

Investigating Safety Signals:
Non-Prescription Retinoids versus Prescription Tretinoin

by

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INVESTIGATING SAFETY SIGNALS OF RETINOIDS

Dedication

To the dear memory of Sylvester John and Anne Marie Marlett

To my dear husband Raymond, the love of my life you - are my rock!

To my three beautiful boys Jacob, Zachary and Matthew, I love you to the moon and back!

Always do your best and finish what you start!

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This study was performed by examination of public data listed in the FDA's Center for Food Safety and Applied Nutrition's Adverse Event Reporting System thus was not subject to review by an internal review board.

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Abstract

Today's cosmetic market is a booming enterprise. Considering the advances achieved by the industry (surgical procedures, high tech laser devices, cosmetics and combination cosmetic-drugs) and the projected market growth expected, the Food and Drug Administration's (FDA) regulatory muscle to has not kept pace. Legislation has essentially stayed the same since enactment of the 1938 Food, Drug and Cosmetic Act. The cosmetic industry is essentially self-policing when it comes to assuring consumer safety. This has prompted the FDA's Center for Food Safety and Applied Nutrition (CFSAN) to establish the CFSAN Adverse Event Reporting System (CAERS). In addition to food and nutritional supplements, this tool helps monitor for cosmetic safety by enabling manufactures, health professionals, and individuals to voluntarily report adverse events (AEs). From a subset of AE reports for retinoid-containing cosmetic (RCC) products extracted from CAERS cosmetic data, it was possible (using qualitative assessments), to demonstrate over-the-counter (OTC) retinoid products exhibit AE symptoms types like those experienced with prescription (Rx) tretinoin (retinoic acid) use. This study identified a higher rate of AEs, similar to side effects of tretinoin (expressed as frequency of occurrence), for OTC RCC products versus the entire set of *all*-cosmetic AEs reported to CAERS. The safety signal was validated by confirming the RCC subset also generated AE symptoms of contact dermatitis at a higher level (again expressed as frequency of occurrence) than did the complete *all*-cosmetic data set. This was done to assure the safety signal was real, not just occurring at a background level of contact dermatitis associated for cosmetic AEs at large (as suggested by Cary et al.). Data obtained from CAERS showed that even less potent OTC retinoids can, and do, exhibit side effects usually associated with the more potent Rx based tretinoin.

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Introduction

Background

Aging well is an ideal that drives Baby Boomers and Gen-Xers to remain vital and invest in ways that maintain or restore youth. This ideal also motivates Millennials to take preventative measures to protect and preserve their youthful appearance. The global anti-aging business is a thriving, multifaceted \$42.51 billion enterprise which is expected to grow by an annual rate of 5.3% over the next 4 years (Orbis, 2018). According to the market research company, Future Market Insights (2018), the anti-wrinkle segment alone is predicted to hit \$12.8 billion by 2027. The anti-aging market encompasses expensive, invasive, surgical procedures, less invasive high-tech devices, aesthetic services, and usually less expensive anti-aging, personal-care, cosmetic products. Consumer demand for efficacious, youth-promoting products continues to drive technology and product innovation. Such innovation has led to the development of novel drug products employed to impart specific anti-aging outcomes (e.g., anti-wrinkle, even-toning, or smoothing effects). Tretinoin (retinoic acid), initially marketed as an acne treatment medication known by the trade name Retin-A[®] and now, also as Renova[®] for the treatment of fine wrinkles, is a good example of such a product (DPT Laboratories, 2012; Valeant Pharmaceuticals North America LLC, 2018; Ortho Pharmaceuticals, 2012).

Cosmetics, Drugs, Cosmeceuticals

In more recent years the cosmetic industry has seen the rise of more efficacious products given the designation “cosmeceuticals” - those products that straddle the line of a combination cosmetic-pharmaceutical (drug) product. Interestingly, the Food and Drug Administration (FDA) does not formally recognize the term “cosmeceutical” within a legal framework (FDA, 2018, “Is it a cosmetic, a drug, or both?”) A cosmetic, which was defined by section 201(i) of

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the 1938 Food, Drug and Cosmetic Act (FD&C Act), is recognized by the FDA as any product “intended to be applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance without affecting the body's structure or functions,” whereas a drug is considered “a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease” [and] “articles (other than food) intended to affect the structure or any function of the body of man” (FDA, 2018, “Summary of cosmetics labeling requirements,” “Legal definition of cosmetics,” para. 1; FDA, 2018, “Is it a cosmetic, a drug, or both?” “How does the law define a drug?” para. 1). Products like fluorinated toothpaste, lotions containing sunscreen, and antiperspirant deodorants are examples of well-established, efficacious, over-the-counter (OTC) combination products. However, many highly-efficacious, newer cosmetic-drug combination products developed for the cosmetic industry are not OTC. For the serious, anti-aging, cosmetic consumer, FDA approved drug-cosmetics are often expensive and inconvenient to obtain, as a patient must first visit a physician before obtaining a prescription (Rx) for such products.

Cosmetic Safety Issues

Public demand to self-treat or reduce the visible signs of aging using less potent, thus less expensive, but generally perceived as safer OTC options, continue to push cosmetic development and anti-aging market growth. Cosmetic manufacturers strive to incorporate new, scientifically-advanced, active ingredients into cosmetic and personal care formulations as viable alternatives for efficacious, anti-aging, youth-promoting products. Retinol and other retinoid compounds like retinyl-palmitate, -acetate, -linaloolate or retinaldehyde are examples of such ingredients. And while the FDA does not rigorously “approve” cosmetics or their ingredients prior to marketing, it does advise personal care manufacturers to perform toxicology evaluation or other necessary

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testing to sufficiently verify product safety (FDA, 2018, “Summary of cosmetics labeling requirements”). Cosmetic products that fail safety assessment, yet reach the market, can be “misbranded and may be subject to regulatory action unless the label bears the following statement: Warning--The safety of this product has not been determined. Sec. 21 CFR 740.10” (FDA, 2018, “Summary of cosmetics labeling requirements,” “Label warnings,” para. 2). A potential concern arises when a consumer reports an adverse reaction to the manufacturer, but the manufacturer is not required to report this to the FDA (FDA, 2017, “Using adverse event reports to monitor cosmetic safety”). Those who use such a product may experience harm if a significant safety issue or signal is ignored by a manufacturer.

Monitoring Cosmetic Safety

To help monitor the cosmetic product landscape, the FDA’s Center for Food Safety and Applied Nutrition (CFSAN) established the CFSAN Adverse Event Reporting System (CAERS), a database whereby consumers, medical professionals, or manufacturers can voluntarily report any adverse events or label/packaging issues relating to food, dietary supplements, or cosmetics (FDA, 2017, “FDA begins posting adverse event report data for foods and cosmetics”; FDA, 2019). In the spirit of further promoting public safety, on December 6, 2016, the FDA opened access to basic (semi-limited) CAERS data obtained from January 2004 until June of 2016, which has recently been updated to include reports up to March of 2019 (FDA, 2017, “FDA begins posting adverse event report data for foods and cosmetics”; FDA, 2019). The FDA uses the publicly available data from this surveillance forum to help recognize safety signals related to various food, dietary supplements, and cosmetic products which may require additional safety investigation (FDA, 2019). Since the establishment of this system the FDA has worked to promote use of, and educate the public, the healthcare industry (physicians, pharmacists), and

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product manufacturers about the value of voluntary reporting (FDA, 2017, “FDA begins posting adverse event report data for foods and cosmetics”).

Objectives

For this study cosmetic data was extracted from the CAERS database and was used to investigate adverse event (AE) symptom profiles of OTC retinol and retinoid-containing facial skincare type products, to determine if there is a qualitative difference to side effects/adverse reactions reported on the drug product label for FDA “approved” Rx Tretinoin (Renova[®] and Retin-A[®]). This study will also assess why any differences or similarities may exist between the OTC retinoid containing cosmetics and Rx-based tretinoin products.

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Methods

Extracting Safety Data from CAERS

Cosmetic adverse event report data was obtained on July 11, 2019 from the U.S. Food & Drug Administration CFSAN Adverse Event Reporting System website available at the following URL:

<https://www.fda.gov/food/compliance-enforcement-food/cfsan-adverse-event-reporting-system-caers>

The total data available from January 2004 to March 2019 was extracted from the two ASCII downloadable files found under the CAERS Data Files section:

Download CAERS ASCII January 2004 – December 2013 (CSV – 9.16 MB)

Download CAERS ASCII January 2014 – March 2019 (CSV – 12.6 MB)

The extracted data was saved as a Microsoft Excel workbook file which was filtered using the “Product Code” 53 (Description: Cosmetics) to display only the cosmetic related AE reports. The CAERS Jan 2004 - March 2019 Cosmetics-only Data (**CAERS 04-19 CD**) spreadsheet was again filtered multiple ways (secondary filters applied) in an attempt to extract youth promoting, anti-aging/anti-wrinkle, facial, skincare type products. The following secondary filters were applied to the “Product” column to extract for facial type product data: Acne (to capture products labeled to address acne), Anti Ag and Anti-Ag (to capture products labeled as anti-aging), Cream (to capture cream based products), Fac (to capture products labeled for face/facial application), Gel (to capture gel-based products), Lotion (to capture lotion based products), Moist (to capture products labeled to moisturize or as moisturizing), Serum (to capture serum based products), Retin (to capture Retinoid labeled products), and Wrinkl (to capture products labeled to address wrinkles/wrinkling). Each secondary filter search was manually screened to

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remove items *not* intended to leave on facial-skin or for treatment around eyes (e.g. shampoos, conditioners, depilatories, hair treatments, nail or body products, soaps, exfoliators, color cosmetics, foundations, mascaras, dyes, inks, etc. were deleted). Once a filtered spreadsheet contained eye and facial skincare items only, an internet Google search was performed for each product (according to information as listed in the “Product” column) to find a complete ingredient list. Product ingredient information was identified in various ways, including product manufacturing websites, distribution websites (Walmart[®], Target[®], QVC[®], etc.), and from images of listed ingredients on product boxes or labels on various e-platforms (Amazon[®], eBay[®], etc.). Ingredient lists were manually reviewed for any retinoid containing materials (e.g. retinol, retinyl-palmitate, retinyl-linaloolate, retinaldehyde, retinoytrimethylsilane, retinyl-acetate, retinyl-propionate, vitamin A and retinoic acid). Products *not* containing retinoids were deleted from the spreadsheet. Products whose information was too generic to provide unique identification (moisture cream vs. Olay Moisturizing Cream) were also deleted, as were products where ingredient data could not be found (mostly due to age). The final spreadsheet of remaining AE product reports identified the retinoid-containing cosmetic products which was used to perform further analysis (see **Appendix 1: Retinoid-Containing Cosmetic Products Reported to CAERS**).

Qualitative Comparisons of AE Data

From the retinoid-containing cosmetic (RCC) products spreadsheet (Appendix 1) a list was generated to log the number and type of AE *outcomes* reported for each product. From Appendix 1, another list was generated to record the number and type of every AE *symptom* (from the “MedDRA Preferred Terms” column of the spreadsheet) for each RCC product reported, which is summarized in **Appendix 2: AE Symptoms Reported to CAERS for RCC’s &**

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Corresponding AE Data for All-Cosmetics. [For additional background about MedDRA terminology refer to the MedDRA website at: <https://www.meddra.org/training-materials>]

From the **CAERS 04-19 CD** spreadsheet, the number of AE symptoms corresponding to the exact same *types* of AE symptoms (listed for the RCC products), were also extracted for *all*-cosmetics (see Appendix 2). Frequency of occurrence, expressed as a percentage, was determined for both the RCC- and *all*-cosmetic product AE symptoms (see Appendix 2).

The known side effects and adverse reactions associated with use of various brands of topical Rx tretinoin were identified from review of several product labels (generic Tretinoin, Renova, Retin-A). Similar effects were combined to create a list which was compared against AE symptom data in Appendix 2 to qualitatively assess similarities/difference between Rx tretinoin (Tretinoin, Renova, Retin A) and OTC facial skincare products reported to CAERS. The AE symptoms that equitably aligned were highlighted yellow in Appendix 2. A summary of the tretinoin aligning AE symptoms and data was tabulated, from which a frequency of occurrence plot was generated for both RCC products and for *all*-cosmetic products reported to CAERS.

