

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209353Orig1s000

OTHER REVIEW(S)

**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: July 10, 2018

To: Kendall Marcus, 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)

From: Morgan Walker, PharmD, MBA, CPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Laurie Buonaccorsi, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name), Dosage Form and Route: ALTRENO (tretinoin) lotion, 0.05%, for topical use

Application Type/Number: NDA 209353

Applicant: Dow Pharmaceutical Sciences, a division of Valent Pharmaceuticals

1 INTRODUCTION

On October 23, 2017, Dow Pharmaceutical Sciences, a division of Valent Pharmaceuticals submitted for the Agency's review an original New Drug Application (NDA) 209353 for ALTRENO (tretinoin) lotion. The proposed indication is for the topical 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 December 6, 2017 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ALTRENO (tretinoin) lotion.

2 MATERIAL REVIEWED

- Draft ALTRENO (tretinoin) lotion PPI received on October 23, 2017, and received by DMPP and OPDP on June 28, 2018.
- Draft ALTRENO (tretinoin) lotion Prescribing Information (PI) received on October 23, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 28, 2018.

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.

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 reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

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

MORGAN A WALKER
07/10/2018

LAURIE J BUONACCORSI
07/10/2018

LASHAWN M GRIFFITHS
07/10/2018

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

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

Memorandum

Date: July 09, 2018

To: Melinda McCord/Clinical Reviewer, M.D.
Division of Dermatology and Dental Products (DDDP)

Barbara Gould, Regulatory Project Manager, (DDDP)

Nancy Xu, Associate Director for Labeling, (DDDP)

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for ALTRENO™ (tretinoin) lotion, 0.05%

NDA: 209353

In response to DDDP's consult request dated December 7, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for ALTRENO™ (tretinoin) lotion, 0.05% (Altreno).

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDDP on June 28, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 4, 2018, and our comments are provided below on the attached label.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

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/s/

LAURIE J BUONACCORSI
07/09/2018

**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 Pharmacovigilance and Epidemiology**

Pharmacovigilance Review

Date: June 27, 2018

Reviewer: Carmen Cheng, PharmD, Safety Evaluator
Division of Pharmacovigilance-I (DPV-I)

Team Leader: Vicky Chan, PharmD, BCPS
DPV-I

Division Director: Cindy Kortepeter, PharmD
DPV-I

Product Names: Altreno (Tretinoin) Lotion, 0.05% and Other Topical Tretinoin
Products (See Appendix A)

Subject: Photosensitivity Reactions

Application Type/Number: NDA 209353 (See Appendix A for Application Numbers for
Other Topical Tretinoin Products)

Applicant/Sponsor: Dow Pharmaceutical Sciences

OSE RCM #: 2018-1369

Special thanks to Dr. Lois La Grenade for her assistance with this review.

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EXECUTIVE SUMMARY

This review evaluates the FDA Adverse Event Reporting System (FAERS) and literature reports for an association between topical tretinoin products and photosensitivity reactions. The Division of Dermatology and Dental Products (DDDP) requested the Division of Pharmacovigilance (DPV) to assess whether there is a safety signal for phototoxicity for topical tretinoin products in postmarketing data. On October 27, 2017, Dow Pharmaceutical Sciences (DPS), the applicant, submitted the New Drug Application (NDA) 209353 for Altreno (tretinoin) lotion, 0.05% for the treatment of acne vulgaris. This application is currently under review by DDDP.

The 58 FAERS and literature cases in this case series support a possible association between topical tretinoin and photosensitivity. Retin-A was the most commonly reported product. None of the cases in our case series were associated with oral tretinoin or the topical combination products containing clindamycin and tretinoin. Although we reviewed cases coded with a serious outcome, none of the cases were life-threatening, required medical intervention, or led to hospitalization. The majority of our case series consisted of consumer reports. Additionally, the majority of the cases reported a photosensitivity reaction at the topical tretinoin application site following exposure to sunlight. Based on the duration of topical tretinoin use, these postmarketing cases are suggestive of a photosensitivity reaction, rather than a hypersensitivity or irritant reaction caused by the drug alone. These reactions occurred after ultraviolet (UV) light exposure, after a long duration of topical tretinoin use in most patients. In the 41 cases that reported a time to onset, the mean duration of topical tretinoin use prior to the photosensitivity reaction was 307 days (median 60 days).

Slade et al. published the results of the negative phototoxicity and photoallergenicity studies for Atralin gel. The authors concluded that the negative phototoxicity and photoallergenicity studies are “consistent with the substantial body of documented evidence which concludes that tretinoin is neither phototoxic nor photoallergenic.” Although the findings were negative, there are several limitations to the studies. As noted in Dr. Kettl’s review from September 4, 2008, two of the studies were inadequately powered. In addition, these studies examined phototoxicity and photoallergenicity after a short duration of tretinoin use; the postmarketing reports show that a photosensitivity reaction may occur with chronic tretinoin use. A potential mechanism for an increased risk of a photosensitivity reaction by topical tretinoin is its potential to cause a thinning of the skin with extended use. Tretinoin can affect cellular proliferation and differentiation, where chronic use can lead to a thinner and more compact stratum corneum.

In conclusion, it is possible that topical tretinoin is associated with phototoxicity based on its known mechanism to thin the stratum corneum. While the limitations of the postmarketing cases preclude a causal association, they highlight the importance of proper sunscreen use and sun protection. With adequate labeling and patient counseling, the risk of photosensitivity can be mitigated by preventative measures such as avoidance of UV light or the use of sun protection (if exposure to UV light cannot be avoided).

Based on this review, DPV recommends maintaining the applicant's proposed WARNINGS AND PRECAUTIONS for photosensitivity reactions in the Altreno labeling. Consider the following addition:

- Advise patients with sunburn not to use ALTRENO until fully recovered.

1 INTRODUCTION

This review evaluates the FDA Adverse Event Reporting System (FAERS) and literature reports for an association between topical tretinoin products and photosensitivity reactions. The Division of Dermatology and Dental Products (DDDP) requested the Division of Pharmacovigilance (DPV) to assess whether there is a safety signal for phototoxicity for topical tretinoin products in postmarketing data.

1.1 BACKGROUND

Consult

On October 27, 2017, Dow Pharmaceutical Sciences (DPS), the applicant, submitted the New Drug Application (NDA) 209353 for Altreno (tretinoin) lotion, 0.05% for the treatment of acne vulgaris. This application is currently under review by DDDP. Consistent with the labeling for the topical tretinoin products, the applicant submitted draft labeling in which the WARNINGS AND PRECAUTIONS section of labeling includes the following text:

5.2 “Ultraviolet Light and Environmental Exposure

(b) (4)

The assessments of phototoxicity and photoallergenicity, conducted as a Postmarketing Commitment, were negative for Atralin (tretinoin) gel, 0.05%. Therefore, DDDP granted a waiver of photostudies for tretinoin lotion based on these results, provided that the risks of photosensitization and phototoxicity are communicated in labeling.^{1,2} DDDP requested DPV to determine if the postmarketing data shows that phototoxicity is a safety concern for the topical tretinoin products.

Photosensitivity

Drug-induced photosensitivity may be defined as a cutaneous reaction to medications triggered by the exposure of the skin to ultraviolet (UV) light. Drug-induced photosensitive rashes are usually eczematous in appearance. Both systemic and topically applied medicines may cause photosensitivity. Widespread eruptions suggest systemic drug involvement, whereas localized rashes are more commonly seen with photosensitivity induced by topical agents. The term photosensitivity is commonly used to refer to both phototoxic and photoallergic reactions.

Phototoxic reactions are far more common than photoallergic reactions, and result from direct tissue damage caused by a photoactivated substance. Compounds that have the potential to cause phototoxicity have at least one resonating double bond or an aromatic ring that can absorb radiation energy. Thus, phototoxicity is the result of a photochemical reaction and is

not immunological in nature. Most compounds are activated by wavelengths in the UVA spectrum, but some may be activated by visible light and/or UVB.

Photoallergic reactions clinically resemble phototoxic reactions with an eczematous rash on light exposed areas. However, there is seldom blistering and healing is not usually associated with hyperpigmentation. Photoallergic skin reactions develop when a medication present in the dermis becomes antigenic on exposure to light. Photoallergy develops in previously sensitized individuals.

Although it may be difficult to distinguish between these two reactions clinically, there are a number of differences, as shown in Table 1 below.

	Photoallergy	Phototoxicity
Relative incidence	Low	High
Dose dependent	No	Yes
Prior exposure necessary	Yes	No
Relative amount of drug	Low	High
Time of onset	Hours to days	Minutes to hours
Clinical appearance	Contact dermatitis	Exaggerated sunburn
Histopathology	Epidermal spongiosis, dermal inflammation	Epidural necrosis
Pigmentary alteration	Uncommon	Common

The diagnosis of photosensitivity is largely a clinical one, with a history of the rash developing within a short time after sun or light exposure (a few minutes to several days), and the clinical finding of a rash on light exposed areas of the skin: the face (sparing the upper eyelids), the ‘V’ of the neck, the external aspects of the arms, the back of the hands and the lower legs. Phototesting and photopatch testing are only undertaken when the diagnosis is unclear and are available only in specialized centers.⁴

1.2 REGULATORY HISTORY

Topical tretinoin is currently available in the United States as creams and gels, in varying strengths. It is also available in fixed-dose combination products with clindamycin. Appendix A provides a list of the currently marketed topical tretinoin products in the United States.

1.3 PRODUCT LABELING

All of the topical tretinoin products contain one of the following in the labeling:

1. WARNINGS AND PRECAUTIONS regarding avoiding unprotected exposure of ultraviolet light, similar to the text detailed in Section 1.1
2. PRECAUTIONS regarding sunburn

Some products have additional language for photosensitivity or sunburn, such as for Atralin (tretinoin) Gel, 0.05%. The ADVERSE REACTIONS section of the labeling states that sunburn occurred in 1% of the subjects in both the Atralin gel and vehicle gel study groups. The Patient Information also provides instructions to avoid the use of Atralin gel in patients with sunburn,

the need to avoid or minimize exposure to UV light or sunlight, instructions for sun protection, and the need to stop Atralin until sunburned skin has healed.⁵

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

Inclusion criteria

We included cases reporting a photosensitivity reaction during the use of a topical tretinoin.

Exclusion criteria

A case was excluded if any of the following was reported:

- Onset of photosensitivity after the discontinuation of a topical tretinoin
- Compounded topical tretinoin product
- Photosensitivity occurred outside of the topical tretinoin application site
- History of photosensitivity or pre-existing skin changes at the site of photosensitivity
- Photosensitivity assessed by reviewer to be unlikely related to the use of a topical tretinoin

2.2 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2. We limited our FAERS search to focus on cases reporting a serious outcome.

Date of Search	May 22, 2018
Time Period of Search	All reports through May 21, 2018
Search Type	FDA Business Intelligence Solution Quick Query
Product Term	Product active ingredient: Tretinoin
MedDRA Search Terms (Version 21.0)	Preferred Terms: <i>Photosensitivity reaction, Sunburn</i>
Outcome	Serious [†]
* See Appendix B for a description of the FAERS database. † For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities	

2.3 DATA MINING SEARCH STRATEGY

DPV used the Empirica Signal software with the strategy described in Table 3 to perform disproportionality analyses on FAERS data and to identify patterns of associations or unexpected occurrences (i.e., “potential signals”). If a drug-event combination has a score (EB05) of ≥ 2 , this score indicates 95% confidence that a drug-event combination appears at least twice the expected rate when considering all other drugs and events in the database. Data mining scores do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation.

