Differin® (adapalene) Gel, 0.1%
For the treatment of acne

Nonprescription Drugs Advisory Committee
April 15, 2016
Differin® (adapalene) Gel, 0.1%

Howard Marsh, MD
Vice President, Medical Affairs
Galderma
Acne is a Common and Chronic Condition

- Affects more than 85% of teenagers but can occur in most age groups
- Frequently persists into adulthood
- Chronic and recurring condition
- 70% of acne sufferers don’t consult their doctor

Acne is Highly Visible
Acne Has High Psychological Burden

- Acne sufferers can feel:
  - Self-conscious
  - Depressed
  - A lack of confidence
  - Embarrassment and shame
  - Socially isolated or withdrawn

Acne is an OTC Condition

- Five active ingredients are allowed for nonprescription use under the Monograph system
- Benzoyl peroxide and salicylic acid make up 99% of the OTC acne drug market
  - Others include sulfur, resorcinol and resorcinol monoacetate
- No new OTC acne active ingredients since the 1980s
What is Adapalene?

- A new chemical entity discovered by Galderma in 1984
- A third generation retinoid designed to be stable in the presence of light and oxygen
- Anti-inflammatory and inhibits comedo formation

Seven FDA Approved Adapalene Formulations

- Differin (adapalene) Gel, 0.1% was approved in 1996
- Approved in 4 other dosage forms and strengths:
  - 0.1% cream, lotion and solution
  - 0.3% gel
- Approved in 2 combination products:
  - Adapalene 0.1% and 0.3% in combination with benzoyl peroxide 2.5%
Differin Gel Meets General Criteria for OTC Drugs

- The consumer must be able to self-diagnose the condition to be treated
- The consumer must be able to read and understand the product labeling to ensure proper usage
- The product must be effective when used as recommended
- The drug must be safe for self-use
Consumers Can Self-Diagnose and Self-Treat Acne

- Self-diagnosed and self-treated by consumers for decades

- Topical acne drugs are currently marketed OTC and have been for decades
Consumers Can Understand the Labeling

- Differin Gel proposed labeling is similar to current OTC acne medications
  - Once-daily use versus up to three times a day
- The following studies were conducted to assess consumer behavior:
  - Label comprehension
  - Actual use
  - Self-selection
Differin Gel is Effective

- Efficacy demonstrated in 5 clinical studies that supported NDA approval
- Long-term efficacy demonstrated in additional studies lasting up to 12 months
Differin Gel Has a Well-established Safety Profile

- Safety aspects have been carefully evaluated including:
  - Potential side effects
  - Teratogenic potential
  - Off-label use
Safety Profile Has Not Changed in Over 20 years

- Over 40 million users in 83 countries since 1995
- More than 140 clinical studies and 6000 subjects treated
- Comprehensive global pharmacovigilance program
- Most common adverse events are dermatologic and include dry skin, erythema, itching and burning
Teratogenicity Has Been Carefully Evaluated

- No teratogenicity from animal studies after high dose dermal application
- Studies have consistently shown that systemic exposure in humans after topical application under maximal use conditions is far below potentially toxic levels
- Supported by assessment of exposures during pregnancy reported
Differin Gel is Appropriate for Nonprescription Use

- Data collected in original and consumer development programs as well as post-marketing experience all support OTC use

- Nonprescription Differin Gel would provide:
  - Broad access to a once-daily, safe and effective treatment
  - An additional treatment option for a condition that impacts the lives of millions of acne sufferers
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# Additional Responders

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<tr>
<th>Name</th>
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<th>Company</th>
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<tbody>
<tr>
<td>Sean Griffin</td>
<td>Director, Regulatory Affairs</td>
<td>Galderma</td>
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<tr>
<td>Nathalie Wagner</td>
<td>Clinical Pharmacokinetics Manager</td>
<td>Galderma</td>
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<tr>
<td>Oliver Watts, PhD</td>
<td>Vice President, Regulatory Affairs</td>
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Characteristics of Acne
The Impact of Acne is Beyond Skin