Research to identify symptoms generally associated with contact dermatitis was also performed. The same comparative procedure outlined above was repeated using contact dermatitis symptoms instead of tretinoin effects. Those AE symptoms similar to dermatitis were marked with an asterisk (*) in Appendix 2. A summary of the dermatitis aligning AE symptoms and data was tabulated and a frequency of occurrence plot was again generated for both RCC products and for *all*-cosmetic products reported to CAERS.

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To assist with yearly trend analysis, the total number of overall product reports (every product type) was extracted from the entire CAERS data. This information was parsed by year and plotted along with the annual number of all-cosmetic products and the yearly number of RCC-products reported.

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Results

Identifying Retinoid Containing Cosmetics (RCCs)

From the entire FDA CAERS database ranging from January 2004 to March 2019, a total of 130,079 AE product reports *overall* were extracted on July 11, 2019. Of this total 34,362 AE product reports were attributed to cosmetic use. Within the cosmetics products subset (**CAERS 04-19 CD**), the number of RCC products were identified ultimately through screening of each of the secondary filter (Acne, Anti-ag, Cream, Fac, etc.) search results. These results are listed in

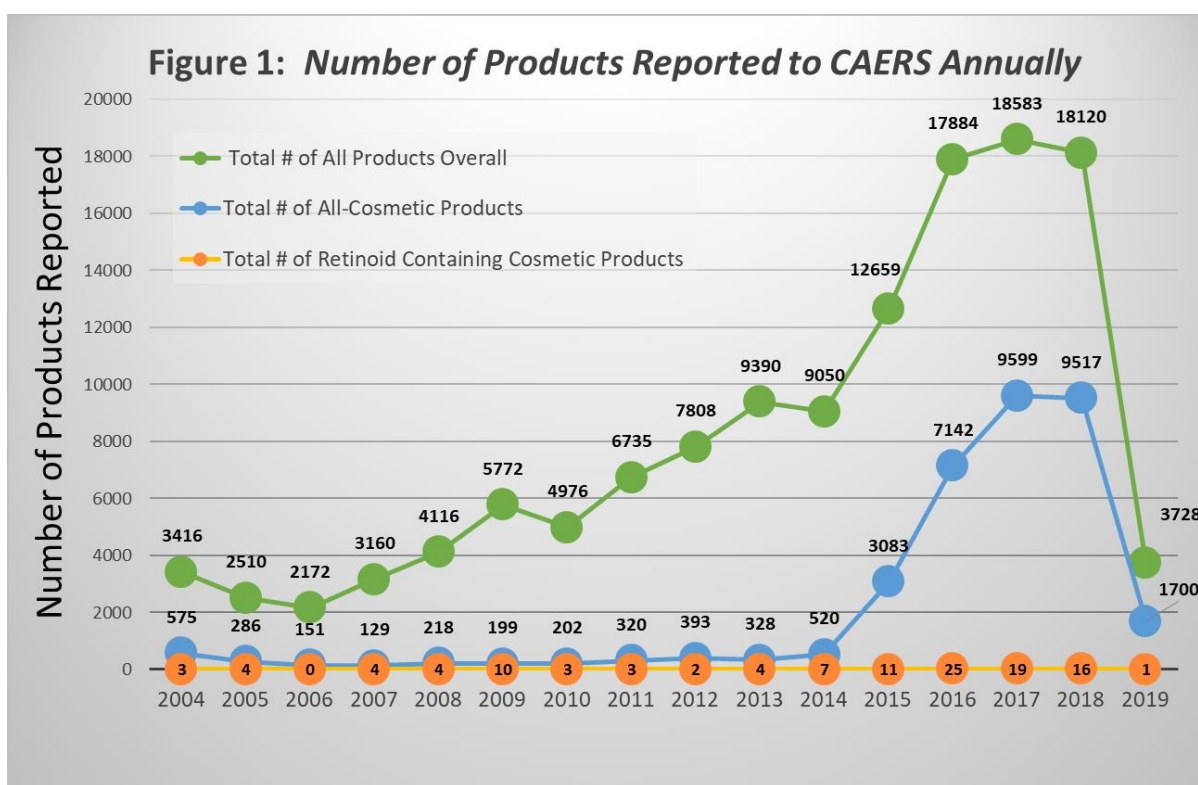
Table 1: Results of Secondary-Filter Searches.

| Search Category | # Skincare of Products Extracted | # of RCC Products Identified |
|------------------------|---|-------------------------------------|
| Acne | 5 | 2 |
| Anti Ag | 7 | 2 |
| Anti-Ag | 19 | 3 |
| Cream | 214 | 55 |
| Fac | 101 | 11 |
| Gel | 30 | 3 |
| Lotion | 23 | 0 |
| Moist | 85 | 9 |
| Retin | 14 | 12 |
| Serum | 106 | 34 |
| Winkl | 40 | 14 |
| Totals: | 644 | 145 |

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Yearly Trends

After the screened secondary-filter searches were combined and duplicate products removed, a total of 116 RCC product reports were ultimately identified (see **Appendix 1: Retinoid-Containing Cosmetic Products Reported to CAERS**). Yearly information of AE reports to the CAERS database for products *overall*, for *all*-cosmetic products and for RCC products is displayed in **Figure 1: Number of Products Reported to CAERS Annually**.



The *overall* AE reports show a moderate, general increase for the first 11-year period, while the *all*-cosmetic AE reports remains relatively flat during this same time. Both categories however, show a sharp increase from 2014 to 2016. For the products *overall*, the dietary supplements category generated most of the AEs during that time. For the cosmetics sector, the increase during this period was largely related to reports pertaining to hair care products. Reports for

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RCC products remain relatively flat with the exception of a spike in 2016, resulting mainly from submission of 17 reports pertaining to a serum-based product.

AE Outcomes

Of the total 116 retinoid-containing cosmetic AE reports, 149 total outcomes were documented (some AE reports recorded multiple outcomes) and are listed in **Table 2: AE Outcomes Reported for RCC Products**.

Table 2: AE Outcomes Reported for RCC Products

| # of Outcomes Reported | Type of Outcome |
|-------------------------------|--------------------------------------|
| 1 | Death |
| 3 | Disability |
| 21 | ER visit |
| 21 | Hospitalization |
| 1 | Intervention required |
| 2 | Life-threatening |
| 21 | Medically important |
| 51 | Other Outcome |
| 1 | Other seriousness |
| 26 | Patient visit to healthcare provider |
| 1 | Required intervention |
| 149 | Total |

Eleven different types of outcomes were identified with those of a more serious nature occurring much less frequently - disability representing 2.8% of the outcomes, life-threatening 1.3%, and one reported death outcome at 0.7%.

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AE Symptoms and Qualitative Assessments

Each of the 116 RCC AE reports recorded had one or more adverse reactions (symptoms described using “MedDRA preferred” terminology) in the CAERS database. From the 116 RCC product reports, 371 total adverse reactions (symptoms) were documented. These AEs were categorized into 109 different *types* of symptoms. For all RCC products, a list of the AE symptoms, the number of those symptoms reported, and their frequency of occurrence (in %) was determined. (See **Appendix 2: AE Symptoms Reported to CAERS for RCC’s & Corresponding AE Data for All-Cosmetics**) The same process above was applied to *all*-cosmetic product data. Of the 34,362 cosmetic AE product reports, a total of 65,070 individual adverse reactions were documented. The same 109 “MedDRA Preferred Term” AE symptom types (as listed for RCC’s) were extracted from this data set. The number of corresponding AE symptoms reported for *all*-cosmetic products, and their frequency of occurrence, are also listed in Appendix 2.

From the Rx product labels of Tretinoin, Renova[®], and Retin-A[®] (all Rx-based retinoic acids) 21 known side-effects or adverse reactions were identified as associated with normal use of topical tretinoin and they are listed in **Table 3: Side-Effects & Adverse Reactions of Rx Tretinoin** (DPT Laboratories, 2012; Ortho Pharmaceuticals, 2012; Valeant Pharmaceuticals North America LLC, 2018).

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Table 3: Side-Effects & Adverse Reactions of Rx Tretinoin

Items in bold text indicate side effects & adverse reactions more commonly experienced

| | |
|----|--|
| 1 | Acne |
| 2 | Blistering of Skin |
| 3 | Burning (Sensation) |
| 4 | Crusting of Skin |
| 5 | Discomfort |
| 6 | Dryness of Skin |
| 7 | Edema / Oedema / Swelling |
| 8 | Erythema (Redness) / Redness of Skin |
| 9 | Feeling of Warmth |
| 10 | Hyper-pigmentation |
| 11 | Hypo-pigmentation |
| 12 | Peeling |
| 13 | Potential for Genetic Toxicity |
| 14 | Potential for Fetotoxicity |
| 15 | Potential for Sun-exposure Induced Tumor Growth/Carcinogenesis |
| 16 | Potential for Teratogenesis |
| 17 | Pruritus (Itching) / Itching |
| 18 | Skin Irritation / Enhanced Irritation of Eczematous Skin |
| 19 | Skin Sensitivity / Enhanced Sunburn & Weather Sensitivity |
| 20 | Stinging |
| 21 | Urticaria (Hives) |

Symptoms can range from moderate to severe but of all those listed, issues most commonly experienced are, stinging/tingling, burning sensation, redness, swelling, feeling of warmth, dryness, itching, peeling, crusting, discomfort, and changes in color of pigmentation (including darkening or lightening of skin) (DPT Laboratories, 2012; Ortho Pharmaceuticals, 2012; Valeant Pharmaceuticals North America LLC, 2018; Mayo Clinic and IBM Watson Health, 2019).

From the qualitative assessment for similarities between Rx tretinoin compared to the 109 types of AE symptoms, as identified for OTC RCC- and all-cosmetic products, 49 AE symptoms

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relatively aligned with the side effects normally associated with Rx use. Those 49 AE symptoms were highlighted yellow in Appendix 2 and are summarized in **Table 4: AE Symptoms**

Qualitatively Similar to Rx Tretinoin Side-Effects. From the frequency of occurrence plot generated for both RCC- and all-cosmetic products aligning with tretinoin side effects, it is apparent that AEs similar to Rx tretinoin occur at a higher rate in RCC products than they do for all-cosmetics reported to CAERS. This is displayed in **Figure 2: AE Symptoms Qualitatively Similar to Rx Tretinoin Side-Effects: RCC's vs All-Cosmetics.**