Table 3. Data Mining Search Strategy*	
Data Refresh Date	May 2, 2018
Product Terms	Tretinoin
Empirica Signal Run Name	Generic (S)
MedDRA Search Strategy	Preferred Terms: <i>Photosensitivity reaction, Sunburn</i>
* See Appendix B for description of data mining of FAERS using Empirica Signal. Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities	

2.4 LITERATURE SEARCH

DPV searched the medical literature with the strategy described in Table 4.

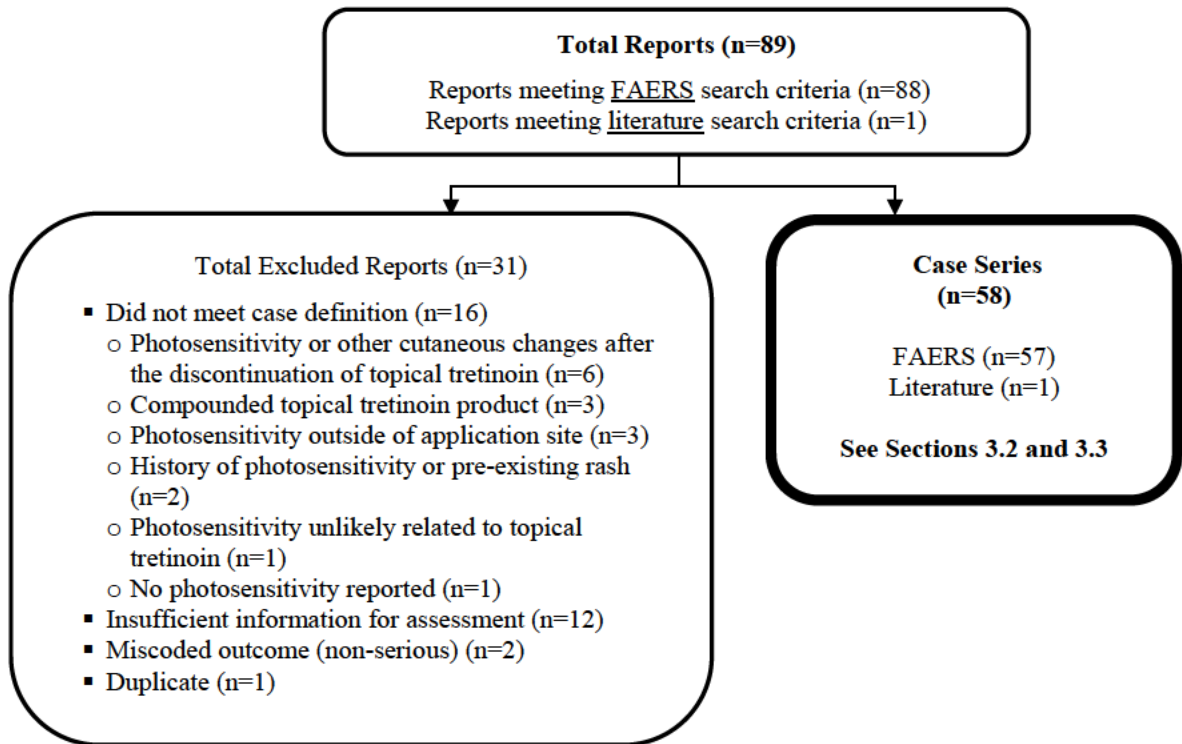
Table 4. Literature Search Strategy	
Date of Search	May 30, 2018
Databases	PubMed and Embase
Search Terms	PubMed: tretinoin AND (photosensitivity OR sunburn OR phototoxicity) Embase: (((('tretinoin'/exp OR tretinoin) AND ('photosensitivity'/exp OR photosensitivity)) OR (('tretinoin'/exp OR tretinoin) AND ('phototoxicity'/exp OR phototoxicity))) AND 'retinoic acid'/de AND ('avita'/tn OR 'renova'/tn OR 'retin a'/tn OR 'retin a micro'/tn OR 'tretinoin'/tn)
Years Included in Search	All

3 RESULTS

3.1 FAERS AND LITERATURE CASE SELECTION

The FAERS search retrieved 88 reports and the medical literature search retrieved one relevant case report. After applying the case definition in Section 2.1 and accounting for duplicate reports, 58 cases were included in the case series of photosensitivity reported with topical tretinoin use (see Figure 1).

Figure 1. FAERS and Literature Case Selection

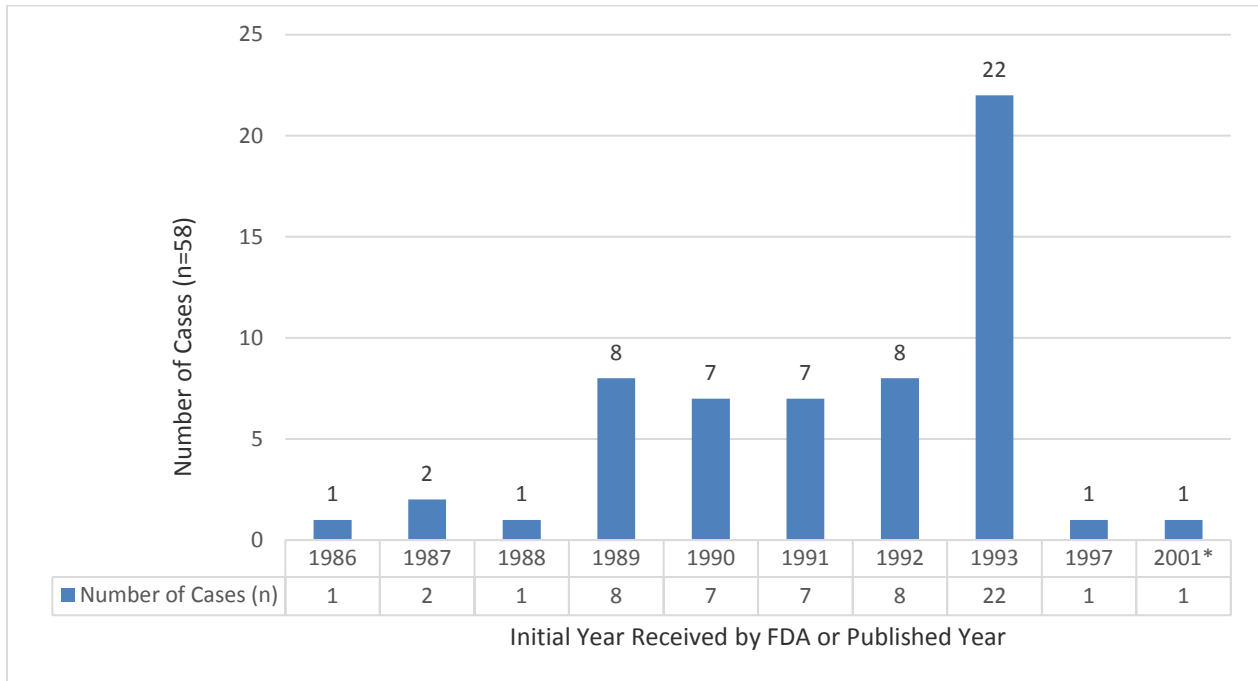


Appendix C contains a line listing of the 57 FAERS cases in this case series.

3.2 CASE CHARACTERISTICS FOR FAERS AND LITERATURE CASES (N=58)

As shown in Figure 2, the serious FAERS cases in our case series were submitted to the FDA on or before 1997; one additional literature case was published in 2001. To identify more recent reporting trends, we performed an additional FAERS search with similar criteria outlined in Table 2, but expanded the search to include reports with a non-serious outcome (see Appendix D). The results show that the FDA continued to receive non-serious reports of photosensitivity with tretinoin, but the number of reports significantly decreased since 2000.

Figure 2. Case Series of Photosensitivity with Topical Tretinoin in FAERS and the Published Medical Literature: Initial Year Received by FDA or Published Year



* Case from 2001 was a published literature report.

Tables 5 and 6 summarizes the 58 cases of photosensitivity reported with topical tretinoin from FAERS and the published medical literature in our case series.

Table 5. Descriptive Case Characteristics of Cases Reporting Photosensitivity with Topical Tretinoin in FAERS and the Published Medical Literature, Received by FDA (Through May 21, 2018) or Published (Through May 30, 2018) (N=58)		
Age, Years (n=24)	Mean	32
	Median	21
	Range	11-72
Sex (n=57)	Female	52
	Male	5
Country	USA	58
Case Source*	FAERS	57
	Literature	1
Report Source	Consumer	48
	Health care professional	10
Report Type (n=57)†	Expedited	2
	Periodic	55
Serious Outcome‡	Other serious	58

Table 5. Descriptive *Case* Characteristics of Cases Reporting Photosensitivity with Topical Tretinoin in FAERS and the Published Medical Literature, Received by FDA (Through May 21, 2018) or Published (Through May 30, 2018) (N=58)

* FAERS - Includes any case identified in either FAERS alone or in both FAERS and the literature
 Literature - Includes cases only identified in the literature
 † Report type applies to 57 FAERS cases.
 ‡ For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events.

Table 6. Descriptive *Event* Characteristics of Cases Reporting Photosensitivity with Topical Tretinoin in FAERS and the Published Medical Literature, Received by FDA (Through May 21, 2018) or Published (Through May 30, 2018) (N=58)

Topical Tretinoin Product	Retin-A	56
	Renova	2
Topical Tretinoin Strength (n=45)*	0.01%	6
	0.025%	17
	0.05%	21
	0.1%	2
Topical Tretinoin Formulation (n=50)	Cream	41
	Gel	8
	Liquid†	1
Reported Reason for Use (n=41)	Acne	29
	Photoaging/photodamage/"wrinkles"	9
	Cancer prophylaxis	2
	"Oily skin/sebaceous cysts"	1
Time to Onset of Photosensitivity Reaction from Initiation of Topical Tretinoin (n=41)‡	4 days – < 1 month	15
	1 month – <6 months	12
	6 months – <1 year	4
	1 year – 5 years	10
Reported Photosensitivity Event§	Sunburn	36
	Erythema	18
	Swelling	12
	Blister/vesicle	9
	Photosensitivity	6
	Peeling	5
	Rash	4
	Brown spots/hyperpigmentation	3
	Hives	2
	Irritation	2
	Second-degree burn	1
Photosensitivity Reaction at Application Site (n=48)	Yes	43
	Suggestive (but not confirmed)	5

Table 6. Descriptive *Event* Characteristics of Cases Reporting Photosensitivity with Topical Tretinoin in FAERS and the Published Medical Literature, Received by FDA (Through May 21, 2018) or Published (Through May 30, 2018) (N=58)

Reported Use of Sunscreen (n=39)	Sunscreen not used	20
	Sunscreen used	19
Concomitant Medication Labeled for Photosensitivity (n=7)[§]	Tetracycline/minocycline	4
	Benzoyl peroxide	2
	Fluorouracil	1
	Prochlorperazine	1
Disposition of Topical Tretinoin (n=25)	Discontinue/On Hold	17
	Continue	8
Improvement upon Discontinuing or Withholding Use of Topical Tretinoin (n=7)	Yes	6
	No	1
Treatment (n=6)	Topical corticosteroid	3
	Aloe vera or moisturizer	2
	None	1
* One case reported the use of two strengths of Retin-A, 0.025% and 0.1%. † Retin-A 0.05% liquid (NDA 016921) is not currently marketed. ‡ Time to onset - Mean: 307 days, Median: 60 days, Range: 4 days to 5 years. § Some cases may have reported more than one photosensitivity event or concomitant medication. Report of continued photosensitivity after the discontinuation of topical tretinoin (patient's concomitant medication was tetracycline).		