- Adolescents report heavy emotional distress
  - Reduced mental health
  - Not thriving at school
  - Problems with interpersonal relationships
- Suffers of all ages feel the broad emotional impact
  - Self-conscious
  - Depressed/suicidal ideation
  - Socially withdrawn

Treatment Improves Psychological Burden

- Improvement of acne has been associated with:
  - Higher self perception
  - Less embarrassment
  - Decreased depression

Pilosebaceous Unit

- Epidermis
- Dermis
- Hair follicle
- Sebaceous glands
- Sebum
Acne is an Inflammatory Disease

Pre-lesion: Subclinical inflammation

Microcomedo: Formation of follicular plug
↑ Inflammatory mediators
↑ P. acnes
↑ Sebum

Acne lesion: Inflammation

Primary Mechanism of Action Targets

Pre-lesion: Subclinical inflammation

Subclinical inflammation

Microcomedo: Formation of follicular plug

Inflammatory mediators

↑ Inflammatory mediators

↑ P. acnes

↑ Sebum

Acne lesion: Inflammation

Adapalene

Benzoyl Peroxide

Salicylic Acid

Adapalene


2016 AAD Treatment Guidelines

- Independent recommendations and guidelines from dermatologists on how to treat acne
  - No commercial affiliation or funding sources
- Based on MOA, evidence and clinical experience
- **Consensus:** Topical retinoids, including adapalene, are the core of topical acne therapy
  - Benzoyl peroxide is also recommended as a first line treatment

Additional OTC Options are Needed

- 64% of adults and 78% of teens do not seek healthcare professional advice

- Teens and young adults try an average of 4.8 and 7.5 OTC acne treatments, respectively

- No new active ingredients for OTC acne since the 1980’s

Nielsen Research Survey of Acne Sufferers. 2015
OTC Differin Gel Will Benefit Acne Sufferers

- There have been no new nonprescription acne treatment options since the 1980s
  - Differin Gel provides greater access to an alternative treatment option
- MOA of adapalene differs from current OTC acne drugs
  - Differin Gel is once-daily dosing
- Differin Gel is safe, effective and appropriate for the nonprescription setting
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Extensive Clinical Data Exists

- Initial development program for Differin Gel consisted of 16 clinical studies
  - 11 studies evaluated cutaneous safety and pharmacokinetics in healthy subjects
  - 5 studies evaluated safety and efficacy in patients with acne
- Including post-marketing period, more than 140 clinical studies have been conducted and 6000 subjects treated
Proven Efficacy of Differin Gel

- Efficacy confirmed in 5 original pivotal studies
  - Mean total acne lesion count reduction from baseline to week 12 typically between 30% and 50%
- Reduction in total lesion count observed within 2 weeks
- Long-term efficacy also demonstrated in a post-marketing study lasting up to 12 months
Safety of Differin Gel

- Safety evaluated in 5 pivotal 12-week studies including 2 uncontrolled 14-week extensions
  - Application site tolerability assessments including erythema, dryness, scaling, pruritus and burning

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
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- Adverse events (AEs)
Tolerability Shown in Original Pivotal Studies

- In all five pivotal studies, the majority of assessments were mild in nature and peaked during the first 2 weeks of treatment, declining thereafter.

- Dryness and erythema were most common side effects, occurring in approximately 40% of subjects.
  - Scaling was reported in approximately 30% of subjects.
  - Pruritus was reported in approximately 20% of subjects.
  - Burning was reported in approximately 10% of subjects.