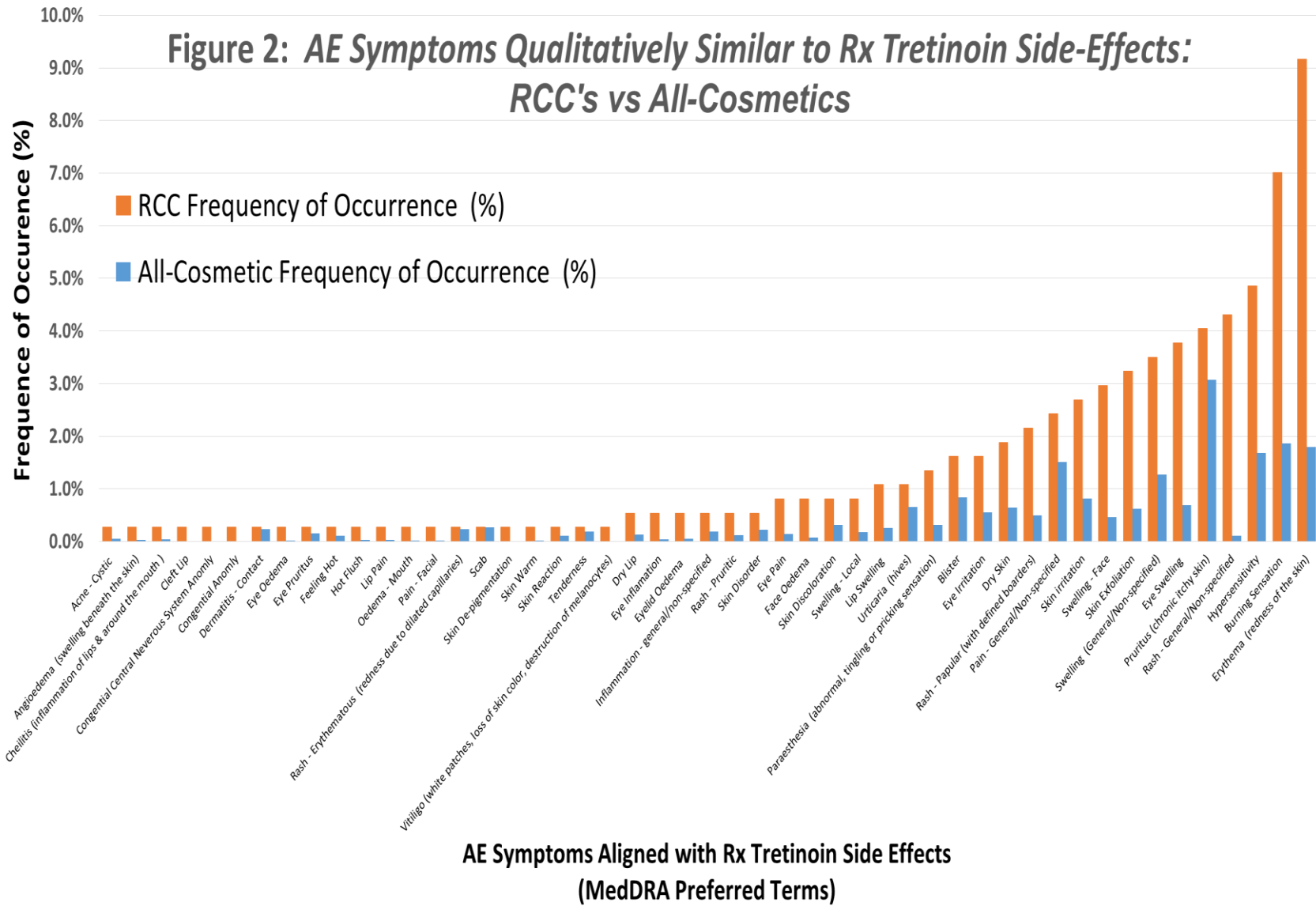
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Table 4: AE Symptoms Qualitatively Similar to Rx Tretinoin Side-Effects

| | RCC Frequency of Occurrence (%) | # of Symptoms for RCC Products | Type of AE Symptoms (as MedDRA Preferred Terms) | All- Cosmetics Frequency of Occurrence (%) | # of Symptoms for All-Cosmetic Products |
|----|--|--------------------------------------|--|---|---|
| 1 | 0.3% | 1 | Acne - Cystic | 0.06% | 36 |
| 2 | 0.3% | 1 | Angioedema (swelling beneath the skin) | 0.03% | 19 |
| 3 | 1.6% | 6 | Blister | 0.83% | 543 |
| 4 | 7.0% | 26 | Burning Sensation | 1.87% | 1216 |
| 5 | 0.3% | 1 | Cheilitis (inflammation of the lips and skin around the mouth) | 0.05% | 30 |
| 6 | 0.3% | 1 | Cleft Lip | 0.00% | 1 |
| 7 | 0.3% | 1 | Congenital Central Nervous System Anomaly | 0.00% | 1 |
| 8 | 0.3% | 1 | Congenital Anomaly | 0.00% | 1 |
| 9 | 0.3% | 1 | Dermatitis - Contact | 0.24% | 156 |
| 10 | 0.5% | 2 | Dry Lip | 0.13% | 86 |
| 11 | 1.9% | 7 | Dry Skin | 0.65% | 423 |
| 12 | 9.2% | 34 | Erythema (redness of the skin) | 1.80% | 1170 |
| 13 | 0.5% | 2 | Eye Inflammation | 0.04% | 29 |
| 14 | 1.6% | 6 | Eye Irritation | 0.56% | 363 |
| 15 | 0.3% | 1 | Eye Oedema | 0.02% | 13 |
| 16 | 0.8% | 3 | Eye Pain | 0.14% | 92 |
| 17 | 0.3% | 1 | Eye Pruritus | 0.16% | 101 |
| 18 | 3.8% | 14 | Eye Swelling | 0.69% | 446 |
| 19 | 0.5% | 2 | Eyelid Oedema | 0.06% | 37 |
| 20 | 0.8% | 3 | Face Oedema | 0.07% | 48 |
| 21 | 0.3% | 1 | Feeling Hot | 0.11% | 71 |
| 22 | 0.3% | 1 | Hot Flush | 0.03% | 19 |
| 23 | 4.9% | 18 | Hypersensitivity | 1.68% | 1096 |
| 24 | 0.5% | 2 | Inflammation - general/non-specified | 0.18% | 120 |
| 25 | 0.3% | 1 | Lip Pain | 0.03% | 20 |
| 26 | 1.1% | 4 | Lip Swelling | 0.25% | 164 |
| 27 | 0.3% | 1 | Oedema - Mouth | 0.01% | 9 |
| 28 | 0.3% | 1 | Pain - Facial | 0.02% | 14 |
| 29 | 2.4% | 9 | Pain - General/Non-specified | 1.51% | 980 |
| 30 | 1.3% | 5 | Paraesthesia (abnormal, tingling or pricking sensation) | 0.31% | 204 |
| 31 | 4.0% | 15 | Pruritus (chronic itchy skin) | 3.07% | 2000 |
| 32 | 0.3% | 1 | Rash - Erythematous (redness due to dilated capillaries) | 0.23% | 150 |
| 33 | 4.3% | 16 | Rash - General/Non-specified | 0.11% | 73 |
| 34 | 2.2% | 8 | Rash - Papular (with defined borders) | 0.50% | 323 |
| 35 | 0.5% | 2 | Rash - Pruritic | 0.12% | 77 |
| 36 | 0.3% | 1 | Scab | 0.27% | 176 |
| 37 | 0.3% | 1 | Skin De-pigmentation | 0.01% | 4 |
| 38 | 0.8% | 3 | Skin Discoloration | 0.31% | 204 |
| 39 | 0.5% | 2 | Skin Disorder | 0.23% | 148 |
| 40 | 3.2% | 12 | Skin Exfoliation | 0.63% | 407 |
| 41 | 0.3% | 1 | Skin Warm | 0.02% | 10 |
| 42 | 2.7% | 10 | Skin irritation | 0.82% | 531 |
| 43 | 0.3% | 1 | Skin Reaction | 0.11% | 72 |
| 44 | 3.0% | 11 | Swelling - Face | 0.46% | 301 |
| 45 | 3.5% | 13 | Swelling (General/Non-specified) | 1.27% | 829 |
| 46 | 0.8% | 3 | Swelling - Local | 0.18% | 115 |
| 47 | 0.3% | 1 | Tenderness | 0.19% | 125 |
| 48 | 1.1% | 4 | Urticaria (hives) | 0.66% | 427 |
| 49 | 0.3% | 1 | Vitiligo (white patches, loss of skin color, destruction of melanocytes) | 0.00% | 3 |

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**Figure 2: AE Symptoms Qualitatively Similar to Rx Tretinoin Side-Effects:
RCC's vs All-Cosmetics**



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From search results of symptoms for contact dermatitis from Mayo Clinic, the Merck Manual, and the American Academy of Allergy, Asthma and Immunology, 17 symptoms were identified as associated with this condition and are listed in **Table 5: Symptoms of Contact Dermatitis** (Gonzalez, 2017; Mayo Clinic, 2019; American Academy of Allergy, Asthma & Immunology [AAAAI], 2019).

| <i>Items in bold text indicate symptoms & adverse reactions more commonly experienced</i> | |
|---|---|
| 1 | Blistering of Skin |
| 2 | Burning (Sensation) |
| 3 | Cracking of Skin |
| 4 | Crusting of Skin |
| 5 | Discomfort |
| 6 | Dryness of Skin |
| 7 | Edema / Oedema / Swelling |
| 8 | Erythema (Redness) / Redness of Skin |
| 9 | Pain |
| 10 | Pruritus (Itching) / Itching |
| 11 | Rash |
| 12 | scaly,scabbing |
| 13 | Skin Irritation |
| 14 | Stinging |
| 15 | Tenderness |
| 16 | Ulceration |
| 17 | Wound secretion |

Symptoms can also range from moderate to severe but itching, burning, stinging, redness, and rash with swelling are the most typical symptoms experienced (Gonzalez, 2017; Mayo Clinic, 2019; AAAAI, 2019). From the qualitative assessment for similarities between contact dermatitis compared to the 109 types of AE symptoms identified for OTC RCC- and all-

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cosmetic products, 30 AE symptoms reasonably aligned with dermatitis symptoms. Those AE symptoms are indicated with an asterisk (*) in Appendix 2 and are summarized in **Table 6: AE Symptoms Qualitatively Similar to Dermatitis**.