3.3 SAMPLE CASE NARRATIVES

We provide three sample FAERS case narratives and a summary of the published literature case report:

FAERS Case #4818676: A female of an unknown age experienced a “sunburn-like area on both cheeks” after being on Retin-A cream 0.05% for over one year. The rash appeared after being in the sun, and her skin “burns easily” despite the use of sunscreen. The patient reported she may have used more Retin-A cream than usual. She was not taking any concomitant medications. As a result of the photosensitivity reaction, the patient discontinued the use of Retin-A, because she needed to be outdoors for her job. At the time of reporting, she did not contact her physician regarding the adverse event.

FAERS Case #4852881: A 19-year-old female who was on Retin-A (unspecified strength and dosage form) nightly for acne experienced a second-degree burn with blistering of her face following sun exposure at the beach. She had been on Retin-A for almost three years at the time of the event. The patient also used Purpose Dual Moisturizer with sun protection factor (SPF). The reporter, a physician, stated that the “sunburn was due to patient using moisturizer instead of waterproof sunscreen.”

Reviewer’s comment: Both FAERS cases report the occurrence of a sunburn after sun exposure, despite the use of sunscreen in one case (FAERS Case #4818676). However, this case was

complicated by possible excessive use of topical tretinoin. These cases are consistent with a drug-induced photosensitivity reaction associated with tretinoin because the sunburns appeared at the tretinoin application sites (without reports of sunburns in other sun-exposed areas). Both of these patients have been on Retin-A for an extended period of time, but the dermal changes occurred shortly following sun exposure.

FAERS Case #4930917: A female of an unknown age experienced a “photosensitive reaction to fluorescent lights at work” while on Retin-A cream 0.025%. She had been using the cream for four months without any adverse reactions; she did not take any concomitant medications. Her face became “swollen, burned, looked red and crispy,” and her physician thought it may be lupus. Her laboratory test included an elevated sedimentation rate of 129 (no units reported, normal limits 1-40), but a repeat sedimentation rate three months later was normal. Retin-A cream was discontinued and the patient’s skin was improving.

Reviewer’s comment: Although the diagnosis of lupus was suggested, the case did not state a confirmed diagnosis. No additional laboratory tests or results were reported. While other cases in our case series reported a photosensitivity reaction as a result of sun exposure, this was the only case that reported a photosensitivity reaction as a result of indoor fluorescent light. Fluorescent lights can emit a low-dose of UV radiation.⁶

Literature Case: Birner and Meyer⁷ reported that a 52-year-old female experienced a photosensitivity reaction three days after the completion of her first cycle of chemotherapy treatment for newly diagnosed colon cancer. Her chemotherapy regimen included fluorouracil and leucovorin for five days, with oral prochlorperazine as premedication. She continued using Renova cream 0.05%, which was applied to her face nightly for about five years. Her additional concomitant medications included conjugated estrogens with medroxyprogesterone as hormone replacement therapy, chloroquine as antimalarial prophylaxis, insulin for diabetes, and multivitamin. The photosensitivity reaction occurred after the patient was outside in the winter sun for one hour, with only her face exposed to the sun. She used an SPF 30 sunscreen. However, her face became “edematous, itchy, and painful.” Within one week, the skin on her face was “completely desquamated.” She discontinued Renova with the advice of the oncology nurse practitioner and applied moisturizer as treatment. Within 10 days, her skin returned to normal. Other than the discontinuation of Renova, other medications remained unchanged when she was treated with five additional cycles of chemotherapy. “Minor erythema of the face and slight peeling of the lips” were reported, but otherwise no significant adverse events. After the completion of the chemotherapy, Renova was resumed without further photosensitivity reactions.

Reviewer’s comment: Three of the patient’s concomitant medications, fluorouracil, chloroquine, and prochlorperazine, are labeled for photosensitivity in the ADVERSE REACTIONS section of the labeling. The patient did not experience a photosensitivity reaction when she was using the topical tretinoin only without additional photosensitizing medications. The authors stated that “the presence in the skin of several drugs identified as single causes of photosensitivity additively reached a threshold for an adverse event in this patient. Removal of just one of the many potentially contributing agents was sufficient to prevent recurrence. Agents known to cause photosensitivity should be administered concurrently with caution.”

3.4 DATA MINING

Table 7 summarizes the results of the data mining search using Empirica Signal for photosensitivity reported with tretinoin use.

	MedDRA Preferred Terms	N	EB05	EBGM	EB95
1	Photosensitivity reaction	266	5.908	6.541	7.228
2	Sunburn	7	1.531	2.908	5.127

* A score (EB05) of ≥ 2 indicates 95% confidence that a drug-event combination appears at least twice the expected rate when considering all other drugs and events in the database.

4 DISCUSSION

The 58 FAERS and literature cases in this case series support a possible association between topical tretinoin and photosensitivity. Data mining of the postmarketing reports show that there is disproportionate reporting of the drug-event combination, tretinoin and photosensitivity reaction, in FAERS. The number of photosensitivity reports with the topical tretinoin, including both serious and non-serious outcomes, has significantly decreased since 2000. Retin-A was the most commonly reported product, accounting for 56 of the 58 cases (the remaining two cases reported the use of Renova). None of the cases in our case series were associated with oral tretinoin or the topical combination products containing clindamycin and tretinoin. Although we reviewed cases coded with a serious outcome, none of the cases were life-threatening, required medical intervention, or led to hospitalization. The majority of our case series consisted of consumer reports, which provided limited details in some cases and none reported confirmatory phototesting or photopatch testing.

The majority of the cases (43 of 58) reported a photosensitivity reaction at the topical tretinoin application site following exposure to sunlight. The cases generally reported facial sunburn, while some cases specified the affected areas (periorbital, nose, cheeks, chin, forehead); two cases also reported sunburn at other application sites such as the chest or back and one case reported sunburn at an unspecified application site. Five additional cases were suggestive (but not confirmed) that the photosensitivity reaction occurred at the application site. In the remaining 10 cases, we were unable to determine the location of the photosensitivity reaction.

While exposure to sunlight was the primary factor for the photosensitivity reactions in our case series, one case described a photosensitivity reaction in a patient as a result of indoor fluorescent lighting while using topical tretinoin. Drug-induced photosensitivity reactions caused by fluorescent lighting has been reported in the literature with another photosensitive drug.⁸ While fluorescent and other indoor lights emit a lower dose of UV radiation, it is important to consider the cumulative exposure of the UV rays for patients who are photosensitive or on photosensitive medications.⁶

Based on the duration of topical tretinoin use, these postmarketing cases are suggestive of a photosensitivity reaction, rather than a hypersensitivity or irritant reaction caused by the drug alone. The most commonly reported terms related to the photosensitivity reactions were: sunburn, erythema, swelling, blister/vesicle, and photosensitivity (more than one term may be reported in one case). These reactions occurred after UV light exposure, after a long duration of topical tretinoin use in most patients. In the 41 cases that reported a time to onset, the mean duration of topical tretinoin use prior to the photosensitivity reaction was 307 days (median 60 days). This long duration of use differentiates the reported reaction from an allergic or skin irritation-type reaction caused by the topical tretinoin alone, which would be expected to occur soon after exposure to the medication.

Additional risk factors for a photosensitivity reaction in the case series included the concomitant use of a medication labeled for photosensitivity and a lack of sunscreen use. Seven of the 58 cases reported the concomitant use of a medication labeled for photosensitivity. Six of the seven cases did not specify the duration of use for the concomitant medication (e.g. tetracyclines and benzoyl peroxide). The literature case report summarized in Section 3.3 described the occurrence of a photosensitivity reaction when multiple photosensitizing medications (fluorouracil, chloroquine, and prochlorperazine) were administered in a patient using a topical tretinoin; this case was suggestive of a possible additive photosensitizing effect. From the postmarketing cases, it is difficult to determine whether the photosensitivity reaction is drug-induced or caused by sun exposure alone because of inadequate sun protection. Despite adequate labeling in the topical tretinoin products recommending to minimize or avoid exposure to UV light and sunlight (in addition to the need for sun protection), 20 of the 58 cases stated sunscreen was not used. Nineteen cases did not provide information on the use of sunscreen. A photosensitivity reaction occurred in the remaining 19 cases even with the use of sunscreen. However, it is unknown whether the patients applied the sunscreen properly and whether sunscreen was reapplied after extended sun exposure. From a 2013 Consumer HealthStyles survey, the Centers for Disease Control and Prevention (CDC) researchers found that fewer than 15% of males and 30% of women applied sunscreen regularly when outside for more than one hour.⁹ The CDC researchers also concluded that more guidance should be provided to consumers regarding sunscreen use.

Tretinoin is a photoreactive chemical, though this does not mean that it is a photosensitizing medication. As previously stated in the background section of this review, the assessments of phototoxicity and photoallergenicity, conducted as a Postmarketing Commitment, were negative for Atralin (tretinoin) gel, 0.05%. Slade et al. published the results of these negative phototoxicity and photoallergenicity studies.¹⁰ The studies included two phototoxicity trials: Trial A (Study 735.126.CL006) and Trial B (Study 029-066-09-001), as well as two photoallergenicity trials: Trial C (Study 735.126.CL005) and Trial D (Study 029-066-09-002).¹ All four trials were conducted in healthy volunteers. Trials A and B showed no phototoxicity after application of tretinoin gel under occlusion for 24 hours. Trials C and D showed no photoallergenicity after a 3-week induction phase (tretinoin gel under occlusion for 24 hours, then applied twice weekly for three weeks), followed by a 9-14 days rest phase, then a challenge and observation period of five days.^{1,10} The authors concluded that the negative phototoxicity and photoallergenicity studies are “consistent with the substantial body of documented evidence which concludes that tretinoin is neither phototoxic nor photoallergenic.”¹⁰ Although the findings were negative, there are several limitations to the studies. As noted in Dr. Kettl’s

review from September 4, 2008, two of the studies (Trials A and C) were inadequately powered (Trials B and D contained adequate enrollment).¹ In addition, these studies examined phototoxicity and photoallergenicity after a short duration of tretinoin use; the postmarketing reports show that a photosensitivity reaction may occur with chronic tretinoin use.