- Mean scores for each were less than 1 (mild) for all assessments at all time points.
# Adverse Events in Original Pivotal Studies

<table>
<thead>
<tr>
<th></th>
<th>Differin Gel (N=632)</th>
<th>Vehicle Gel (N=162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td>210 (33.2)</td>
<td>72 (44.4)</td>
</tr>
<tr>
<td>Nondermatologic</td>
<td>155 (24.5)</td>
<td>68 (42.0)</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>55 (8.7)</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>Mild</td>
<td>33 (60.0)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>Moderate</td>
<td>19 (34.5)</td>
<td>0</td>
</tr>
<tr>
<td>Severe</td>
<td>3 (5.5)</td>
<td>0</td>
</tr>
<tr>
<td>Serious</td>
<td>1 (0.2)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>(accident – concussion/laceration)</td>
<td></td>
<td>(influenza, myalgia)</td>
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</tbody>
</table>
## Adverse Events in Original Pivotal Studies: Dermatologic

### Events Occurring in ≥0.5% of Subjects on Differin 0.1% Gel, n (%)

<table>
<thead>
<tr>
<th>Event</th>
<th>Differin Gel N=632 n (%)</th>
<th>Vehicle Gel N=162 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>8 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Dry skin</td>
<td>7 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>Skin discomfort</td>
<td>5 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>Acne flare</td>
<td>5 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>4 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Sunburn</td>
<td>3 (0.5)</td>
<td>2 (1.2)</td>
</tr>
</tbody>
</table>
Discontinuations in Original Pivotal Studies

- **Subjects discontinued due to adverse events**
  - Adapalene group – 10 (1.5%)
  - Eight were dermatologic
    - Acne flare – 2
    - Skin irritation/erythema - 1
    - Skin irritation – 1
    - Erythema/pruritus/vesicular rash – 1
    - Contact dermatitis – 1
    - Cyst on face – 1
    - Sunburn – 1
  - Vehicle group – 3 (1.9%)
Established Post-marketing Safety Profile

- Over 40 million people have been treated globally with adapalene
- Extensive pharmacovigilance database exists
- Other data sources include FDA (FAERS) and WHO databases and literature review
- Consistent safety with Phase 2 and Phase 3 studies
  - Most common adverse events are dermatologic and include dry skin, erythema, itching and burning
  - In over 20 years of market use no new safety signals noted
No Incremental Safety Risks Due to Off-label Use

- Differin Gel is approved for the treatment of acne globally
- Retinoids, including adapalene, have been studied for the treatment of additional indications including fine lines, wrinkles and photoaging
- Side effects reported for adapalene similar to those observed when treating acne
  - Dry skin, erythema, skin irritation and skin discomfort
Adolescent Use Does Not Pose a Safety Risk

- Pivotal trials and most post marketing studies included subjects aged 12-17 years
  - Safety profile similar to adults
- Maximal use PK study included adolescents
  - No difference in systemic exposure
Pediatric Use Does Not Pose a Safety Risk

- The Drug Facts Label for Differin Gel states it is for those 12 years and older.
- Epiduo Gel proven safe and effective in children as young as 9 y (adapalene 0.1% and benzoyl peroxide 2.5%)
  - Prescription label indicated for 9 years and older.
## Dermatologic Adverse Events: Epiduo 9 – 11 Year Old Study

### Events Occurring in 2 or More Subjects on Either Treatment

<table>
<thead>
<tr>
<th>Event</th>
<th>Epiduo Gel N=142 n (%)</th>
<th>Vehicle Gel N=143 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin burning sensation</td>
<td>14 (9.9)</td>
<td>0</td>
</tr>
<tr>
<td>Skin discomfort</td>
<td>8 (5.6)</td>
<td>0</td>
</tr>
<tr>
<td>Dry skin</td>
<td>4 (2.8)</td>
<td>0</td>
</tr>
<tr>
<td>Sunburn</td>
<td>4 (2.8)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Erythema</td>
<td>3 (2.1)</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>2 (1.4)</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis contact</td>
<td>1 (0.7)</td>
<td>2 (1.4)</td>
</tr>
</tbody>
</table>
Pediatric Post Marketing Safety: Global Database