Table 6: AE Symptoms Qualitatively Similar to Dermatitis

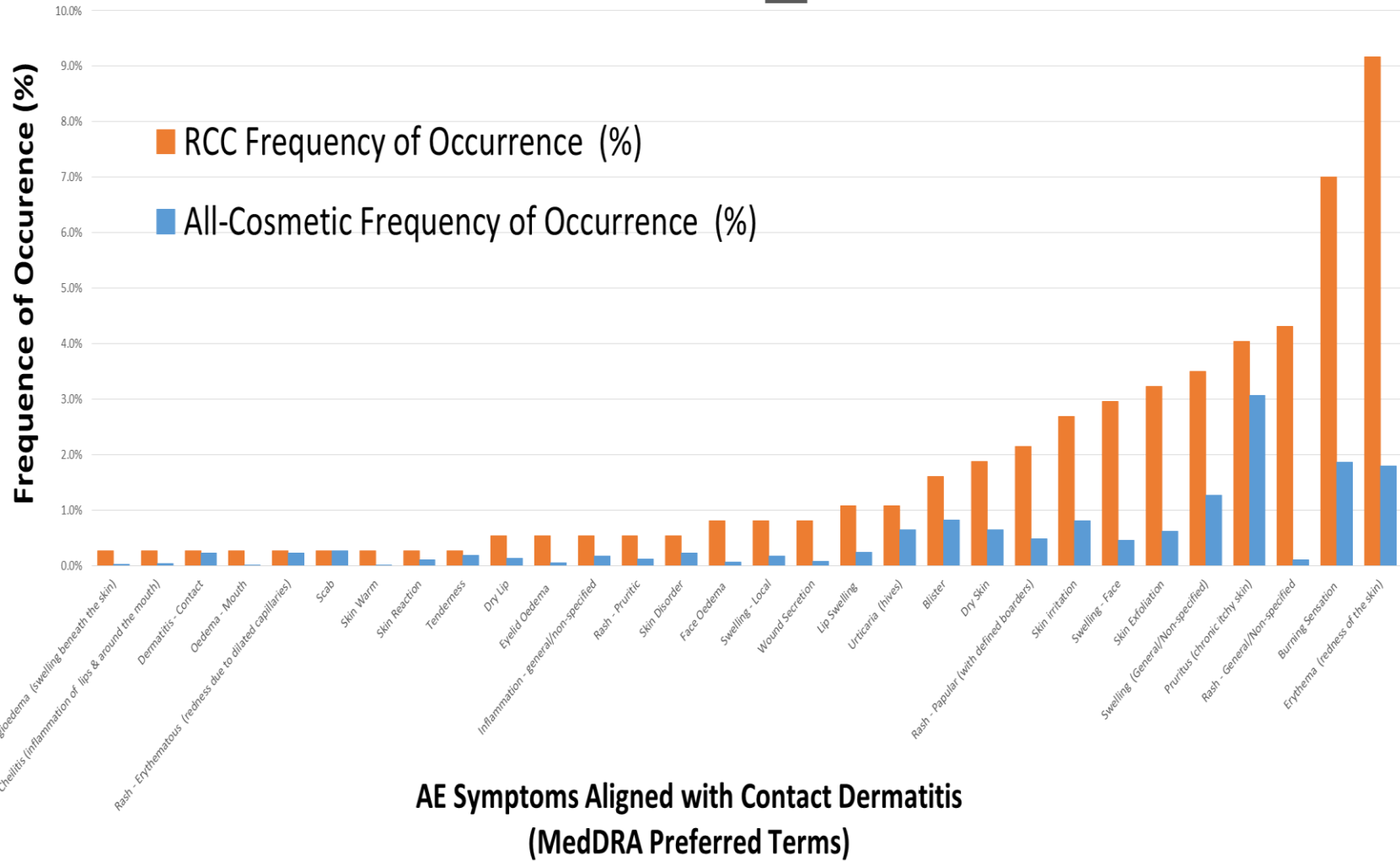
| | RCC Frequency of Occurrence (%) | # of Symptoms for RCC Products | Type of AE Symptoms (as MedDRA Preferred Terms) | All- Cosmetics Frequency of Occurrence (%) | # of Symptoms for All-Cosmetic Products |
|----|---------------------------------|--------------------------------|--|--|---|
| 1 | 0.3% | 1 | Angioedema (swelling beneath the skin) | 0.03% | 19 |
| 2 | 1.6% | 6 | Blister | 0.83% | 543 |
| 3 | 7.0% | 26 | Burning Sensation | 1.87% | 1216 |
| 4 | 0.3% | 1 | Cheilitis (inflammation of the lips and skin around the mouth) | 0.05% | 30 |
| 5 | 0.3% | 1 | Dermatitis - Contact | 0.24% | 156 |
| 6 | 0.5% | 2 | Dry Lip | 0.13% | 86 |
| 7 | 1.9% | 7 | Dry Skin | 0.65% | 423 |
| 8 | 9.2% | 34 | Erythema (redness of the skin) | 1.80% | 1170 |
| 9 | 0.5% | 2 | Eyelid Oedema | 0.06% | 37 |
| 10 | 0.8% | 3 | Face Oedema | 0.07% | 48 |
| 11 | 0.5% | 2 | Inflammation - general/non-specified | 0.18% | 120 |
| 12 | 1.1% | 4 | Lip Swelling | 0.25% | 164 |
| 13 | 0.3% | 1 | Oedema - Mouth | 0.01% | 9 |
| 14 | 4.0% | 15 | Pruritus (chronic itchy skin) | 3.07% | 2000 |
| 15 | 0.3% | 1 | Rash - Erythematous (redness due to dilated capillaries) | 0.23% | 150 |
| 16 | 4.3% | 16 | Rash - General/Non-specified | 0.11% | 73 |
| 17 | 2.2% | 8 | Rash - Papular (with defined boarders) | 0.50% | 323 |
| 18 | 0.5% | 2 | Rash - Pruritic | 0.12% | 77 |
| 19 | 0.3% | 1 | Scab | 0.27% | 176 |
| 20 | 0.5% | 2 | Skin Disorder | 0.23% | 148 |
| 21 | 3.2% | 12 | Skin Exfoliation | 0.63% | 407 |
| 22 | 0.3% | 1 | Skin Warm | 0.02% | 10 |
| 23 | 2.7% | 10 | Skin irritation | 0.82% | 531 |
| 24 | 0.3% | 1 | Skin Reaction | 0.11% | 72 |
| 25 | 3.0% | 11 | Swelling - Face | 0.46% | 301 |
| 26 | 3.5% | 13 | Swelling (General/Non-specified) | 1.27% | 829 |
| 27 | 0.8% | 3 | Swelling - Local | 0.18% | 115 |
| 28 | 0.3% | 1 | Tenderness | 0.19% | 125 |
| 29 | 1.1% | 4 | Urticaria (hives) | 0.66% | 427 |
| 30 | 0.8% | 3 | Wound Secretion | 0.08% | 55 |

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From the frequency of occurrence plot generated for both RCC- and all-cosmetic products which aligned with dermatitis symptoms, it is apparent that AEs similar to dermatitis occur at a higher rate in RCC products than they do for all-cosmetics reported to CAERS. This is graphically displayed in **Figure 3: AE Symptoms Qualitatively Similar to Dermatitis: RCC Products vs. All-Cosmetic Products.**

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Figure 3: AE Symptoms Qualitatively Similar to Dermatitis: RCC Products vs. All-Cosmetic Products



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Discussion

Retinoic Acid (Rx Tretinoin)

Retinoic acid, known generically as the prescription drug tretinoin, is a derivative of vitamin A. Of the class of compounds collectively known as retinoids, retinoic acid is the biologically active form which gives rise to the potency of the medication. Originally used in dermatology since the 1960s, and patented by Stephen Kligman as Retin-A[®] for the treatment of acne in 1973, it was further discovered in the 1980s by Kligman and his colleagues that this drug was also effective as a treatment for photo-aging (Dhatt, 2013; Mukherjee, Date, Patravale, Korting, Roeder, & Weindl, 2006). Today tretinoin commonly known as Retin-A[®] or Renova[®], and several other brand names, is also used to treat other signs of aging skin including rough facial skin, hyperpigmentation, fine lines, wrinkles, and rosacea (Mayo Clinic & IBM Watson Health [Mayo], 2019). Tretinoin is also utilized for “treatment of actinic keratosis, seborrhea, acne vulgaris, ichthyosis, psoriasis, lichen, precancerous lesions and skin melanomas” (Mriouah, 2012,” para. 9). The retinoic acid molecule can penetrate below the skin’s surface and bind with DNA by receptors which in turn stimulate genes, ultimately resulting in improved cell proliferation (Dhatt, 2013). This cellular turnover is what clarifies and brightens skin tone. Retinoic acid also helps to protect the structure of skin by preventing DNA damage which leads to collagen breakdown (Dhatt, 2013). The lower dermis is thickened which results in a smoothing effect, minimizing fine lines, and wrinkles (Dhatt, 2013). And while this potent retinoid carries out important functions regarding cell growth, keratinization, and desquamation, it also has harsh, irritating effects on skin, especially in the first few weeks of treatment (Mriouah, 2012; DPT Laboratories, 2012) The product label for Renova[®] even declares it as a “dermal irritant” for the 0.02% tretinoin cream (Ortho Pharmaceutical, 2012, “Warnings,” para.

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1). As an active ingredient retinoic acid is the most efficacious of the retinoids, but is also the most unstable, and has the most problematic side effects profile (Mukherjee et al., 2006).

Retinoids

Retinol, the purest form of Vitamin A, and other vitamin A derivatives like retinyl - palmitate, -acetate, -propionate, and retinaldehyde (retinal) were developed to provide similar anti-aging, anti-acne effects with less adverse reactions. Their use in cosmetics started in the mid-1980s. By 1995, Kang and associates demonstrated comparable efficacy of retinol therapy to mitigate photo-aging effects with reduced adverse reactions as well (Mukherjee et al., 2006). As a class, retinoids all work to effect cellular functions that control cell development, differentiation, surface changes, and immune response (Mukherjee et al., 2006). These derivatives offer milder options with respect to adverse skin reactions because they are precursors to the active form of retinoic acid. They must undergo enzymatic conversion by the skin to convert to the active moiety, retinoic acid. As Dhatt (2013) explains, the derivatives are less irritating and more stable the farther away they are on their metabolic pathway to retinoic acid conversion, however they are less potent as well. For example, retinol is 20 times less effective than retinoic acid (Kurlandsky, Xiao, Duell, Voorhees, & Fisher, 1994). “Retinyl palmitate is about 20 percent less potent than retinol, according to the website FutureDerm.com” (Nall, 2018). The enzymatic breakdown order that takes place in the skin to exhibit the desired efficacious result is as follows (Dhatt, 2013; Valiani, 2013; Nall, 2018):

[retinyl acetate→retinyl propionate→retinyl palmitate→retinol→retinaldehyde→retinoic acid]
 (most stable, least potent, mildest) (least stable, most potent, most irritating)

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Yet, despite their milder, less potent reputation, multiple studies show with steady, prolonged use they too can provide efficacious anti-aging outcomes often close to results obtained with Rx tretinoin (Mukherjee et al., 2006). These retinoids are also ultimately able to affect cell formation of the skin and work to diminish cellular build-up, to boost collagen production, to control acne, and minimize appearance of scars (Allison, 2015; Valiani, 2013). Interestingly, from a randomized, double-blind, controlled trial to evaluate differences between non-prescription tri-retinol 1.1% slow-release cream and 0.025% tretinoin cream, Ho and colleagues (2012) determined minimal difference in efficacy *and* adverse reactions between the products. Again, confirming that OTC retinoids can exhibit similar characteristics of the more potent Rx tretinoin. The list of adverse reactions (skin redness, itching, burning/stinging, dryness, and peeling) typically associated with use of retinoids is so common a condition that it's recognized as "retinoid-reaction" (Mukherjee et al., 2006, p. 342; DPT Laboratories, 2012). And while it is most associated with Rx based tretinoin, it also manifests with use of OTC retinoids as well.

OTC Retinoids vs. Rx Tretinoin

For this study, qualitative assessment reveals a fair amount of overlap between AE symptoms associated with OTC RCC products (identified from CAERS), compared to adverse reactions associated with topical Rx tretinoin (as listed in Table 3). Of the 109 *types* of AE symptoms experienced from use of RCC products, 45% (n=49) characteristically aligned with side effects listed on the product label for Rx tretinoin as shown in Appendix 2 and summarized in Table 4. From Figure 2, it's clear the most frequently occurring (highest rate of occurrence) AE symptoms for RCC's also closely match those more commonly known "retinoid-reaction"-type side effects of redness, burning/stinging, itching, dry skin and exfoliation (peeling of skin).

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Also, of a moderately high occurrence rate, are RCC AE symptoms that closely align to the more intense adverse reactions associated with tretinoin such as swelling, rash, blistering, hypersensitivity, and pain, or discomfort. Together this data, along with all the remaining RCC AE symptoms that qualitatively align (albeit at a lower percent frequency) to side-effects associated with tretinoin, would suggest that RCCs exhibit a similar safety concern for OTC facial skincare products. In order for this to be true, a comparison of the frequency of occurrence for RCC AE symptoms reported to CAERS would have to be *higher* than the frequency of occurrence for the exact same *types* of AE symptoms for all-cosmetics reported. Figure 2, a plot of the frequency of occurrence for RCC-products versus all-cosmetic products, against the 49 AE symptom types qualitatively similar to retinoic acid, clearly demonstrates this to be true.

Cosmetic Safety Concerns

Since enactment of the 1938 FD&C Act, there has been no significant evolution in regulations related to cosmetics to address the exponential growth and variation this market category has experienced. Presently, the law holds manufacturers responsible for assuring cosmetic ingredients they incorporate are safe for use. This means the industry is essentially self-policing. The lack of federal regulatory muscle to require that manufacturers ensure safety of their cosmetic products, report known safety issues associated with their use, or to force a recall of such products, has lead states like California and Hawaii to legislate regulations for the protection of their constituents. From individuals like senator Susan Collins of Maine, and Diane Feinstein from California (champions of the proposed Personal Care Products Safety Act), to groups like the Personal Care Products Council and the Environmental Working Group, there are

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many who advocate for regulatory change (“Senators propose a bill for greater cosmetic regulatory oversight,” 2015; “PCPC announces support for cosmetic safety,” 2015).

This need for change has been duly recognized by the FDA and was a motivating force for establishment of the CFSAN’s adverse event reporting system, CAERS. Since its inception the CAERS database has seen a steady rise in AE reporting. Yearly trend data from this study clearly shows an increase in AE reports for products overall (for all industry categories - food, dietary supplements, and cosmetics), and a fairly similar annual trend for the cosmetic industry segment (see Figure 1). However, from 2014 to 2016 there was a sharp increase in AE reports for both products *overall* and for the cosmetics industry segment. Increases for the overall curve came largely from a high volume of reporting form Industry Code 54 relating to vitamins, minerals and dietary supplements. According to Linda Katz, M.D., MPH, director for the Office of Cosmetics and Colors at the FDA, the sharp increase seen from 2014 to 2016 for *all-cosmetics* correlates to heightened public awareness resulting from media attention surrounding issues reported for WEN by Chaz Dean hair care products (over 21,000+ AE reports) and the talc-ovarian cancer class action litigation proceedings (FDA, 2017, “Using adverse event reports to monitor cosmetic safety”). The moderate spike in AE reports for RCC products during 2016, was essentially due to 17 reports of a products called Skinshift Vitamin C Serum. Various FDA initiatives over the years to promote voluntary reporting by health professionals and raise general public awareness has also helped encourage more reporting.