A potential mechanism for an increased risk of a photosensitivity reaction by topical tretinoin is its potential to cause a thinning of the skin with extended use. Tretinoin can affect cellular proliferation and differentiation, where chronic use can lead to a thinner and more compact stratum corneum (outermost layer of the epidermis).¹⁰ Although Slade et al. reported on the negative phototoxicity and photoallergenicity studies, the authors stated that tretinoin is an irritant and suggested “photoirritation” may be a better term (“sunburn imposed on tretinoin inflamed skin”), although over time, photoirritation became synonymous with phototoxicity.¹⁰

5 CONCLUSION

In conclusion, it is possible that topical tretinoin is associated with phototoxicity based on its known mechanism to thin the stratum corneum. While the limitations of the postmarketing cases preclude a causal association, they highlight the importance of proper sunscreen use and sun protection. With adequate labeling and patient counseling, the risk of photosensitivity can be mitigated by preventative measures such as avoidance of UV light or the use of sun protection (if exposure to UV light cannot be avoided). Therefore, we support maintaining a WARNINGS AND PRECAUTIONS for photosensitivity reactions in the Altreno lotion labeling (and equivalent sections for the currently approved topical tretinoin products).

6 RECOMMENDATIONS

Based on this review, DPV recommends maintaining the applicant’s proposed WARNINGS AND PRECAUTIONS for photosensitivity reactions in the Altreno labeling. Consider the following addition:

- Advise patients with sunburn not to use ALTRENO until fully recovered.

7 REFERENCES

1. Kettl D. Medical officer review of Atralin (tretinoin) Gel, 0.05%. Postmarketing Commitment #3. NDA 22070. September 15, 2008.
2. McCord M. Memorandum - Waiver request for conduct of phototoxicity and photoallergenicity studies with IDP-121 (tretinoin) Lotion, 0.05%. IND 126753. July 21, 2016.
3. Stein KR, Scheinfeld NS. Drug-induced photoallergic and phototoxic reactions. *Expert Opin. Drug Saf.* 2007;6(4):431-443.
4. Trakatelli M, Charalampidis S, Novakovic LB, Patsatsi A, Kalabalikis D, Sotiriadis D. Photodermatoses with onset in the elderly. *Br. J. Dermatol.* 2009;161 Suppl 3:69-77.
5. Atralin (tretinoin) Gel, 0.05% [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; August 2014.
6. Sayre RM, Dowdy JC, Poh-Fitzpatrick M. Dermatological risk of indoor ultraviolet exposure from contemporary lighting sources. *Photochem Photobiol.* 2004 Jul-Aug;80:47-51.
7. Birner AM, Meyer LP. Photosensitivity associated with fluorouracil, prochlorperazine, and topical tretinoin. *Pharmacotherapy.* 2001 Feb;21(2):258-60.
8. Boudewijns S, Gerritsen WR, Koornstra RST. Case series: indoor-photosensitivity caused by fluorescent lamps in patients treated with vemurafenib for metastatic melanoma. *BMC Cancer.* 2014;14(1):967.
9. Holman DM, Berkowitz Z, Guy GP, Jr., Hawkins NA, Saraiya M, Watson M. Patterns of sunscreen use on the face and other exposed skin among U.S. adults. *Journal of the American Academy of Dermatology* 2015;73(1):83–92 e81.
10. Slade HB, Shroot B, Feldman SR, Cargill DI, Stanfield J. Reappraising the phototoxicity of tretinoin: a report of four controlled clinical trials. *Photodermatol Photoimmunol Photomed.* 2009 Jun;25(3):146-52.

8 APPENDICES

8.1 APPENDIX A. TOPICAL TRETINOIN PRODUCT LIST

Trade Name	Dosage Form	Strength	NDA/ Related ANDAs	NDA Sponsor(s)	Indication for Use	FDA Approval Date
Retin-A	Cream	0.1%	NDA 017340 ANDA 075213	Valeant Pharmaceuticals North America LLC	Acne vulgaris	Prior to Jan 1, 1982
Retin-A	Cream	0.05%	NDA 017522 ANDA 075265	Valeant International Bermuda		Prior to Jan 1, 1982
Retin-A	Gel	0.025%	NDA 017579 ANDA 075529	Valeant International Barbados SRL		Prior to Jan 1, 1982
Retin-A	Gel	0.01%	NDA 017955 ANDA 075589	Valeant International Barbados SRL		Prior to Jan 1, 1982
Retin-A Avita	Cream	0.025%	NDA 019049 NDA 020404 ANDA 075264	Valeant International Bermuda Mylan Pharmaceuticals Inc		Sep 16, 1988 Jan 14, 1997
Avita	Gel	0.025%	NDA 020400	Mylan Pharmaceuticals Inc		Jan 29, 1998
Retin-A Micro	Gel	0.1%	NDA 020475 ANDA 202026	Valeant International Barbados SRL		Feb 7, 1997
Retin-A Micro	Gel	0.04%	NDA 020475 ANDA 202567	Valeant International Barbados SRL		May 10, 2002
Retin-A Micro	Gel	0.08%	NDA 020475	Valeant International Barbados SRL		Jan 28, 2014
Retin-A Micro	Gel	0.06%	NDA 020475	Valeant International Barbados SRL		Oct 23, 2017
Atralin	Gel	0.05%	NDA 022070 ANDA 207955	Dow Pharmaceutical Sciences		Jul 26, 2007
Renova	Cream	0.05%	NDA 019963 ANDA 076498	Valeant Pharmaceuticals North America LLC	Adjunctive agent for use in the mitigation (palliation) of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin	Dec 29, 1995
Renova	Cream	0.02%	NDA 021108	Valeant Pharmaceuticals North America LLC		Aug 31, 2000

^a Drugs@FDA: FDA Approved Drug Products. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>. March 2018. Accessed May 28, 2018.

^b Electronic Orange Book. U.S. Food and Drug Administration. <https://www.accessdata.fda.gov/scripts/cder/ob/>. April 2018. Accessed May 28, 2018.

APPENDIX A. TOPICAL TRETINOIN PRODUCT LIST (CONTINUED)

Table 2. Combination Topical Clindamycin and Tretinoin Trade Names, Dosage Forms, FDA Application Numbers, Sponsors, Indications, and FDA Approval Dates^{a,b}						
Trade Name	Dosage Form	Strength (Clindamycin Phosphate/Tretinoin)	NDA/ Related ANDAs	NDA Sponsor(s)	Indication for Use	FDA Approval Date
Ziana	Gel	1.2%/0.025%	NDA 050802 ANDA 202564	Medicis Pharmaceutical Corp	Acne vulgaris	Nov 7, 2006
Veltin	Gel	1.2%/0.025%	NDA 050803	Aqua Pharmaceuticals LLC	Acne vulgaris	Jul 16, 2010

^a Drugs@FDA: FDA Approved Drug Products. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>. March 2018. Accessed May 28, 2018.

^b Electronic Orange Book. U.S. Food and Drug Administration. <https://www.accessdata.fda.gov/scripts/cder/ob/>. April 2018. Accessed May 28, 2018.

8.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

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 postmarketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the 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. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. “Data mining” refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., “potential signals”) in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

8.3 APPENDIX C. FAERS LINE LISTING OF PHOTOSENSITIVITY AND TOPICAL TRETINOIN CASE SERIES (N=57)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome*
1	8/15/1986	4504506	1	RETA63	Non- Expedited	NR	F	U.S.	OT
2	8/3/1987	4562008	1	RETA80	Non- Expedited	NR	F	U.S.	OT
3	11/12/1987	4577832	1	RETA95	Non- Expedited	15	F	U.S.	OT
4	8/3/1988	4607616	1	RETA244	Non- Expedited	60	F	U.S.	OT
5	2/10/1989	4639317	1	RETA155	Non- Expedited	71	F	U.S.	OT
6	2/10/1989	4639329	1	RETA247	Non- Expedited	17	F	U.S.	OT
7	4/27/1989	4649962	1	RETA258	Non- Expedited	70	F	U.S.	OT
8	7/31/1989	4665727	1	RETA357	Non- Expedited	NR	F	U.S.	OT
9	10/26/1989	4680537	1	RETA334	Non- Expedited	NR	M	U.S.	OT
10	10/26/1989	4680541	1	RETA421	Non- Expedited	NR	F	U.S.	OT
11	10/31/1989	4681405	1	RETA436	Non- Expedited	NR	F	U.S.	OT
12	10/31/1989	4681407	1	RETA415	Non- Expedited	NR	F	U.S.	OT
13	2/6/1990	4703352	1	RETA365	Non- Expedited	NR	F	U.S.	OT
14	2/6/1990	4704498	1	RETA423	Non- Expedited	NR	F	U.S.	OT
15	9/4/1990	4741853	1	90104459	Non- Expedited	NR	F	U.S.	OT
16	9/4/1990	4742361	1	RETA440	Non- Expedited	NR	F	U.S.	OT
17	9/4/1990	4742376	1	90104264	Non- Expedited	NR	F	U.S.	OT
18	10/4/1990	4747519	1	90104334	Non- Expedited	NR	F	U.S.	OT
19	10/29/1990	4755177	1	90104696	Non- Expedited	NR	F	U.S.	OT
20	9/6/1991	4817809	1	90104536	Non- Expedited	NR	F	U.S.	OT
21	9/6/1991	4817949	1	91104491	Non- Expedited	NR	F	U.S.	OT
22	9/6/1991	4818009	1	90104638	Non- Expedited	NR	F	U.S.	OT
23	9/6/1991	4818676	1	91104409	Non- Expedited	NR	F	U.S.	OT
24	9/6/1991	4818694	1	91104229	Non- Expedited	NR	M	U.S.	OT
25	9/6/1991	4818797	1	91104070	Non- Expedited	NR	F	U.S.	OT
26	11/14/1991	4833636	1	91104870	Non- Expedited	20	F	U.S.	OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome*
27	2/26/1992	4852881	1	91104583	Non- Expedited	19	F	U.S.	OT
28	2/26/1992	4853142	1	91104633	Non- Expedited	NR	F	U.S.	OT
29	2/26/1992	4853174	1	91104159	Non- Expedited	NR	F	U.S.	OT
30	5/28/1992	4880331	1	92104306	Non- Expedited	NR	F	U.S.	OT
31	9/9/1992	4907652	1	92104639	Non- Expedited	NR	F	U.S.	OT
32	11/16/1992	4929821	1	921041003	Non- Expedited	12	F	U.S.	OT
33	11/16/1992	4930917	1	92104413	Non- Expedited	NR	F	U.S.	OT
34	12/16/1992	4940683	1	92104775	Non- Expedited	11	F	U.S.	OT
35	4/6/1993	4975838	1	92104070	Non- Expedited	NR	NR	U.S.	OT
36	4/6/1993	4975924	1	92104078	Non- Expedited	NR	M	U.S.	OT
37	4/6/1993	4976170	1	92104414	Non- Expedited	NR	F	U.S.	OT
38	4/6/1993	4976183	1	92104383	Non- Expedited	51	F	U.S.	OT
39	4/6/1993	4976545	1	92104669	Non- Expedited	NR	F	U.S.	OT
40	4/6/1993	4977714	1	92104753	Non- Expedited	18	F	U.S.	OT
41	4/6/1993	4978206	1	921041094	Non- Expedited	NR	F	U.S.	OT
42	4/6/1993	4979632	1	92104946	Non- Expedited	NR	F	U.S.	OT
43	6/23/1993	5003655	1	92104930	Non- Expedited	NR	F	U.S.	OT
44	9/20/1993	5033870	1	921041260	Expedited (15-Day)	32	F	U.S.	OT
45	9/20/1993	5033882	1	92104983	Non- Expedited	16	F	U.S.	OT
46	9/20/1993	5035460	1	930409107010843	Non- Expedited	22	M	U.S.	OT
47	9/20/1993	5035480	1	930511107011150	Non- Expedited	21	F	U.S.	OT
48	9/20/1993	5042015	1	921041126	Non- Expedited	12	F	U.S.	OT
49	12/14/1993	5063824	1	93107094	Non- Expedited	72	F	U.S.	OT
50	12/14/1993	5064502	1	921041267	Non- Expedited	15	F	U.S.	OT
51	12/14/1993	5064503	1	921041259	Non- Expedited	NR	M	U.S.	OT
52	12/14/1993	5064525	1	930707107011477	Non- Expedited	16	F	U.S.	OT
53	12/14/1993	5064908	1	930624107011398	Non- Expedited	NR	F	U.S.	OT
54	12/14/1993	5064928	1	930624107011396	Non- Expedited	18	F	U.S.	OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome*
55	12/14/1993	5064992	1	921041532	Non- Expedited	23	F	U.S.	OT
56	12/14/1993	5066076	1	930517107011174	Non- Expedited	41	F	U.S.	OT
57	5/16/1997	5568152	1	970417107052528	Expedited (15-Day)	62	F	U.S.	OT

