product.

Study 735.126.CL006/01 assessed the phototoxicity potential following application to the skin of healthy volunteer subjects. 16 subjects were enrolled, and all 16 completed the study. No erythema reactions greater than a score of 2 (moderate erythema) were observed. The applicant concluded that no subjects were considered to have had a phototoxic reaction to the study drug. There were no serious adverse events reported. No adverse event was considered related to the study drug.

Study 735.126.CL005 evaluated the photo-allergenic potential of tretinoin 0.05% gel following repeated applications to the skin of healthy volunteer subjects. 19 subjects were enrolled, and 15 completed the study. No suspected or proven cases of photo-allergenic contact dermatitis were seen in the 15 evaluable subjects. No serious adverse events were reported. Nine subjects reported 13 adverse reactions. Two were considered by the applicant to be possibly related to the study medication. These were complaints of headache. No adverse event was considered clinically significant.

During discussions with the applicant in the review of the application since the original clinical review was filed, it was concluded that the dermal safety studies which were conducted were inadequate in terms of the numbers of subjects included. The photoallergy study included 15 subjects in place of the Agency suggested 50. The phototoxicity study included only 16 subjects instead of the recommended 30 subjects. The cumulative irritation assessed in the 007 protocol did not apply sufficient exposures of the product.

The applicant submitted in serial number 049 of IND 63,067 a protocol for the assessment of 21 day cumulative irritation. This study included 32 evaluable subjects instead of the suggested 35 subjects, and a final report will be submitted by the applicant by 12/31/07. This is acceptable to this reviewer as a phase 4 post-marketing commitment.

The applicant has agreed to complete phototoxicity and photoallergenicity protocols with adequate numbers of evaluable subjects as an additional post-marketing commitment. The final study reports are to be submitted by June 30, 2008.

Recommendation:

This reviewer again recommends approval of Atralin Gel 0.05% for the treatment of acne vulgaris. The applicant has presented adequate evidence from two adequate and well-controlled studies in subjects with acne vulgaris, that this product is superior to placebo, when evaluated after 12 weeks of treatment.

Systemic and local safety relative to the reference listed product, Retin A Micro Gel 0.1% in two phase 2 pharmacokinetic studies as well as the phase 3 three arm study, 009. This clinical bridge to Retin A Micro Gel 0.1% is sufficient to support approval for a 505(b)(2) application.

While this reviewer anticipates no issues of local dermal safety beyond those seen in the phase 3 efficacy trials, the applicant has agreed to conduct more adequate dermal safety studies to ensure that no signals related to differences in formulation are identified. These phase 4 post-marketing commitments are expected to be completed by June 30, 2008.

David Kettl, MD
Medical Officer

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