Yet, there is a general consensus among health professionals that cosmetic AEs go largely unreported. People affected by a cosmetic adverse reaction will usually discontinue product use and self-medicate unless symptoms become more severe at which point, they usually seek medical care from a health professional. A common adverse reaction resulting from

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cosmetic use is most often skin inflammation, also referred to as dermatitis (Cary, Li, & Maibach, 2018). Dermatitis is a loosely defined condition which the Merck Manual, defines as “a superficial inflammation of the skin characterized by redness, edema, oozing, crusting, scaling, [and] vesicles (sometimes)” (Gonzalez, 2017, para 1). It also includes pruritus, blistering, burning, stinging, rash, tenderness, and discomfort (Mayo Clinic, 2019). “When dermatitis is caused by exogenous materials coming into direct contact with skin, it is termed contact dermatitis” (Cary, Li, & Maibach, 2018, “Cosmetics and Contact Dermatitis,” para 1). Referring to his own practical experience dealing with cosmetic reactions as a physician, Dr. Howard Maibach, of the University of California, expressed “that most adverse reactions – mainly irritant and allergic contact dermatitis – are not reported” (Cary, Li, & Maibach, 2018, “Surveillance Data,” para 2). From examination of various studies to associate cosmetics and dermatitis, Cary, Li & Maibach (2018), seem to suggest that contact dermatitis is a major cause of cosmetic AEs.

OTC Retinoids vs. Contact Dermatitis

Their opinion is a point of interest with regard to this study. The product label for Renova[®] declares that it is a dermal irritant, and the majority of side effects (refer to Table 3) confirm it is so – tretinoin (retinoic acid) essentially induces contact dermatitis. It was also previously shown above, that AE symptoms for OTC RCC products are qualitatively very similar to side effects of Rx tretinoin, and they occur more frequently in RCCs, suggesting they are indeed more problematic compared to *all*-OTC-cosmetics reported to CAERS. This would suggest that a real safety signal (more AEs associated with OTC RCC products) is indeed present for data gathered from the CAERS database. But if most cosmetic AEs result in dermatitis, as

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Cary and colleagues suggest, then the “signal” may not be real. It may be coincidence or some other factor (e.g. small sample size) causing RCC’s to exhibit dermatitis symptoms as expected of most cosmetic AEs (suggested by Cary et al., 2018).

To reconcile the issue, the rate of occurrence for RCC products reported to CAERS would have to be higher than that of *all*-cosmetics reported to CAERS, for respective symptoms qualitatively similar to those of contact dermatitis. This was the rationale for performing the same comparative process, as done with tretinoin, but a second time with comparison to contact dermatitis symptoms (see Table 5). The 30 AE symptoms that qualitatively aligned and their frequency of occurrence for both RCC- and *all*-cosmetic products are listed in Table 6. The plot generated from this data (see Figure 3) comparing the frequency of occurrence between OTC RCC products and *all*-cosmetic OTC products against the 30 AE symptoms qualitatively similar to dermatitis, again shows RCCs have a higher frequency of occurrence. As such, the AE symptom reports extracted from the CAERS database for OTC-RCC products do indeed seem to indicate a heightened safety issue with OTC RCC products. This finding is also supported by a Journal of Dermatological Treatment study where researchers “noted that irritation was the most frequent side effect of topical retinoids, occurring in 85% of nonprescription retinoid users and up to 95% in patients treated with tretinoin” (Dhatt, 2013, “Improving Outcomes,” para. 1).

Limitations of Data

Due to the ambiguous, non-descript language for several of the AE outcomes listed in Table 2, it is difficult to draw sound conclusion of the seriousness of safety outcomes as a whole. The percentage of deaths, disabilities, and life-threatening outcomes overall were quite low (0.6 - 2 % of the total outcomes), yet hospitalizations represented 14% of the outcomes and some

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ambiguous “other outcome” accounted for 34%. Knowing that contact dermatitis is a transient condition that resolves upon discontinued use of a product, and that it’s not a life-threatening condition, except perhaps in the case of a rare anaphylactic reaction, it remains unclear just what the associated risks may be (DPT Laboratories, 2012; Ortho Pharmaceuticals, 2012; Valeant Pharmaceuticals North America LLC, 2018). The non-descript, ambiguous types of outcome entries (mentioned above), and other lacking information (duration of use, co-morbidities, concomitant drug or supplement use, age, sex) represent just some of the limitations of this data source from voluntarily reporting. Despite limitations, the CAERS database remains a vital tool for FDA safety surveillance of the cosmetic market landscape. Until enactment of new legislation affords the FDA expanded authority over cosmetic regulations, industry, healthcare professionals and the public at large need more education and encouragement to use this important forum.

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Conclusion

From the subset of AE reports for RCC products extracted from CAERS cosmetic data, it was possible to demonstrate that OTC retinoid products exhibit adverse symptoms similar to the types experienced with Rx tretinoin use. This study identified a higher rate of AEs, similar to side effects of tretinoin (expressed as frequency of occurrence), for OTC RCC products versus the entire set of *all*-cosmetic AEs reported to CAERS. To confirm this signal was real, not just contact dermatitis as suggested by Cary et al., this study demonstrated the safety signal was valid by confirming the RCC subset generated AE symptoms of contact dermatitis at a higher level (again expressed as frequency of occurrence) than did the *all*-cosmetic data set at large. This indicates that even less potent OTC retinoids can, and do, exhibit side effects usually associated with the more potent Rx based tretinoin. While Rx tretinoin and the OTC retinoid family remain a power house “gold-standard” for efficacious, anti-aging skincare, the cosmetic market will continue to innovate. As we develop more skincare products incorporating peptides, use high-tech lasers, or various light therapy devices, as we experiment with new types of injectable products, and even as we move towards use of more “natural,” organic products, people will expect items they use to be safe. Better regulations need to be in place to assure this safety. The FDA needs the regulatory power to require that manufactures use safe ingredients or to force a recall of problematic products. Manufacturers should also be required to register their facilities with the government. As our concept of “aging-well” develops, so too, should our national mindset of cosmetic safety.

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Appendix 1: Retinoid-Containing Cosmetic Products Reported to CAERS