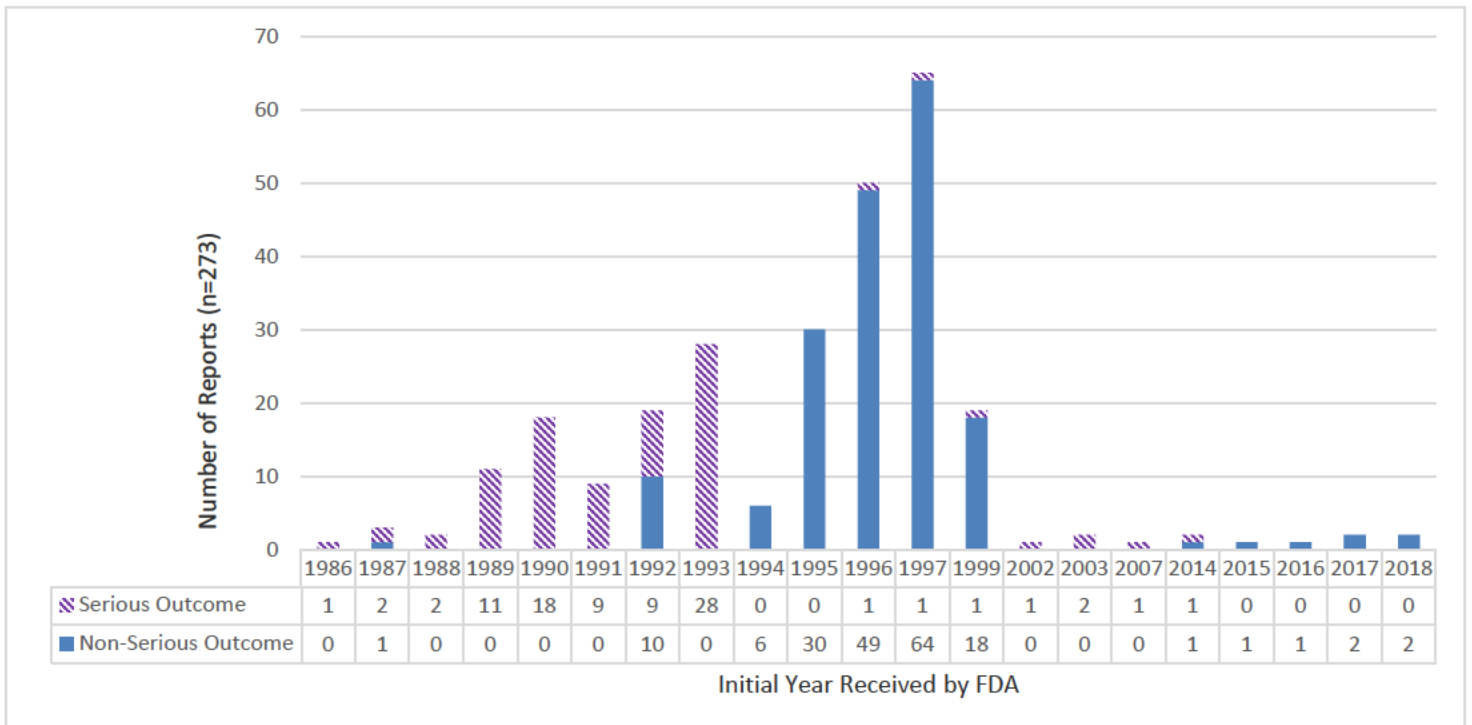
*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A report may have more than one serious outcome.
Abbreviations: F=Female, M=Male, NR=Not reported, OT=Other medically significant, U.S.=United States

8.4 APPENDIX D. NUMBER OF FAERS REPORTS (SERIOUS AND NON-SERIOUS) OF PHOTSENSITIVITY WITH TRETINOIN THROUGH MAY 21, 2018

To provide context to the number of serious reports described in our review, we additionally performed the following FAERS search (see Table 1 below) to identify any trends for the non-serious reports. Note that the results in this section (Figure 1 below) are total counts of FAERS reports and a hands-on analysis of the reports has not been performed. Therefore, case counts in this section may include duplicate reports, miscoded reports, or reports with insufficient information for assessment. Additionally, the case counts may include oral tretinoin products.

Table. FAERS Search Strategy	
Date of Search	May 22, 2018
Time Period of Search	All reports through May 21, 2018
Search Type	Quick Query
Product Terms	Product active ingredient: Tretinoin
MedDRA Search Terms (Version 21.0)	Preferred Terms: <i>Photosensitivity reaction, Sunburn</i>

Figure 1. Number of FAERS Reports (Serious and Non-Serious) of Photosensitivity with Tretinoin by Initial Year Received by FDA



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/s/

CARMEN CHENG
06/27/2018

VICKY C CHAN
06/27/2018

CINDY M KORTEPETER
06/27/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: June 8, 2018
Requesting Office or Division: Division of Dermatology and Dental Products (DDDP)
Application Type and Number: NDA 209353
Product Name and Strength: Altreno (tretinoin) lotion, 0.05%
Applicant/Sponsor Name: Dow Pharmaceutical Sciences, Inc.
FDA Received Date: June 4, 2018
OSE RCM #: 2017-2211-1
DMEPA Safety Evaluator: Madhuri R. Patel, PharmD
DMEPA Team Leader: Sarah K. Vee, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Dermatology and Dental Products (DDDP) requested that we review the revised container labels and carton labeling for Altreno (tretinoin), NDA 209353 (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container labels and carton labeling for Altreno are acceptable from a medication error perspective. We have no further recommendations at this time.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

^a Patel M. Label and Labeling Review for Altreno (NDA 209353). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 3. RCM No.: 2017-2211.

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/s/

MADHURI R PATEL
06/08/2018

SARAH K VEE
06/08/2018

INTRODUCTION AND BACKGROUND

On October 27, 2017, Dow Pharmaceutical Sciences submitted a 505(b) (1) new drug application (NDA) for ALTRENO (tretinoin) lotion, 0.05% for the treatment of acne vulgaris. DDDP consulted DPMH on December 20, 2017, to assist with the Pregnancy and Lactation subsections of labeling.

- ALTRENO (tretinoin) lotion 0.05% is a retinoid indicated for the treatment of acne vulgaris.
- This application is cross-referenced to the following applications:
 - NDA 022070 ATRALIN (tretinoin) Gel 0.05% approved July 26, 2007 for the treatment of acne vulgaris.
 - Nonclinical toxicology including genotoxicity and reproductive and developmental toxicity.
 - NDA 020475 for RETIN-A MICRO (tretinoin) Gel 0.1%, 0.08%, and 0.04% approved February 7, 1997 for treatment of acne vulgaris.
 - Supportive efficacy and safety information of tretinoin in the treatment of acne vulgaris.
 - NDA 017552 for RETIN-A (tretinoin) Cream 0.05%
 - Supportive efficacy and safety information of tretinoin in the treatment of acne vulgaris.
 - NDA 021108 for RENOVA (tretinoin) Cream 0.02% approved August 31, 2000 for the treatment of fine facial wrinkles.
 - Supportive long-term safety information of tretinoin for the treatment of another chronic dermatological condition (mitigation of fine facial wrinkles).
 - NDA 019963 for RENOVA (tretinoin) Cream 0.05% approved December 29, 1995 for treatment of fine facial wrinkles.
 - Supportive long-term safety information of tretinoin for the treatment of another chronic dermatological condition (mitigation of fine facial wrinkles).

Current State of the Labeling of Related Products

- None of the tretinoin topical labelings is in PLLR formatting.
- Labeling for RETIN-A gel 0.1%, and ATRALIN gel is in PLR, but not PLLR formatting. Labeling for RENOVA Cream 0.05% and 0.2% Cream is in pre-PLR formatting.
- There is no boxed warning on embryofetal toxicity for any of the products referenced above.
- All of the above products are listed as Pregnancy Category C.
- The Pregnancy Section for RETIN-A MICRO states, “Thirty human cases of temporally associated congenital malformations have been reported during two decades of use of [REDACTED] (b) (4). Although no definitive pattern of teratogenicity and no causal association has been established, 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.”

- ATRALIN Gel and RENOVA products list only animal data.
- The Nursing Mother’s section for ATRALIN and RETIN-A Cream states, “It is not known (b) (4) excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when [Drug] is administered to a nursing woman.” RENOVA labeling states, “It is not known (b) (4) this drug is excreted in human milk. Since many drugs are excreted in human milk, (b) (4) may be postponed in nursing mothers until after completion of the nursing period.”
- There are no pregnancy testing or contraception recommendations for any of the products listed above.
- There are no listed interactions with hormonal contraceptives for any of the products listed above.

REVIEW

PREGNANCY

Nonclinical Experience

Animal (b) (4) studies have not been conducted with ALTRENO (b) (4) in a different formulation to pregnant rats was associated with (b) (4) (craniofacial abnormalities (hydrocephaly), asymmetrical thyroids, variations in ossification, and increased supernumerary ribs) at doses up to (b) (4) tretinoin/kg/day, approximately 2 times the (b) (4) based on body surface area (b) (4) Oral (b) (4) cynomolgus monkey, (b) (4) at 10 mg/kg/day (100-times the (b) (4) based on body surface area comparison) (b) (4)

The reader is referred to the full Pharmacology/Toxicology review by Jill Merrill, Ph.D., and Barbara Hill, Ph.D.

Review of Pharmacovigilance Database

The applicant reported six patients who became pregnant during the Phase 3 studies. Of these six pregnancies, four were exposed to tretinoin lotion 0.05% (listed as IDP-121 in Table 1), and the other two were exposed to the vehicle lotion.

The applicant’s table of these cases is below.