- No safety signals from post marketing database
  - 78 reported cases of intentional exposure with all dosage forms of adapalene
  - The most common adverse events were erythema, dry skin, and skin burning sensation
## Additional Aspects Related to Safety

- Not carcinogenic
- Not phototoxic or photoallergenic
- No known drug-drug interactions
- Potential teratogenicity
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Topical application of Differin Gel poses no risk for teratogenicity in humans.
Retinoids are Present and Important in Adults and Embryos

- Retinoids are a class of compounds that are related to Vitamin A
  - Current non-prescription retinoids include cosmetic creams with retinol
  - Vitamin A dietary supplements are also common

- Retinoids are essential for normal embryonic development
  - Typical plasma concentrations: 1 – 7 ng/mL in adults\(^1\)
  - Both excess and deficiency of retinoids can cause adverse health consequences, including malformations

---

\(^1\) Schaefer et al, *Skin Permeability*. Springer-Verlag, Berlin 1982
How Retinoids Interact with DNA

- Retinoids translocate to nucleus
  - Facilitated by Cellular Retinoic Acid Binding Protein (CRABP-II in skin)
- Retinoids interact with DNA by activating specific receptors
  - RARα
  - RARβ
  - RARγ: found predominantly in skin
Retinoic Acid is a derivative of Vitamin A (Retinol)

Vitamin A

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{OH} & \quad \text{Alcohol}
\end{align*}
\]

Retinoic Acid

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{COOH} & \quad \text{Carboxylic acid}
\end{align*}
\]
Adapalene Designed to Interact with Cells Differently than Retinoic Acid

- Chain of double bonds replaced with stable aromatic backbone of naphthoic acid
- Adamantyl group prevents CRABP II binding

Adapalene
- Low RARα affinity (1100 nM)\(^1\)
- Very Low CRABP II affinity (>>1000 nM)\(^2\)

Retinoic Acid (Tretinoin)
- High RARα affinity (16 nM)\(^1\)
- High CRABP II affinity (4 nM)\(^2\)

---

\(^2\) Bernard BA, *Skin Pharmacol.* 1993; 6(Suppl): 61-69
Exposure to High Doses of Oral Retinoic Acid During Pregnancy Can Cause Malformations

- Characteristic malformations after oral retinoic acid exposure¹:  
  - Small/malformed/missing external ears  
  - Short lower jaw  
  - Cleft palate  
  - Defects of the outflow tract of heart  
  - Ocular anomalies involving retina and/or optic nerve  
  - Hydrocephalus  
  - Thymus defects

Teratology Background

- Endpoints of concern in embryo-fetal development studies:
  - Death of offspring
  - Malformation
  - Growth retardation
Teratology Background

- A background rate of malformations exists\(^1\)
  - 3% in humans
  - 1-2% in most strains of rat
  - 2-5% in rabbits

\(^1\)Schardein JL. 2000. *Chemically Induced Birth Defects, 3rd Ed.*
Teratology Background

- For an exogenous agent to cause a malformation
  - Exposure occurs when organs are forming (organogenesis)
    - Gestational days 6-17 in rats
    - Gestational days 7-19 in rabbits
    - Gestational weeks 3-6 in humans
  - Agent must cross the placenta to reach embryo
  - Amount at target tissue must exceed a threshold
Teratology Background

- Abnormalities related to exogenous agents are associated with:
  - Findings in multiple fetuses
  - Findings in multiple litters
  - Findings in the same organ systems
  - Findings exhibit a dose-response
Adapalene Non-clinical Safety Data: Potential Teratogenicity and Systemic Exposure

- Placental transfer of oral adapalene
- Oral embryo-fetal development studies
- Dermal embryo-fetal development studies
Levels of Radioactivity in Maternal Plasma and Whole Rat Fetuses After a Repeated Oral Dose of $^{14}$C-Adapalene

Maternal $C_{\text{max}}$ is approximately 5-6 times greater than fetal $C_{\text{max}}$