| Report ID | CAERS Created Date | Date of Event | Product Type | Product | Product Code | Description | Patient Age | Age Units | Sex | MedDRA Preferred Terms | Outcomes |
|-----------|--------------------|---------------|--------------|--|--------------|-------------|-------------|-----------|-----|--|--|
| 67865 | 4/1/2004 | | SUSPECT | L'OREAL REVITALIFT EYE CREAM | 53 | Cosmetics | | | | TENDERNESS, SWELLING FACE, SKIN BURNING SENSATION | Patient Visited Healthcare Provider |
| 69008 | 5/15/2004 | | SUSPECT | PHILOSOPHY HELP ME ANTI AGING CREAM | 53 | Cosmetics | | | | DEATH, CONGENITAL CENTRAL NERVOUS SYSTEM ABNORMALITY | Death |
| 69506 | 6/5/2004 | | SUSPECT | NUTRIMINC NIGHT CREAM WITH BIO-HYDRIA | 53 | Cosmetics | | | | PROGESTERONE INCREASED | Patient Visited Healthcare Provider |
| 75597 | 1/26/2005 | | SUSPECT | NEUTROGENA PORE REFINING CREAM SPF 15 | 53 | Cosmetics | | | | TELANGIECTASIA, SKIN BLEEDING, PETECHIAE | Other Outcome |
| 78331 | 5/23/2005 | 5/18/2005 | SUSPECT | NICEL DAILY REPAIR VITAMIN A RETINOL CREAM | 53 | Cosmetics | 55 | Yrs | F | LACRIMATION INCREASED, EYE PAIN | Other Outcome |
| 79018 | 6/22/2005 | 6/14/2005 | SUSPECT | GNC RETINOL (CREAM) | 53 | Cosmetics | 79 | Yrs | F | RASH, PRURITUS | Patient Visited Healthcare Provider |
| 79585 | 7/19/2005 | 5/1/2005 | SUSPECT | BIOACCEL SB SERUM | 53 | Cosmetics | | | | SWELLING, RIGORS, MUSCLE SPASMS, ERYTHEMA, DRY SKIN | Patient Visited Healthcare Provider |
| 90518 | 1/11/2007 | | SUSPECT | NEUTROGENA ANTI WRINKLE INTENSIVE SERUM | 53 | Cosmetics | | | | SWELLING, PARAESTHESIA, FACE OEDEMA, ERYTHEMA | Patient Visited Healthcare Provider |
| 95600 | 8/18/2007 | | SUSPECT | LILY OF THE DESERT 99% ALOE VERA GELLY | 53 | Cosmetics | | | | SKIN WARM, SKIN IRRITATION, RASH, ERYTHEMA | Other Outcome |
| 97977 | 11/14/2007 | | SUSPECT | GARNIER NUTRITIONISTS ULTRA-LIFT ANTI WRINKLE FIRMLIFT NIGHT CREAM | 53 | Cosmetics | | | | RASH PAPULAR, RASH | Other Outcome |
| 99028 | 12/20/2007 | | SUSPECT | BARE ESSENTIALS BARE VITAMINS CREAM | 53 | Cosmetics | | | | SKIN DISORDER, PAIN, BLISTER | Patient Visited Healthcare Provider |
| 100357 | 2/14/2008 | | SUSPECT | HYROXATONE ANTI-WRINKLE AM PM TREATMENT CREAM | 53 | Cosmetics | | | | RASH PAPULAR | Other Outcome |
| 100358 | 2/14/2008 | | SUSPECT | HYROXATONE ANTI-WRINKLE AM PM TREATMENT CREAM | 53 | Cosmetics | | | | RASH PAPULAR | Other Outcome |
| 100744 | 2/27/2008 | 5/5/2007 | SUSPECT | DEAD SEA EYE SERUM | 53 | Cosmetics | 46 | Yrs | F | EYE SWELLING | Patient Visited Healthcare Provider, Required |
| 101042 | 3/7/2008 | 1/21/2008 | SUSPECT | MYCHELLE DERMACEUTICALS CLEAR SKIN SERUM | 53 | Cosmetics | 24 | Yrs | F | SKIN IRRITATION, SKIN EXFOLIATION, SCAR, RASH, BURNING SENSATION | Other Outcome |
| 109132 | 1/12/2009 | | SUSPECT | LIFE EXTENSION ULTRA REJUVENEX FACE CREAM | 53 | Cosmetics | | | | SKIN EXFOLIATION, RASH, RASH, PAIN, ERYTHEMA, BURNING SENSATION | Other Outcome |
| 109769 | 2/3/2009 | 1/1/2009 | SUSPECT | DEAD SEA PREMIERE EYE CREAM | 53 | Cosmetics | | | | SKIN IRRITATION, EYE IRRITATION | Medically Important |
| 109769 | 2/3/2009 | 1/1/2009 | SUSPECT | DEAD SEA PREMIERE EYE SERUM | 53 | Cosmetics | | | | SKIN IRRITATION, EYE IRRITATION | Medically Important |
| 110745 | 3/4/2009 | 2/24/2009 | SUSPECT | COSMEDIUM CLARITY SERUM | 53 | Cosmetics | | | | SKIN REACTION, BURNING SENSATION | Medically Important |
| 111158 | 3/16/2009 | | SUSPECT | L'OREAL ADVANCED REVITALIFT NIGHT CREAM | 53 | Cosmetics | | | | VITILIGO, SKIN DEPIGMENTATION | Other Outcome |
| 112247 | 4/22/2009 | | SUSPECT | L'OREAL ADVANCED REVITALIFT NIGHT CREAM | 53 | Cosmetics | | | | SINUSITIS, MUSCLE SPASMS, IMPAIRED WORK ABILITY | Patient Visited Healthcare Provider, Patient Visited Healthcare Provider |
| 117425 | 9/1/2009 | 8/14/2009 | SUSPECT | HYDROXATONE FACIAL WRINKLE CREAM | 53 | Cosmetics | | | | SWELLING, HYPERSENSITIVITY, BURNING SENSATION | Other Outcome |
| 119165 | 10/17/2009 | | SUSPECT | MAKARI DE SUISSE NIGHT CREAM | 53 | Cosmetics | | | | RASH PAPULAR, PRURITUS, BURNING SENSATION | Patient Visited Healthcare Provider |
| 119165 | 10/17/2009 | | SUSPECT | MAKARI DE SUISSE CAVIAR FACE CREAM | 53 | Cosmetics | | | | RASH PAPULAR, PRURITUS, BURNING SENSATION | Patient Visited Healthcare Provider |
| 119452 | 10/24/2009 | | SUSPECT | AVON ANEW ULTIMATE TRANSFORMING LIFT EYE CREAM | 53 | Cosmetics | | | | SWELLING, RASH, FACE OEDEMA, EYE SWELLING | Patient Visited Healthcare Provider |
| 123837 | 3/2/2010 | | SUSPECT | Z. BIGATTI RE-STORATION DEW HYDRATING FACIAL MASK | 53 | Cosmetics | | | | MALaise, INFECTIOUS MONONUCLEOSIS, HYPERSENSITIVITY | Patient Visited Healthcare Provider |
| 126780 | 5/28/2010 | 5/7/2010 | SUSPECT | L'OREAL ADVANCED REVITALIFT FACE | 53 | Cosmetics | 50 | Yrs | M | SWELLING FACE, SWELLING, SKIN EXFOLIATION, HYPERSENSITIVITY | Hospitalization, Medically Important |
| 132286 | 11/18/2010 | 9/15/2010 | SUSPECT | GARNIER NUTRITIONISTE ULTRA LIFT ANTI WRINKLE FIRMLIFT MOISTURIZER | 53 | Cosmetics | | | | VISION BLURRED, SWOLLEN TONGUE, SWELLING FACE | Medically Important |
| 136164 | 3/1/2011 | 5/15/2010 | SUSPECT | IQQU ACNE SERUM | 53 | Cosmetics | 22 | Yrs | F | SKIN DISCOLOURATION, PARAESTHESIA, ERYTHEMA | Medically Important |
| 140390 | 6/21/2011 | 10/10/2010 | SUSPECT | CINDY CRAWFORD MEANINGFUL BEAUTY NIGHT CREAM AND FACE | 53 | Cosmetics | 57 | Yrs | F | RASH, EYE SWELLING, ERYTHEMA | Other Outcome |
| 143058 | 9/1/2011 | | SUSPECT | PREMIER REGENERATING NIGHT CREAM ALL SKIN TYPES | 53 | Cosmetics | 38 | Yrs | F | SWELLING, SKIN DISORDER, PRURITUS, PARAESTHESIA | Patient Visited Healthcare Provider |
| 152213 | 5/11/2012 | | SUSPECT | PHILOSOPHY KEEP THE PEACE SUPER SOOTHING SERUM | 53 | Cosmetics | 57 | Yrs | F | CHEMICAL BURN OF SKIN, BURNING SENSATION | Patient Visited Healthcare Provider |
| 155308 | 8/10/2012 | 8/4/2012 | SUSPECT | MEANINGFUL BEAUTY INTRO PRODUCT KIT - 0.5 FL OZ ANTI-AGING I | 53 | Cosmetics | 50 | Yrs | F | VISUAL ACUITY REDUCED, SCAR, EYE SWELLING, BURNING SENSATION | Life Threatening, Patient Visited Healthcare Provider |
| 165102 | 5/2/2013 | 2/13/2013 | CONCOMITANT | PROACTIV SOLUTION GREEN TEA MOISTURIZER | 53 | Cosmetics | 16 | Yrs | F | RASH PAPULAR, RASH, PAIN, NAUSEA, MYALGIA, BURNING SENSATION | Hospitalization, Patient Visited Healthcare Provider |
| 165561 | 5/15/2013 | 12/22/2012 | SUSPECT | OROGOLD COSMETICS 24K INTENSIVE EYE FORMULA CREAM | 53 | Cosmetics | 54 | Yrs | F | SWELLING FACE, LOCAL SWELLING, HYPERSENSITIVITY | Other Outcome |
| 167482 | 7/5/2013 | | SUSPECT | GARNIER ULTRA LIFT ANTI WRINKLE FIRMLIFT CREAM | 53 | Cosmetics | 61 | Yrs | F | SWELLING, PRURITUS, ERYTHEMA, BURNING SENSATION | Other Outcome |
| 172343 | 12/4/2013 | 11/23/2013 | SUSPECT | GARNIER ANTI WRINKLE FIRMLIFT EYE CREAM | 53 | Cosmetics | | | | WOUND SECRETION, LACRIMATION INCREASED, INFLAMMATION | Hospitalization, Patient Visited Healthcare Provider |
| 176905 | 6/4/2014 | 4/18/2014 | SUSPECT | SECRET BALANCING FACIAL SERUM, ALL SKIN TYPES | 53 | Cosmetics | 61 | Yrs | F | SWELLING, PRURITUS | Disability, Patient Visited Healthcare Provider |
| 178022 | 7/21/2014 | 2/10/2014 | SUSPECT | GARNIER ULTRA-LIFT FIRMLIFT EYE CREAM | 53 | Cosmetics | 20 | Yrs | F | OCULAR HYPERAEMIA, HYPERSENSITIVITY, EYE SWELLING | Disability, Patient Visited Healthcare Provider |
| 178052 | 7/23/2014 | 7/22/2014 | SUSPECT | GARNIER NUTRITIONISTE ULTRA-LIFT ANTI-WRINKLE FIRMLIFT | 53 | Cosmetics | 30 | Yrs | F | EYE SWELLING, EYE PRURITUS | Medically Important |
| 178846 | 8/26/2014 | 8/24/2014 | SUSPECT | GARNIER ULTRA LIFT EYE CREAM | 53 | Cosmetics | 49 | Yrs | F | RASH PRURITIC, RASH PAPULAR | Other Outcome |
| 179079 | 9/5/2014 | | SUSPECT | BRILLIANCE NEW YORK GOLD INSTANT FACE LIFT CREAM | 53 | Cosmetics | | | | FACIAL PAIN, FACE OEDEMA, ERYTHEMA, BURNING SENSATION | Other Outcome |
| 179380 | 9/18/2014 | 9/15/2014 | SUSPECT | GARNIER ULTRA-LIFT EYE CREAM | 53 | Cosmetics | 40 | Yrs | F | SWELLING FACE, SWELLING, SKIN IRRITATION, RASH | Other Outcome |
| 180533 | 11/4/2014 | 9/1/2013 | SUSPECT | KIEHL'S AVOCADO EYE CREAM | 53 | Cosmetics | 32 | Yrs | F | WOUND SECRETION, PAIN, CHALAZION | Disability |
| 183197 | 2/24/2015 | 2/11/2015 | SUSPECT | RETINOL PRODUCTS | 53 | Cosmetics | 56 | Yrs | F | OCULAR HYPERAEMIA, HYPERSENSITIVITY, EYE SWELLING | Patient Visited Healthcare Provider, Medically Important |
| 185392 | 4/27/2015 | 4/4/2015 | SUSPECT | 24K DMAE DEEP WRINKLE | 53 | Cosmetics | 65 | Yrs | F | HYPERSENSITIVITY | Other Outcome |
| 185471 | 4/29/2015 | 4/27/2015 | SUSPECT | ADORE EYE CREAM - ADVANCED AGING EYE CREAM | 53 | Cosmetics | 48 | Yrs | F | EYE SWELLING, BURNING SENSATION | Other Outcome |
| 189345 | 9/1/2015 | 8/6/2015 | SUSPECT | JAMIESON PROVITAMINA RETINOL RENEWAL NIGHT CREAM | 53 | Cosmetics | 44 | Yrs | F | SWELLING FACE, RASH ERYTHEMATOUS, PRURITUS | Other Outcome |
| 189445 | 9/7/2015 | 9/1/2015 | CONCOMITANT | ENVIRON IONZYME C-QUENCE EYE CREAM | 53 | Cosmetics | 40 | Yrs | F | SKIN EXFOLIATION, HYPERSENSITIVITY, DRY SKIN | Other Outcome |
| 189445 | 9/7/2015 | 9/1/2015 | SUSPECT | ENVIRON IONZYME C-QUENCE MOISTURIZER | 53 | Cosmetics | 40 | Yrs | F | SKIN EXFOLIATION, HYPERSENSITIVITY, DRY SKIN | Other Outcome |