Table 1. Study-related Pregnancies¹

Subject ID	Event Term	Treatment Arm	Outcome of Event	GPA (Obstetric and Gynecologic History)	Risk Factors	Lifestyle Factors	Congenital Anomalies
(b) (6)	Screening Preg	N/A	N/A	N/A	N/A	N/A	N/A
	Screening Preg	N/A	N/A	N/A	N/A	N/A	N/A
	Preg	(b) (6)	(b) (6)	(b) (6)	Gestational Diabetes	None Reported	None Reported
	Preg				None Reported	None Reported	None Reported
	Preg				XRay Exposure	None Reported	None Reported
	Preg				Recreational use of alcohol (wine) HTN	None Reported	Unknown
	Preg				None Reported	None Reported	None Reported
	Preg				None Reported	None Reported	None Reported

The applicant also searched the safety database for other tretinoin-based products owned by the applicant. Forty-three cases were identified by the search. The applicant stated, “There was no single report of a congenital anomaly found in the database.” The following pregnancy outcomes were reported:

- Five spontaneous abortions
- One abortion (unclear as to whether it was spontaneous or induced)
- Thirty-three cases with no outcome reported
- Four confirmed normal pregnancy outcomes

¹Safety Information Amendment, Dow Pharmaceutical Sciences, received 3/27/2018

Reviewer Comment:

While data from the applicant’s clinical trial and pharmacovigilance database are limited in their description of pregnancy outcomes, the applicant reports no cases of congenital anomalies related to topical tretinoin products. The applicant has marketed topical tretinoin products since 1995. Given the number of years of exposure, the likelihood that topical tretinoin (at least at the doses marketed) is a major teratogen is low.

Applicant’s Review of Literature

The applicant performed a cumulative search of the literature using the following terms, “tretinoin,” “tretinoin lotion,” “RETIN-A,” and “pregnancy” The applicant reported 930 publications that met search criteria, and stated that 32 articles were considered relevant to the topic of tretinoin exposure during pregnancy and/or lactation. Only two papers are described in detail the applicant’s review. One was a review article with no original data;² the other paper is described below.

Publication; author/date/ Country	Type of study	Population/control pop.; n	Exposure during pregnancy or pre-conception; to what drug/dose	Pregnancy/infant outcomes	Comments /limitations
Panchaud A ³ 2012 European Network of Teratology Services	Prospective, controlled, multicenter, observational study (11 teratology information services in Europe and Israel)	235 exposed pregnant women; 444 pregnant controls	First trimester exposure (most exposed prior to conception) to topical retinoids, including adapalene (n=24), tretinoin (n=143), isotretinoin (n=52), retinol (n=10), or motretinide (n=1) or combination (n=5)	No significant differences in spontaneous abortion (OR 1.5, (% CI 0.8-2.7), p=0.19; minor birth defects (OR 1.3, 95% CI 0.4-3.7), or major birth defects (OR1.8, 95% CI 0.6-5.4). No cases of retinoid embryopathy. Elective terminations in exposed group were 3 times higher than controls.	No confirmation of birth defects by dysmorphologist

The applicant stated that, “among the reviewed articles, the consensus is that no anomalies occurred in children whose mothers used topical tretinoin during pregnancy. However, tretinoin should only be used if the potential benefit justified the potential risk to the fetus, which is in accordance with the current understanding of tretinoin use.”

² Patel V, et al. Safety of topical dermatological medications in pregnancy. J Drugs Dermatol. 2016;15(7):830-834.

³ Panchaud A, et al. Pregnancy outcome following exposure to topical retinoids: a multicenter, prospective study. J Clin Pharmacol. 2012;52:1844-1851,

Reviewer comment:

*The applicant's literature review did not contain a detailed review of the published literature, and the bibliography did not include the entire citations of the articles listed. A review of the literature by DPMH (described below) indicates that larger prospective studies, in general, do not indicate an increased risk of major malformations or spontaneous abortion with topical tretinoin. (Oral tretinoin is a known teratogen.) Systemic absorption under maximal use conditions of topical tretinoin is very low compared to oral. (The baseline C_{max} and AUC following topical administration are 0.33 ng/mL and 6.46 ng*h/ML, respectively).⁴ In comparison, the labeling of an oral form of tretinoin reports that "a single 45 mg/m² (approximately 80 mg) oral dose to APL patients resulted in a mean ± SD peak tretinoin concentration of 347 ± 266 ng.mL."⁵*

DPMH Review of Literature

DPMH conducted a search of the literature using PUBMED, Embase, and Reprotox using the search terms, "tretinoin lotion and pregnancy," "tretinoin lotion and birth defects," "tretinoin lotion and fetal malformations," "tretinoin lotion and stillbirth," "tretinoin lotion and spontaneous abortion," and "tretinoin lotion and miscarriage."

Reprotox⁶ states, "Based on experimental animal data and experience with other retinoids, tretinoin is expected to increase the risk of birth defects if the exposure level is sufficiently high. Intravenous use of tretinoin therapy of leukemia might result in such levels, although there are no human data to confirm this possibility. Controlled studies of topical tretinoin use during pregnancy did not suggest that this use increases the risk of adverse pregnancy outcome; however, there are case reports of birth defects after topical tretinoin that form the basis topical tretinoin avoidance during pregnancy."

Briggs⁷ states, "Elevated serum concentrations of all-trans retinoic acid in early gestation are considered teratogenic in humans. Because of its relatively poor systemic absorption (if occlusive dressings are not used) after topical administration, tretinoin is not thought to present a significant fetal risk. Because some absorption does occur, however, it is not possible to exclude a teratogenic risk.⁸ Congenital malformations, some of which are consistent with those observed in retinoic acid embryopathy, have been reported after topical use, but a causal association has yet to be established. The reports may reflect (a) greater-than-normal fetal exposure from higher-than-usual maternal doses or enhanced systemic absorption, or (b) selective reporting of adverse outcomes that are not caused by tretinoin. Until more data are available, however, the safest course is to avoid the use of tretinoin during pregnancy, especially in the 1st trimester. But if inadvertent exposure does occur during early pregnancy, the fetal risk, if any, appears to be very low."

⁴ Email communication with Chinmay Shukla, Ph.D, Clinical Pharmacology, 5/22/2018.

⁵ VESANOID (tretinoin) capsules package insert (discontinued) Drugs@FDA

⁶ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 4/23/2018

⁷ Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015. Online, accessed 4/24/2018

⁸ Rothman KF and Pochi PE. Use of oral and topical agents for acne in pregnancy. J Am Acad Dermatol. 1988;19:431-42.

A review of the literature (see Appendix A for Table) yielded:

- two additional prospective controlled observational studies^{9,10}
- a retrospective study that examined pharmacy and medical records of pregnant women exposed to tretinoin versus control women¹¹
- A pharmacokinetic study of topical isotretinoin indicating that tretinoin has limited systemic absorption (plasma levels increased by 1.7% after 42 days of daily use)¹²
- Six reports of fetal malformations associated with topical tretinoin, and one case with another topical retinoin (adapalene) – malformations included craniofacial, heart and central nervous system (CNS) anomalies.^{13,14,15,16,17,18}

The studies (prospective and retrospective) did not indicate an increased risk of major malformations with topical tretinoin. There are limitations to these studies including lack of examination by a dysmorphologist, small sample size, and in the case of the retrospective study, a lack of confirmation that prescriptions were used by patients. Causation could not be proven with the individual cases of fetal malformations.

Reviewer comment:

Systemic absorption appears to be limited, and exposure of a fetus would be expected to be low. Prospective observational studies do not indicate an increased risk of birth defects or other adverse maternal or fetal effects with topical tretinoin exposure. These studies have methodological limitations, including limited sample size and, in some studies, lack of direct examination of the infants by a dysmorphologist. Six cases in the literature report birth defects; however, these case reports do not establish a pattern or association with tretinoin-related embryopathy.

LACTATION

Nonclinical Experience

Vitamin A and all trans-retinoic acid are present in rat milk.¹⁹

⁹Loureriro KD, et al. Minor malformations characteristic of the retinoic acid embryopathy and other birth outcomes in children exposed to topical tretinoin during early pregnancy. *Am J Med Genetics* 2005;136A:117-121.

¹⁰Shapiro L, et al. Safety of first-trimester exposure to topical tretinoin: prospective cohort study. *Lancet*. 1997;350:1143-1144.

¹¹Jick SS, et al. First trimester topical tretinoin and congenital disorders. *Lancet*. 1993;341:1181-1182.

¹²Chen C, et al. Negligible systemic absorption of topical isotretinoin cream: implications for teratogenicity. *J Clin Pharmacol*. 1997;37:279-284.

¹³Navarre-Belhassen C, et al. Multiple congenital anomalies associated with topical tretinoin. *Ann Pharmacothera*. 1998;32(4):505-6.

¹⁴Lipson AH, et al. Multiple congenital defect associated with maternal use of topical tretinoin. *Lancet* 1993;341:1352-3.

¹⁵Selcen D, et al. Otocerebral anomalies with topical tretinoin use. *Brain and Development*. 2000;22:218-220.

¹⁶Colley SM, et al. Topical tretinoin and fetal malformations. *Med J Australia*. 1998;168(9):467.

¹⁷Camera G and Pregniasco P. Ear malformation in baby born to mother using tretinoin cream. *Lancet*. 1992;339:687.

¹⁸Autret E, et al. Anophthalmia and agenesis of optic chiasma associated with adapalene gel in early pregnancy. *Lancet*. 1997;350:339.

¹⁹Gaal A and Csaba G. Effect of retinoid (vitamin A or retinoic acid) treatment (hormonal imprinting) through breastmilk on the glucocorticoid receptor and estrogen receptor binding capacity of the adult rat offspring. *Hum and Experiment Toxicol* 1998;17:560-563.

Review of Pharmacovigilance Database

The applicant reports one case of exposure to topical tretinoin via breastmilk. The applicant reports there were no adverse effects; details of the case were not provided.

Applicant's Review of Literature

The applicant performed a cumulative search of the literature using the following terms, "tretinoin," "tretinoin lotion," "RETIN-A," and "lactation." The applicant did not discuss any papers related to lactation and topical tretinoin in their review.

DPMH Review of Literature

DPMH conducted a search of *Medications in Mother's Milk*,²⁰ the Drugs and Lactation Database (LactMed),²¹ Micromedex,²² *Drugs in Pregnancy and Lactation*,²³ and of the published literature in PubMed and Embase using the search terms "topical tretinoin" and "lactation" or "breastfeeding."

Briggs²³ states, "Vitamin A and, presumably, tretinoin (all-trans retinoic acid) are natural constituents of human milk. There are no data available on the amount of all-trans retinoic acid excreted into milk after topical use. Although other retinoids are excreted, the minimal absorption that occurs after topical application of tretinoin probably precludes the detection of clinically significant amounts in breast milk from this source. Thus, use of tretinoin while breastfeeding does not appear to represent a significant risk to a nursing infant."

Topical tretinoin is referenced in LactMed,²¹ which states, "Because it is poorly absorbed after topical application, it is considered a low risk to the nursing infant."^{24,25}

Topical tretinoin is rated by Hale²⁶ as "L3- probably compatible."

A search of the published literature did not yield any cases of tretinoin use during lactation.

Reviewer comment:

Data on the safety of topical tretinoin use during breastfeeding are not available; however, systemic absorption is low and infant exposure is expected to be minimal. The applicant

²⁰ Hale, Thomas and Rowe, Hilary E. (2017). *Medications and Mother's Milk*. New York, NY. Springer Publishing.

²¹ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

²² Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 4/23/2018

²³ Briggs GG, Freeman RK. *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk* 10th Ed. 2015. Online, accessed 4/24/2018

²⁴ Leachman SA, Reed BR. The use of dermatologic drugs in pregnancy and lactation. *Dermatol Clin*. 2006;24:167-97.

²⁵ Butler DC, Heller MM, Murase JE. Safety of dermatologic medications in pregnancy and lactation: Part II Lactation. *J Am Acad Dermatol*. 2014;70:417.e1-417.e10.

²⁶ Hale, Thomas and Rowe, Hilary E. (2017). *Medications and Mother's Milk*. New York, NY. Springer Publishing. pp. 949-950.

recommends that women not apply topical tretinoin to the nipple and areola to avoid direct infant exposure, which is a reasonable precaution.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

In dermal fertility studies of another tretinoin formulation in rats, slight (not statistically significant) decreases in sperm count and motility were seen at 0.5 mg/kg/day (approximately 2 times the (b) (4) and slight (not statistically significant) increases in the number and percent of nonviable embryos in females treated with 0.25 mg/kg/day and above (approximately (b) (4) were observed.

The reader is referred to the full Pharmacology/Toxicology review by Jill Merrill, Ph.D., and Barbara Hill, Ph.D.

Review of Pharmacovigilance Database

The applicant did not provide a review of their pharmacovigilance database related to fertility.

Applicant's Review of Literature

The applicant did not provide a review of the literature related to fertility or hormonal contraceptives.

DPMH Review of Literature:

DPMH conducted a review of Micromedex, Embase, and PubMed using the terms, "topical tretinoin" and "fertility," "contraception," "oral contraceptives," and "infertility."

No papers on the effects of topical tretinoin on fertility or interactions with hormonal contraceptives were located in the search.

Reviewer comment:

The applicant does not include subsection 8.3 in the proposed labeling. DPMH agrees that since data do not indicate a clear risk for use during pregnancy or infertility, subsection 8.3 is not required in labeling.

DISCUSSION AND CONCLUSIONS

Pregnancy

Topical tretinoin has teratogenic effects in animal models. Data from the literature and the applicant's database from the past >20 years do not demonstrate a clear association of topical tretinoin with major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Limited published cases in the literature describing birth defects do not establish a pattern of retinoid embryopathy.

Lactation

Data on the safety of topical tretinoin during lactation are lacking, but systemic absorption is low and infant exposure is expected to be minimal. DPMH recommends the following language be added to labeling,

The developmental and health benefits of breastfeeding should be considered along with

the mother's clinical need for ALTRENO lotion and any potential adverse effects on the breastfed infant from the ALTRENO lotion or from the underlying maternal condition.

DPMH agrees with the applicant's proposal to add a (b) (4)

Females and Males of Reproductive Potential

There are no data on topical tretinoin and infertility or interaction with hormonal contraceptives. Since data do not provide a clear association of risk with topical use of tretinoin during pregnancy, pregnancy testing and contraception subheadings will not be added to labeling.

DPMH recommends (b) (4)

LABELING RECOMMENDATIONS

DPMH revised sections 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----USE IN SPECIFIC POPULATIONS-----

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published observational studies of topical tretinoin in pregnant women have not established a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are no data on ALTRENO use in pregnant women. The systemic levels following topical administration are substantially lower than with oral tretinoin; however, absorption of this product may result in fetal exposure. There are rare reports of major birth defects similar to those seen in infants exposed to oral retinoids, but these case reports do not establish a pattern or association with tretinoin-related embryopathy.

Animal reproduction studies have not been conducted with ALTRENO (b) (4). Topical administration of tretinoin in a different formulation to pregnant rats during organogenesis was associated with malformations (craniofacial abnormalities [hydrocephaly], asymmetrical thyroids, variations in ossification, and increased supernumerary ribs) at doses up to 0.5 mg tretinoin/kg/day, approximately 2-times the maximum recommended human dose (MRHD) based on body surface area (BSA) comparison and assuming 100% absorption. Oral administration of tretinoin to pregnant cynomolgus monkeys during organogenesis was associated with malformations at 10 mg/kg/day (approximately 100-times the MRHD, based on BSA comparison and assuming 100% absorption) (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, (b) (4) other

adverse outcomes.

(b) (4) background risk

(b) (4)

Data

Human Data

While available studies cannot definitively establish the absence of risk, published data from multiple prospective controlled observational studies on the use of topical tretinoin products during pregnancy have not identified an association with topical tretinoin and major birth defects or miscarriage. The available studies have methodological limitations, including small sample size and in some cases, lack of physical exam by an expert in birth defects. There are published case reports of infants exposed to topical tretinoin during the first trimester that describe major birth defects similar to those seen in infants exposed to oral retinoids; however, no pattern of malformations has been identified and no causal association has been established in these cases. The significance of these spontaneous reports in terms of risk to the fetus is not known.

Animal Data

Tretinoin in a 0.05% gel formulation was topically administered to pregnant rats during organogenesis at doses of 0.1, 0.3 and 1 g/kg/day (0.05, 0.15, 0.5 mg tretinoin/kg/day). Possible tretinoin malformations (craniofacial abnormalities (hydrocephaly), asymmetrical thyroids, variations in ossification, and increased supernumerary ribs) were observed at maternal doses of 0.5 mg tretinoin/kg/day (approximately 2 times the MRHD based on BSA comparison and assuming 100% absorption). These findings were not observed in control animals. Other maternal and reproductive parameters in tretinoin treated-animals were not different from control. For purposes of comparison of the animal exposure to human exposure, the MRHD is defined as 4 g of ALTRENO (b) (4) applied daily to a 60 kg person.

Other topical tretinoin embryofetal development studies have generated equivocal results. There is evidence for malformations (shortened or kinked tail) after topical administration of tretinoin to pregnant Wistar rats during organogenesis at doses greater than 1 mg/kg/day (approximately 5 times the MRHD based on BSA comparison and assuming 100% absorption). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day (approximately 50 times the MRHD based on BSA comparison and assuming 100% absorption) was topically applied to pregnant rats during organogenesis. Supernumerary ribs have been a consistent finding in rat fetuses when pregnant rats were treated topically or orally with retinoids.

Oral administration of tretinoin during organogenesis has been shown to induce malformations in rats, mice, rabbits, hamsters and nonhuman primates. Fetal malformations were observed when tretinoin was orally administered to pregnant Wistar rats during organogenesis at doses greater than 1 mg/kg/day (approximately 5 times the MRHD based on BSA comparison). In the cynomolgus monkey, fetal malformations were reported when an oral dose of 10 mg/kg/day was administered to pregnant monkeys during organogenesis (approximately 100 times the MRHD based on BSA comparison). No fetal malformations were observed at an oral dose of 5 mg/kg/day (approximately 50 times the MRHD based on BSA comparison). Increased skeletal variations were observed at all doses in this study and dose-related increases in embryoletality and abortion were reported in this study. Similar results have also been reported in pigtail macaques.

Oral tretinoin has been shown to be fetotoxic in rats when administered at doses 10 times the MRHD based on BSA comparison. Topical tretinoin has been shown to be fetotoxic in rabbits when administered at doses 4 times the MRHD based on BSA comparison.

8.2 Lactation

Risk Summary

There are no data on the presence of topical tretinoin in human milk, the effects on the breastfed infant or the effects on milk production. It is not known whether topical administration of tretinoin could result in sufficient systemic absorption to produce detectable (b) (4) in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ALTRENO (b) (4) and any potential adverse effects on the breastfed (b) (4) from the ALTRENO (b) (4).

(b) (4)

17 PATIENT COUNSELING INFORMATION

(b) (4)

APPENDIX A

Table 2. Studies of Topical Tretinoin and Pregnancy*

Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; to what drug/dose	Pregnancy/infant outcomes	Comments/limitations
Loureiro KD, et al. ²⁷ 2005 California Teratogen Information Service	Prospective, controlled observational study	106 exposed pregnant women; 389 pregnant controls	First trimester exposure to topical tretinoin	No significant differences between groups (exposed vs control) for spontaneous abortion (6.5% vs 8% p=0.53); major birth defects (2.2% vs 1.2%, p=0.62); or minor birth defects (12.9% vs 9.9%, p=0.51)	Included 62 exposed infants examined by dysmorphologist
Shapiro L, et al. ²⁸ 1997 Motherisk, Canada	Prospective, controlled, observational study	94 exposed pregnant women; 133 pregnant controls	First trimester exposure to topical tretinoin	No difference in spontaneous abortion (p=0.63), elective terminations (p= 0.69), or major birth defects (p=0.30)	Reports by mother and pediatricians, no examination by dysmorphologist
Jick SS, et al. ²⁹ 1993 USA	Retrospective medical/pharmacy records review	215 exposed pregnant women; 430 age-matched pregnant controls	First trimester exposure (defined as obtaining a prescription for topical tretinoin 4 months before and 3 months after conception)	Prevalence of major anomalies in exposed women was 1.9% compared to controls 2.6. RR=0.7, 95% CI 0.2-2.3)	Unclear if prescriptions were actually used, concomitant medication/illnesses not reported
Navarre-Belhassen ³⁰ 1998	Case report	Infant born at 40 weeks' gestation	First trimester exposure (gestational months 1 and 2) to topical tretinoin 0.05% and benzoyl peroxide 2.5%, and doxycycline 100 mg bid	Coarctation of the aorta, hypoplastic left hand, hypertelorism, small ear canals	

²⁷ Loureriro KD, et al. Minor malformations characteristic of the retinoic acid embryopathy and other birth outcomes in children exposed to topical tretinoin during early pregnancy. *Am J Med Genetics* 2005;136A:117-121.

²⁸ Shapiro L, et al. Safety of first-trimester exposure to topical tretinoin: prospective cohort study. *Lancet*. 1997;350:1143-1144.

²⁹ Jick SS, et al. First trimester topical tretinoin and congenital disorders. *Lancet*. 1993;341:1181-1182.

³⁰ Navarre-Belhassen C, et al. Multiple congenital anomalies associated with topical tretinoin. *Ann Pharmacothera*. 1998;32(4):505-6.

Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; to what drug/dose	Pregnancy/infant outcomes	Comments/limitations
Lipson AH ³¹ 1993 Australia	Case report	Female infant (gestational age not reported)	Pre-conception and first trimester (up to week 5 gestation) to topical tretinoin 0.05% with 45% alcohol	Supraumbilical exomphalos, anterior diaphragmatic hernia, inferior pericardial defect, dextroposition of the heart, right sided upper limb reduction defect (hypoplastic scapula and humerus, absence of the radius and ulna, fused fourth and fifth digits and hypoplastic hand)	
Selcen D, et al. ³² USA	Case report	Infant born at 41 weeks' gestation	Prior to conception and first trimester to topical tretinoin 0.025%	Absence of right ear and external auditory canal, cerebral calcification right posterior hemisphere, encephalomalacia right parietooccipital lobe, infarct of basal ganglia	Father also using oral isotretinoin prior to conception
Colley SM, et al. ³³ 1998 Australia	Case report	Female infant born at term	Exposure throughout pregnancy to topical tretinoin 0.05%	Cleft lip and palate, fused palpebral fissures, hypertelorism, depressed nasal bridge and deficient left nares, optic tract dysgenesis, arrhinencephalopathy, agenesis of the corpus callosum, fornices, and	

³¹ Lipson AH, et al. Multiple congenital defects associated with maternal use of topical tretinoin. *Lancet* 1993;341:1352-3.