INVESTIGATING SAFETY SIGNALS OF RETINOIDS

| | | | | | | | | | | | |
|-----------------|------------|------------|-------------|---|----|-----------|----|-----|---|---|--|
| 189516 | 9/10/2015 | 8/28/2015 | SUSPECT | LIONESSE WHITE PEARL FACELIFT FILLER | 53 | Cosmetics | | | | SWELLING, RASH, PRURITUS, HYPERSENSITIVITY | Medically Important |
| 191054 | 10/29/2015 | | SUSPECT | ADORE ORGANIC INNOVATIONS EYE CREAM | 53 | Cosmetics | 61 | Yrs | F | SWELLING FACE, EYE OEDEMA, BURNING SENSATION | Other Outcome |
| 191163 | 11/3/2015 | | SUSPECT | FOREVER FLAWLESS BLACK DIAMOND ANTI AGING COLLECTION - DIAMOND | 53 | Cosmetics | 70 | Yrs | F | INFLAMMATION, EYE SWELLING, EYE SWELLING, EYE SWELLING | Patient Visited Healthcare Provider |
| 191675 | 11/25/2015 | | SUSPECT | MILEOX SKIN CARE TESTERS - PLACENTOX CELL INFUSION REPAIR CREAM | 53 | Cosmetics | | | | SWELLING FACE, SKIN DISCOLOURATION, PAIN, LOCAL SWELLING | Other Outcome |
| 191833 | 12/4/2015 | | SUSPECT | LAVISH SKIN CREAM | 53 | Cosmetics | | | | CHEMICAL INJURY | Other Outcome |
| 192650 | 1/11/2016 | 1/2/2016 | SUSPECT | AURORA EYE SERUM | 53 | Cosmetics | 59 | Yrs | F | PAIN, ERYTHEMA | Other Outcome |
| 193759 | 2/22/2016 | 2/16/2016 | SUSPECT | VINE VERA FACE LIFT CREAME | 53 | Cosmetics | | | | NAUSEA, MALAISE, HEADACHE, HEADACHE, BLOOD SWELLING | Other Outcome |
| 194030 | 3/2/2016 | 1/1/2015 | SUSPECT | SKINSHIFT VITAMIN C SERUM | 53 | Cosmetics | 35 | Yrs | F | ADVERSE REACTION | Hospitalization, Patient Visited ER |
| 194687 | 3/25/2016 | | SUSPECT | GARNIER ULTRA LIFT ANTI-WRINKLE FIRMING EYE CREAM | 53 | Cosmetics | 57 | Yrs | F | SWELLING FACE, SWELLING, STAPHYLOCOCCAL INFECTION | Patient Visited Healthcare Provider, Patient Visited ER |
| 194773 | 3/29/2016 | 1/1/2015 | SUSPECT | SKINSHIFT VITAMIN C SERUM | 53 | Cosmetics | | | | ADVERSE REACTION | Hospitalization, Patient Visited ER |
| 194781 | 3/29/2016 | 1/1/2015 | SUSPECT | SKINSHIFT VITAMIN C SERUM | 53 | Cosmetics | | | | ADVERSE REACTION | Hospitalization, Patient Visited ER |
| 194787 | 3/29/2016 | 1/1/2015 | SUSPECT | SKINSHIFT VITAMIN C SERUM | 53 | Cosmetics | | | | ADVERSE REACTION | Hospitalization, Patient Visited ER |
| 194772 | 3/29/2016 | 1/1/2015 | SUSPECT | SKINSHIFT VITAMIN C SERUM | 53 | Cosmetics | | | | ADVERSE REACTION | Hospitalization, Patient Visited ER |
| 194783 | 3/29/2016 | 1/1/2015 | SUSPECT | SKINSHIFT VITAMIN C SERUM | 53 | Cosmetics | | | | ADVERSE REACTION | Hospitalization, Patient Visited ER |
| 194776 | 3/29/2016 | 1/1/2015 | SUSPECT | SKINSHIFT VITAMIN C SERUM | 53 | Cosmetics | | | | ADVERSE REACTION | Hospitalization, Patient Visited ER |
| 194775 | 3/29/2016 | 1/1/2015 | SUSPECT | SKINSHIFT VITAMIN C SERUM | 53 | Cosmetics | | | | ADVERSE REACTION | Hospitalization, Patient Visited ER |
| 194778 | 3/29/2016 | 1/1/2015 | SUSPECT | SKINSHIFT VITAMIN C SERUM | 53 | Cosmetics | | | | ADVERSE REACTION | Hospitalization, Patient Visited ER |
| 194780 | 3/29/2016 | 1/1/2015 | SUSPECT | SKINSHIFT VITAMIN C SERUM | 53 | Cosmetics | | | | ADVERSE REACTION | Hospitalization, Patient Visited ER |
| 194779 | 3/29/2016 | 1/1/2015 | SUSPECT | SKINSHIFT VITAMIN C SERUM | 53 | Cosmetics | | | | ADVERSE REACTION | Hospitalization, Patient Visited ER |
| 194774 | 3/29/2016 | 1/1/2015 | SUSPECT | SKINSHIFT VITAMIN C SERUM | 53 | Cosmetics | | | | ADVERSE REACTION | Hospitalization, Patient Visited ER |
| 194782 | 3/29/2016 | 1/1/2015 | SUSPECT | SKINSHIFT VITAMIN C SERUM | 53 | Cosmetics | | | | ADVERSE REACTION | Hospitalization, Patient Visited ER |
| 194786 | 3/29/2016 | 1/1/2015 | SUSPECT | SKINSHIFT VITAMIN C SERUM | 53 | Cosmetics | | | | ADVERSE REACTION | Hospitalization, Patient Visited ER |
| 194785 | 3/29/2016 | 1/1/2015 | SUSPECT | SKINSHIFT VITAMIN C SERUM | 53 | Cosmetics | | | | ADVERSE REACTION | Hospitalization, Patient Visited ER |
| 194777 | 3/29/2016 | 1/1/2015 | SUSPECT | SKINSHIFT VITAMIN C SERUM | 53 | Cosmetics | | | | ADVERSE REACTION | Hospitalization, Patient Visited ER |
| 194784 | 3/29/2016 | 1/1/2015 | SUSPECT | SKINSHIFT VITAMIN C SERUM | 53 | Cosmetics | | | | ADVERSE REACTION | Hospitalization, Patient Visited ER |
| 196285 | 5/17/2016 | 4/19/2016 | SUSPECT | REVITALIFT L'OREAL MOISTURE BLUR | 53 | Cosmetics | 25 | Yrs | F | RASH, PRURITUS, ERYTHEMA, DERMATITIS CONTACTA | Medically Important |
| 196295 | 5/17/2016 | 4/11/2016 | SUSPECT | GARNIER ULTRA-LIFT ANTI WRINKLE FIRMING EYE CREAM | 53 | Cosmetics | 46 | Yrs | F | RASH, OCULAR HYPERAEMIA, EYE SWELLING, EYE IRRITATION | Medically Important |
| 198247 | 7/8/2016 | 6/18/2016 | SUSPECT | B LUE DIAMOND INFUSED EYE CREAM | 53 | Cosmetics | 66 | Yrs | F | RASH, PARAESTHESIA, ERYTHEMA | Other Outcome |
| 198753 | 7/22/2016 | 7/16/2016 | SUSPECT | DERMASIL OIL FREE DAILY RETINOL FACIAL CREAM W/ VITAMIN A & B | 53 | Cosmetics | 50 | Yrs | F | URTICARIA | Medically Important |
| 205853 | 12/30/2016 | 12/23/2016 | SUSPECT | EVENTONE FADE CREAM | 53 | Cosmetics | 46 | Yrs | F | SWELLING FACE, RASH, PRURITUS, EYE SWELLING, EYE SWELLING | Hospitalization, Patient Visited ER |
| 206975 | 1/31/2017 | 4/21/2016 | SUSPECT | REMEDY OLIVAMINE SKIN REPAIR CREAM | 53 | Cosmetics | 44 | Yrs | F | ANAPHYLACTIC REACTION | Life Threatening |
| 207172 | 2/3/2017 | | SUSPECT | BIOPELLE TENSAGE STEM CELL EYE CREAM | 53 | Cosmetics | | | | OCULAR HYPERAEMIA, HYPERSENSITIVITY, EYE SWELLING | Patient Visited Healthcare Provider |
| 208495 | 3/6/2017 | 2/24/2017 | CONCOMITANT | IT COSMETICS ANTI-AGING MOISTURIZER | 53 | Cosmetics | 44 | Yrs | F | SKIN EXFOLIATION | Other Outcome |
| 208495 | 3/6/2017 | 2/24/2017 | SUSPECT | LUCANA EYE SERUM | 53 | Cosmetics | 44 | Yrs | F | SKIN EXFOLIATION | Other Outcome |
| 208626 | 3/8/2017 | 3/1/2017 | SUSPECT | REJUVICARE RETINOL AGE DEFYING COMPLEX CREAM | 53 | Cosmetics | 64 | Yrs | F | WOUND, SKIN EXFOLIATION, ERYTHEMA, CHEMICAL BURN | Medically Important |
| 208775 | 3/10/2017 | 1/2/2017 | SUSPECT | MICROWATER COMPLEX TOPICAL DAILY GLOW MOISTURIZER | 53 | Cosmetics | 68 | Yrs | M | URTICARIA, MALAISE, BLOOD PRESSURE INCREASED | Medically Important, Other Seriousness |
| 209549 | 3/27/2017 | 12/28/2016 | SUSPECT | LUCIENNE SKIN FACE CREAM | 53 | Cosmetics | 90 | Yrs | F | SWELLING, SKIN IRRITATION, ERYTHEMA | Medically Important |
| 209783 | 3/30/2017 | | SUSPECT | LA MER REGENERATING SERUM | 53 | Cosmetics | 30 | Yrs | F | SECRETION DISCHARGE, SCAB, LIP SWELLING, LIP PAIN | Other Outcome |
| 210768 | 4/24/2017 | 11/20/2016 | SUSPECT | DERMA E - PSORZEMA, 4 OZ CREAM | 53 | Cosmetics | | | | SKIN EXFOLIATION, PAIN, ERYTHEMA, BURNING SENSATION | Other Outcome |
| 211556 | 5/8/2017 | | SUSPECT | Soleil Phytoceramide Eye Cream | 53 | Cosmetics | | | | Skin irritation, Erythema, Dry skin | Other Outcome |
| 211556 | 5/8/2017 | | SUSPECT | LUMANERE AGELESS FACE COMPLEX | 53 | Cosmetics | | | | Skin irritation, Erythema, Dry skin | Other Outcome |
| 211556 | 5/8/2017 | | SUSPECT | LUMANERE AGELESS FACE COMPLEX | 53 | Cosmetics | | | | Skin irritation, Erythema, Dry skin | Other Outcome |
| 213531 | 6/13/2017 | 6/10/2017 | SUSPECT | NEUTROGENA DEEP WRINKLE | 53 | Cosmetics | 59 | Yrs | F | BURNING SENSATION, BLISTER | Medically Important |
| 213959 | 6/20/2017 | 6/18/2017 | SUSPECT | HONEY BEE SKIN HEALING CREAM | 53 | Cosmetics | | | | Swelling, Paraesthesia | Other Outcome |
| 214973 | 7/8/2017 | | SUSPECT | DR. DENNIS GROSS SERULIC ACID & RETINOL BRIGHTENING SOLUTION | 53 | Cosmetics | | | | ACNE CYSTIC | Other Outcome |
| 2017-CFS-000333 | 9/27/2017 | | SUSPECT | Ageless Facial Serum Lumanere | 53 | Cosmetics | | | | Rash, Pruritus | Other Outcome |
| 2017-CFS-000910 | 10/13/2017 | | SUSPECT | GOLD BOND ULTIMATE SKIN THERAPY CREAM SOFTENING SHEA BUTTER | 53 | Cosmetics | | | | Pyrexia, Nausea, Malaise, Hypersensitivity, Hyperthermia | Other Outcome |
| 2017-CFS-002160 | 11/30/2017 | | SUSPECT | PURITAN'S PRIDE RETINOL CREAM | 53 | Cosmetics | | | | Swollen tongue, Oedema mouth, Lip swelling, Lip pain | Patient Visited Healthcare Provider, Medically Important |
| 2017-CFS-002462 | 12/11/2017 | | SUSPECT | COLLAGEN MOISTURE FILLER | 53 | Cosmetics | | | | Skin exfoliation, Rash, Erythema, Dry skin | Medically Important |
| 2018-CFS-000231 | 1/10/2018 | | SUSPECT | DAB TO INDULGE VITAMIN-ENRICHED RENEWAL CREAM | 53 | Cosmetics | | | | Rash, Hypersensitivity | Other Outcome |
| 2018-CFS-004046 | 3/9/2018 | 3/7/2018 | SUSPECT | GLOBAL BEAUTY CARE RETINOL SPA TREATMENT MASK ANTI-AGING | 53 | Cosmetics | | | | Skin irritation, Pruritus | Other Outcome |
| 2018-CFS-006289 | 4/25/2018 | 4/2/2018 | SUSPECT | MINT PEAR COLLAGEN SERUM | 53 | Cosmetics | | | | Urticaria, Pruritus, Hypersensitivity, Erythema | Other Outcome |
| 2018-CFS-006371 | 4/26/2018 | 4/6/2018 | SUSPECT | COLD PLASMA+ FACE | 53 | Cosmetics | | | | Skin exfoliation, Hypersensitivity, Erythema, Burn | Other Outcome |
| 2018-CFS-006399 | 4/26/2018 | 12/26/2017 | SUSPECT | RADIANT REVIVE MOISTURIZER | 53 | Cosmetics | | | | Pruritus, Lacrimation increased, Erythema | Other Outcome |
| 2018-CFS-006607 | 5/2/2018 | 3/15/2018 | SUSPECT | PAULA'S CHOICE CLINICAL 1% RETINOL TREATMENT | 53 | Cosmetics | | | | Visual acuity reduced, Vision blurred, Impaired driving | Other Outcome |
| 2018-CFS-007347 | 5/23/2018 | 3/15/2018 | SUSPECT | ROC RETINOL CORREXION MAX DAILY HYDRATION CREME (ROC RETINOL) | 53 | Cosmetics | | | | Swelling face, Pyrexia, Lip swelling, Application site reaction | Other Outcome |

INVESTIGATING SAFETY SIGNALS OF RETINOIDS

| | | | | | | | | | | |
|-----------------|------------|------------|---------|---|----|-----------|--|--|--|-------------------------------------|
| 2018-CFS-007755 | 6/4/2018 | | SUSPECT | IT COSMETICS FOUNDATION AND BYE BYE LINES SERUM | 53 | Cosmetics | | | Hypersensitivity | Medically Important |
| 2018-CFS-008248 | 6/17/2018 | 6/15/2018 | SUSPECT | BOX: RETINOL-PRO: ADVANCED REGENERATING FORMULA BOTTLE: | 53 | Cosmetics | | | Burning sensation | Other Outcome |
| 2018-CFS-009056 | 7/9/2018 | 7/5/2018 | SUSPECT | DR. PERRICONE COLD PLASMA +FACE | 53 | Cosmetics | | | Rash pruritic, Erythema, Burning sensation | Other Outcome |
| 2018-CFS-009601 | 7/25/2018 | 3/3/2017 | SUSPECT | LUX ALLURE EYE CREAM | 53 | Cosmetics | | | Rash | Other Outcome |
| 2018-CFS-009917 | 8/2/2018 | | SUSPECT | TRESOR RARE WRINKLE CREAM | 53 | Cosmetics | | | Headache | Patient Visited Healthcare Provider |
| 2018-CFS-010614 | 8/24/2018 | 7/21/2018 | SUSPECT | SENEGENCE TINTED MOISTURIZER | 53 | Cosmetics | | | Urticaria, Skin exfoliation, Pruritus, Eye swelling, B | Other Outcome |
| 2018-CFS-011875 | 9/27/2018 | | SUSPECT | FRUIT OF THE EARTH VITAMIN E SKIN CARE CREAM | 53 | Cosmetics | | | Ocular hyperaemia, Eyelid oedema, Eyelid oedema | Patient Visited Healthcare Provider |
| 2018-CFS-013683 | 11/19/2018 | 11/14/2018 | SUSPECT | SECRET COLLAGEN AGE DEFYING STEM CELL EYE LIFTING CREAM | 53 | Cosmetics | | | Chemical injury | Other Outcome |
| 2018-CFS-014965 | 12/24/2018 | 12/22/2018 | SUSPECT | VINE VERA EYE CREAM | 53 | Cosmetics | | | Burning sensation, Blister | Other Outcome |
| 2019-CFS-002923 | 3/21/2019 | 2/11/2019 | SUSPECT | TRIXELIN ACNE AND SCAR MAXIMUM REVERSAL CONCENTRATE | 53 | Cosmetics | | | Skin discolouration | Medically Important |

INVESTIGATING SAFETY SIGNALS OF RETINOIDS

Appendix 2: AE Symptoms Reported to CAERS for RCC's & Corresponding AE Data for All-Cosmetics

Symptoms highlighted yellow = OTC-RCC product symptoms qualitatively similar to side effects of Rx Tretinoin.