³² Selcen D, et al. Otocerebral anomalies with topical tretinoin use. *Brain and Development*. 2000;22:218-220.

³³ Colley SM, et al. Topical tretinoin and fetal malformations. *Med J Australia*. 1998;168(9):467.

Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; to what drug/dose	Pregnancy/infant outcomes	Comments/limitations
				cingulate gyri and hydrocephalus.	
Camera G and Pregliasco P ³⁴ 1992 Italy	Case report	Infant born at 41 weeks' gestation	Exposure before conception and up to 11 weeks' gestation tretinoin 0.05% cream	Hypoplastic ear, atresia of external auditory meatus	
Autret et al. ³⁵ 1997 France	Case report	Termination at 22 weeks	Exposure before conception and up to 13 weeks' gestation adapalene 0.1% gel	Anophthalmia agenesis of the optic chiasma	
Chen C, et al. ³⁶	Open-label, multiple dose pharmacokinetic study	18 non-pregnant female patients between ages 18-45	42 days of isotretinoin cream 0.1% 0.3 g on 300 cm ² face or 0.15 g on each forearm. Blood samples taken at baseline and day 42	Levels of tretinoin increased by an average of 1.7% at day 42 over the baseline level	

*Reviewer's Table

³⁴ Camera G and Pregliasco P. Ear malformation in baby born to mother using tretinoin cream. *Lancet*. 1992;339:687.

³⁵ Autret E, et al. Anophthalmia and agenesis of optic chiasma associated with adapalene gel in early pregnancy. *Lancet*. 1997;350:339.

³⁶ Chen C, et al. Negligible systemic absorption of topical isotretinoin cream: implications for teratogenicity. *J Clin Pharmacol*. 1997;37:279-284.

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/s/

CATHERINE A ROCA
05/25/2018

MIRIAM C DINATALE
05/25/2018

LYNNE P YAO
06/02/2018

Clinical Inspection Summary

Date	May 24, 2018
From	Bei Yu, Ph.D., Reviewer Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Angela Brown, Regulatory Project Manager Melinda McCord, M.D., Clinical Reviewer Gordana Diglisic, M.D., Clinical Team Leader Division of Dermatology and Dental Products (DDDP)
NDA #	209353
Applicant	Dow Pharmaceutical Sciences, Inc
Drug	Tretinoin
NME	No
Review Priority	Standard Review
Proposed Indication	Acne Vulgaris
Consultation Request Date	January 4, 2018
Summary Goal Date	June 8, 2018
Action Goal Date	Aug 10, 2018
PDUFA Date	Aug 27, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Eichenfeld, and Jazayeri were inspected in support of NDA 209353. Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites and as reported by the sponsor to the NDA appear acceptable in support of the respective indication.

The final compliance classification for the inspection of Dr. Eichenfeld is No Action Indicated (NAI). The preliminary compliance classification of Dr. Jazayeri is NAI.

II. BACKGROUND

The Applicant submitted this NDA to support the use of tretinoin lotion, 0.05% (IDP-121 lotion) for the treatment of acne vulgaris in patients 9 years of age and older. Inspections were requested for the following two identical protocols in support of this application:

V01-121A-301 and **V01-121A-302**, both entitled “A Phase 3, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, 2-Arm, Parallel Group Comparison Study Comparing the Efficacy and Safety of IDP-121 and IDP-121 Vehicle Lotion in the Treatment of Acne Vulgaris”.

Study 301 was conducted at 42 clinical sites in the U.S. (40 sites) and El Salvador (2 sites) between November 2015 and February 2017. A total of 820 subjects were enrolled. Study 302 was conducted at 36 clinical sites in the U.S. (34 sites), Dominican Republic (1 site), and Honduras (1 site) between November 2015 and February 2017. A total of 820 subjects were enrolled.

The two identical studies were randomized, double-blind, parallel-group, multicenter studies designed to assess the safety and efficacy of tretinoin lotion in comparison with its vehicle for treatment of acne vulgaris in patients 9 years of age and older. Eligible subjects were randomized in a 1:1 ratio to receive once daily application of either IDP-121 lotion or IDP-121 vehicle lotion. The duration of treatment was 12 weeks.

The co-primary efficacy endpoints were:

1. Absolute change in the mean noninflammatory lesion count from baseline to Week 12
2. Absolute change in the mean inflammatory lesion count from baseline to Week 12
3. Percentage of subjects who had a least a 2-grade reduction at Week 12 from baseline in the EGSS and had an EGSS at Week 12 that equated to “clear” or “almost clear” (considered “treatment success”)

Rationale for Site Selection:

Both sites were selected due to high site efficacy effect, and no prior clinical inspection.

III. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol # / # of Subjects Enrolled	Inspection Dates	Compliance Classification
Site #202 Eichenfield, Lawrence 8010 Frost Street #600 San Diego, CA 92123	V01-121A-302 Subjects: 28	16 - 19 April 2018	NAI
Site #115 Jazayeri, Sadra 4045 East Bell Road, Suite 125 Phoenix, AZ 85032	V01-121A-301 Subjects: 28	30 April - 3 May 2018	NAI*

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

* Pending: Classification is preliminary pending receipt of the EIR and issuance of correspondence to the inspected entity. An addendum to the Clinical Inspection Summary will be issued if the finalized EIR differs significantly from the draft EIR received from the ORA investigator.

Clinical Investigator Sites**1. Lawrence F. Eichenfield, M.D.**

At this site for Protocol V01-121A-302, a total of 39 subjects were screened and 28 subjects were enrolled, 23 of whom completed the study. The informed consent forms for all 39 screened subjects were reviewed to ensure that subjects were properly consented.

The records for all enrolled subjects were reviewed. These included, but were not limited to, medical records, IRB/CI correspondences, source documents, subject diaries, and test article accountability logs. The co-primary efficacy endpoints data were verifiable. There was no evidence of underreporting of adverse events.

A Form FDA 483 was not issued at the conclusion of the inspection.

2. Sadra Sasha Jazayeri, M.D.

At this site for Protocol V01-121A-301, 28 subjects were screened and enrolled, 26 of whom completed the study. The informed consent forms for all 28 screened subjects were reviewed to ensure that subjects were properly consented.

The records for all enrolled subjects were reviewed. These included, but were not limited to, source documents, case report forms, subject eligibility, drug accountability logs, and sponsor correspondence. The co-primary efficacy endpoints data were verifiable. There was no evidence of underreporting of adverse events.

A Form FDA 483 was not issued at the conclusion of the inspection.

{See appended electronic signature page}

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OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague

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/s/

BEI YU
05/24/2018

JANICE K POHLMAN
05/25/2018

KASSA AYALEW
05/25/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 3, 2018
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 209353
Product Name and Strength:	Altreno (tretinoin) lotion, 0.05%
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Dow Pharmaceutical Sciences, Inc.
FDA Received Date:	October 27, 2017 and January 19, 2018
OSE RCM #:	NDA 209353
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 REASON FOR REVIEW

The Division of Dermatology and Dental Products (DDDP) requested that we review the proposed container labels, carton labeling, and Prescribing Information (PI) for Altreno (tretinoin), NDA 209353, submitted by Dow Pharmaceutical Sciences, Inc. on October 27, 2017 to determine if it is acceptable from a medication error perspective. On January 19, 2018, the Applicant submitted a revised PI that included replacing the NDC placeholder with the NDC number in the HOW SUPPLIED section and an updated “manufactured for” company name.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA reviewed the proposed container labels, carton labeling, and PI to determine whether there are any significant concerns in terms of safety related to preventable medication errors. DMEPA finds the PI acceptable from a medication error perspective. However, we note the container label and carton labeling can be revised to specify the National Drug Code (NDC) number and ensure the lot number and expiration date are differentiated and in a format that would minimize confusion. We also did not locate a linear barcode on the container label.

4 CONCLUSION & RECOMMENDATIONS

DMEPA finds the PI acceptable from a medication error perspective. We conclude that the proposed container labels and carton labeling can be improved to increase the clarity of information to promote the safe use of the product and provide our recommendations in Section 4.1 below.

4.1 RECOMMENDATIONS FOR DOW PHARMACEUTICAL SCIENCES, INC.

We recommend the following be implemented prior to approval of this NDA:

- A. All Container Labels and Carton Labeling
 - a. As currently presented, the National Drug Code (NDC) number is denoted by a placeholder (XXXXX-XXX-XX). We request that you add the intended numbers to the labels and labeling in accordance with 21 CFR 201.2. Please ensure the NDC number for the professional samples is a unique NDC number per 21 CFR 207.33.
 - b. Revise the “Manufactured for” site, (b) (4) with “Dow Pharmaceutical Sciences” to match the updated Prescribing Information.
 - c. Ensure that the lot number and expiration date are presented in accordance with 21 CFR 201.10(i) and 21 CFR 201.17, and that they are clearly differentiated from one another.¹ As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use (see below for examples):
 - i. DDMMYYYY (e.g., 31JAN2013)
 - ii. MMMYYYY (e.g., JAN2013)
 - iii. YYYY-MMM-DD (e.g., 2013-JAN-31)
 - iv. YYYY-MM-DD (e.g., 2013-01-31)
- B. Container Label
 - a. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product’s linear barcode to each individual container label as required per 21CFR 201.25(c)(2). We also ask that you add a linear barcode to the Professional Sample Container Label if possible.

¹ Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Altreno received on October 27, 2017 and January 19, 2018 from Dow Pharmaceutical Sciences, Inc.

Table 2. Relevant Product Information for Altreno	
Initial Approval Date	N/A
Active Ingredient	tretinoin
Indication	treatment of acne vulgaris
Route of Administration	topical
Dosage Form	lotion
Strength	0.05%
Dose and Frequency	apply a thin layer once daily, (b) (4) (b) (4)
How Supplied	opaque, pale yellow topical lotion and available as 45 g tube (and 3 g professional sample)
Storage	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F)
Container Closure	n/a

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 15, 2018, we searched DMEPA's previous reviews using the terms, 'altreno' and "NDA 209353". Our search did not identify any previous label and labeling reviews.

APPENDIX C. HUMAN FACTORS STUDY – N/A

APPENDIX D. ISMP NEWSLETTERS – N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) – N/A

APPENDIX F. OTHER – N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Altreno labels and labeling submitted by Dow Pharmaceutical Sciences, Inc.

- Container label received on October 27, 2017 and January 19, 2018
- Carton labeling received on October 27, 2017
- Professional Sample Container Label received on October 27, 2017
- Professional Sample Carton Labeling received on October 27, 2017
- Prescribing Information (Image not shown) received on January 19, 2018

G.2 Label and Labeling Images

Container Label

(b) (4)



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

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/s/

MADHURI R PATEL
04/03/2018

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04/03/2018