Symptoms with an (*) = OTC-RCC product symptoms qualitatively similar to AE's associated with contact dermatitis.

Bolded numbers indicate frequency of occurrence levels of 1% or higher.

| | RCC Frequency of Occurrence (%) | # of Symptoms for RCC Products | Type of AE Symptoms (as MedDRA Preferred Terms) | All- Cosmetics Frequency of Occurrence (%) | # of Symptoms for All-Cosmetic Products |
|----|--|--------------------------------------|---|---|---|
| 1 | 0.3% | 1 | Acne - Cystic | 0.06% | 36 |
| 2 | 4.6% | 17 | Adverse Reaction | 0.08% | 49 |
| 3 | 0.5% | 2 | Anaphylactic Reaction | 0.09% | 61 |
| 4 | 0.3% | 1 | *Angioedema (swelling beneath the skin) | 0.03% | 19 |
| 5 | 0.3% | 1 | Asthenia (abnormal weakness, lack of energy) | 0.07% | 47 |
| 6 | 0.3% | 1 | Bed-ridden | 0.00% | 1 |
| 7 | 1.6% | 6 | *Blister | 0.83% | 543 |
| 8 | 0.3% | 1 | Blood Pressure Fluctuation | 0.01% | 7 |
| 9 | 0.3% | 1 | Blood Pressure Increase | 0.06% | 37 |
| 10 | 0.3% | 1 | Bloody Discharge | 0.00% | 3 |
| 11 | 0.5% | 2 | Blurred Vision | 0.22% | 142 |
| 12 | 0.3% | 1 | Brain Injury | 0.00% | 2 |
| 13 | 0.3% | 1 | Bronchitis | 0.01% | 9 |
| 14 | 7.0% | 26 | *Burning Sensation | 1.87% | 1216 |
| 15 | 0.3% | 1 | Caustic Injury | 0.22% | 144 |
| 16 | 0.3% | 1 | Chalazion (swollen eyelid from inflamed oil gland) | 0.01% | 5 |
| 17 | 0.3% | 1 | *Cheilitis (inflammation of the lips and skin around the mouth) | 0.05% | 30 |
| 18 | 0.8% | 3 | Chemical Burn of Skin | 0.20% | 128 |
| 19 | 0.3% | 1 | Chemical Injury | 0.40% | 261 |
| 20 | 0.3% | 1 | Chills | 0.03% | 20 |
| 21 | 0.3% | 1 | Cleft Lip | 0.00% | 1 |
| 22 | 0.3% | 1 | Conjunctivitis Allergic | 0.01% | 5 |
| 23 | 0.3% | 1 | Congenital Central Nervous System Anomaly | 0.00% | 1 |
| 24 | 0.3% | 1 | Congenital Anomaly | 0.00% | 1 |
| 25 | 0.3% | 1 | Confusional State | 0.05% | 31 |
| 26 | 0.3% | 1 | Contusion | 0.06% | 40 |
| 27 | 0.3% | 1 | Death | 7.55% | 4913 |
| 28 | 0.3% | 1 | *Dermatitis - Contact | 0.24% | 156 |
| 29 | 0.3% | 1 | Dizziness | 0.26% | 169 |
| 30 | 0.5% | 2 | *Dry Lip | 0.13% | 86 |
| 31 | 0.3% | 1 | Dry Mouth | 0.02% | 13 |
| 32 | 1.9% | 7 | *Dry Skin | 0.65% | 423 |
| 33 | 0.3% | 1 | Dysgeusia (parageusia, taste distortion) | 0.05% | 32 |
| 34 | 0.3% | 1 | Dysphagia (difficult or painful swallowing) | 0.06% | 38 |
| 35 | 0.5% | 2 | Dyspnoea (labored breathing) | 0.56% | 363 |
| 36 | 9.2% | 34 | *Erythema (redness of the skin) | 1.80% | 1170 |
| 37 | 0.5% | 2 | Eye Discharge | 0.05% | 30 |
| 38 | 0.5% | 2 | Eye Infection | 0.10% | 67 |
| 39 | 0.5% | 2 | Eye Inflammation | 0.04% | 29 |
| 40 | 1.6% | 6 | Eye Irritation | 0.56% | 363 |
| 41 | 0.3% | 1 | Eye Oedema | 0.02% | 13 |
| 42 | 0.8% | 3 | Eye Pain | 0.14% | 92 |
| 43 | 0.3% | 1 | Eye Pruritus | 0.16% | 101 |

INVESTIGATING SAFETY SIGNALS OF RETINOIDS

| | | | | | |
|----|-------------|-----------|--|--------------|-------------|
| 44 | 3.8% | 14 | Eye Swelling | 0.69% | 446 |
| 45 | 0.3% | 1 | Eye Ulcer | 0.00% | 1 |
| 46 | 0.5% | 2 | *Eyelid Oedema | 0.06% | 37 |
| 47 | 0.3% | 1 | Exposure to Toxic Agent | 0.01% | 4 |
| 48 | 0.8% | 3 | *Face Oedema | 0.07% | 48 |
| 49 | 0.3% | 1 | Fatigue | 0.16% | 104 |
| 50 | 0.3% | 1 | Fear | 0.01% | 9 |
| 51 | 0.3% | 1 | Feeling Abnormal | 0.05% | 33 |
| 52 | 0.3% | 1 | Feeling Hot | 0.11% | 71 |
| 53 | 0.3% | 1 | Hot Flush | 0.03% | 19 |
| 54 | 1.1% | 4 | Headache | 0.46% | 297 |
| 55 | 0.3% | 1 | Hyperhidrosis | 0.03% | 22 |
| 56 | 1.6% | 6 | Hyperaemia -Ocular (excess of blood vessel supply) | 0.26% | 169 |
| 57 | 4.9% | 18 | Hypersensitivity | 1.68% | 1096 |
| 58 | 0.5% | 2 | Hypoaesthesia - Facial (numbness) | 0.01% | 5 |
| 59 | 0.3% | 1 | Impaired Driving Ability | 0.00% | 1 |
| 60 | 0.3% | 1 | Impaired Work Ability | 0.02% | 16 |
| 61 | 0.5% | 2 | *Inflammation - general/non-specified | 0.18% | 120 |
| 62 | 0.5% | 2 | Infection - General/Non-specified | 0.18% | 120 |
| 63 | 0.3% | 1 | Infection - Herpes Virus | 0.01% | 5 |
| 64 | 0.3% | 1 | Infection - Herpes Zoster | 0.01% | 6 |
| 65 | 0.3% | 1 | Infection - Staphylococcal | 0.05% | 33 |
| 66 | 0.3% | 1 | Infectious Mononucleosis | 0.00% | 1 |
| 67 | 0.3% | 1 | Insomnia | 0.11% | 71 |
| 68 | 0.8% | 3 | Lacrimation - Increased | 0.17% | 109 |
| 69 | 0.3% | 1 | Lip Pain | 0.03% | 20 |
| 70 | 1.1% | 4 | *Lip Swelling | 0.25% | 164 |
| 71 | 1.1% | 4 | Malaise (general feeling of discomfort, illness, uneasiness) | 0.16% | 105 |
| 72 | 0.3% | 1 | myalgia (muscle pain) | 0.03% | 20 |
| 73 | 0.5% | 2 | Muscle Spasms | 0.08% | 49 |
| 74 | 0.8% | 3 | Nausea | 0.28% | 181 |
| 75 | 0.3% | 1 | *Oedema - Mouth | 0.01% | 9 |
| 76 | 0.3% | 1 | Pain - Facial | 0.02% | 14 |
| 77 | 2.4% | 9 | Pain - General/Non-specified | 1.51% | 980 |
| 78 | 1.3% | 5 | Paraesthesia (abnormal, tingling or pricking sensation) | 0.31% | 204 |
| 79 | 0.3% | 1 | Petechiae (1-2mm purple spots -under skin bleeding) | 0.00% | 2 |
| 80 | 0.3% | 1 | Progesterone Increased | 0.00% | 1 |
| 81 | 4.0% | 15 | *Pruritus (chronic itchy skin) | 3.07% | 2000 |
| 82 | 0.8% | 3 | Pyrexia (fever, increased body temperature) | 0.07% | 45 |
| 83 | 0.3% | 1 | *Rash - Erythematous (redness due to dilated capillaries) | 0.23% | 150 |
| 84 | 4.3% | 16 | *Rash - General/Non-specified | 0.11% | 73 |
| 85 | 2.2% | 8 | *Rash - Papular (with defined boarders) | 0.50% | 323 |
| 86 | 0.5% | 2 | *Rash - Pruritic | 0.12% | 77 |
| 87 | 0.3% | 1 | Rigors (violent shivers w/ temperature) | 0.01% | 7 |
| 88 | 0.3% | 1 | *Scab | 0.27% | 176 |
| 89 | 0.5% | 2 | Scar | 0.30% | 198 |
| 90 | 0.3% | 1 | Sinusitis | 0.03% | 17 |
| 91 | 0.3% | 1 | Skin Bleeding | 0.01% | 4 |
| 92 | 0.3% | 1 | Skin De-pigmentation | 0.01% | 4 |
| 93 | 0.8% | 3 | Skin Discoloration | 0.31% | 204 |
| 94 | 0.5% | 2 | *Skin Disorder | 0.23% | 148 |

INVESTIGATING SAFETY SIGNALS OF RETINOIDS

| | | | | | |
|-----|-------------|-----------|--|--------------|------------|
| 95 | 3.2% | 12 | *Skin Exfoliation | 0.63% | 407 |
| 96 | 0.3% | 1 | *Skin Warm | 0.02% | 10 |
| 97 | 2.7% | 10 | *Skin irritation | 0.82% | 531 |
| 98 | 0.3% | 1 | *Skin Reaction | 0.11% | 72 |
| 99 | 3.0% | 11 | *Swelling - Face | 0.46% | 301 |
| 100 | 3.5% | 13 | *Swelling (General/Non-specified) | 1.27% | 829 |
| 101 | 0.8% | 3 | *Swelling - Local | 0.18% | 115 |
| 102 | 0.5% | 2 | Swollen Tongue | 0.08% | 53 |
| 103 | 0.3% | 1 | Telangiectasia (capillary dilation/purple clusters) | 0.00% | 1 |
| 104 | 0.3% | 1 | *Tenderness | 0.19% | 125 |
| 105 | 1.1% | 4 | *Urticaria (hives) | 0.66% | 427 |
| 106 | 0.5% | 2 | Visual Acuity Reduced | 0.06% | 36 |
| 107 | 0.3% | 1 | Vitiligo (white patches, loss of skin color, destruction of melanocytes) | 0.00% | 3 |
| 108 | 0.3% | 1 | Wound | 0.21% | 137 |
| 109 | 0.8% | 3 | *Wound Secretion | 0.08% | 55 |