These data show that placental transfer is poor, resulting in much lower fetal exposures compared to maternal plasma levels at both maternal doses.
Oral Embryo-fetal Development Studies

- High dose oral adapalene studies performed in rats and rabbits
- Adapalene *oral* doses $\geq$ 25mg/kg/day in rats and rabbits caused malformations
  - Low incidence of neural tube and palate defects in rats
  - Low incidence of tail and peri-umbilical defects in rabbits
- Malformations are *not* consistent with retinoid embryopathy
No Malformations in Rat Dermal Embryo-Fetal Development Studies

- **Design**
  - N=25 mated females per group
  - Doses: Adapalene at 0, 0.6, 2, 6 mg/kg/day (0.03, 0.1, 0.3 % gel)
  - Duration: GD 6-15
  - C-section: GD 20

- **Results**
  - No fetal malformations
  - NOAEL = 6 mg/kg/day
  - Systemic exposure at NOAEL
    - $AUC_{0-24}$ = 204 ng·h/mL
    - $C_{\text{max}}$ = 14.47 ng/mL
No Malformations in Rabbit Dermal Embryo-Fetal Development Studies

- **Results**
  - No fetal malformations
  - Systemic exposure at NOAEL
    - $\text{AUC}_{0-24} = 1036 \text{ ng} \cdot \text{h/mL}$
    - $C_{\text{max}} = 48.47 \text{ ng/mL}$
  - Adapalene applied dermally to both rats and rabbits does not result in birth defects and is not teratogenic
Design of Human Dermal Maximal Use Study to Evaluate Systemic Exposure

- **Application**
  - Differin 0.1% gel, once-daily for 4 weeks
  - Face, shoulders, upper chest, and upper back
  - Average amount applied = 2g (1.2g to 2.9g)
    - Normal use ~0.5g per day

- **Subjects:**
  - Adolescents: 12-17 years old (10 ♂ and 8 ♀)
    - Moderate to severe acne vulgaris
  - Adults: ≥18 years of age (3 ♂ and 3 ♀)
    - Severe acne vulgaris

- **Pharmacokinetics**
  - Complete PK profiles (Days 1, 15 and 30)
    - Limit of Quantitation = 0.02 ng/mL
Adapalene Does Not Accumulate in Adults and Adolescents

Adapalene Plasma Concentration (ng/mL) vs. Study Day

- Mean ± SD, N=24

0.10
0.08
0.06
0.04
0.02
0.00
0 5 10 15 20 25 30 35

Study Day
Human Systemic Exposure to Topical Adapalene is Very Low

- Systemic exposure after topical application of Differin Gel is extremely low
  - The highest measurement of adapalene was 0.17 ng/mL
  - This represents 1.2% of the $C_{\text{max}}$ for adapalene in the rat at the systemic NOAEL (14.47 ng/mL)
- No difference was discerned by sex
- No difference was discerned by age (adult vs. adolescent)
Adapalene Safety Margin Calculation

- Safety margin is the difference in multiples of exposure between the NOAEL in the most sensitive species and human maximal exposure conditions:

\[
\text{Safety Margin} = \frac{\text{Animal Systemic Exposure at Dermal NOAEL Dose}}{\text{Highest Human Systemic Exposure at Maximum Dermal Exposure Conditions}}
\]

- The larger the number you have, the safer the drug
### Teratogenicity Safety Margin for Topical Differin Gel is Very Wide

The teratogenicity safety margin for topical Differin Gel is very wide. The ratio of the lowest dermal systemic exposure in rat at the NOAEL for teratology to the highest individual human systemic exposure under maximized conditions in subjects with moderate to severe acne (\(C_{\text{max}}: 14.47 \text{ ng/mL}, \text{AUC}_{0-24h}: 204 \text{ ng.hr/mL}\)) is calculated.

#### Adapalene 0.1% Gel

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Study No.</th>
<th>Subjects</th>
<th>N</th>
<th>Number Quantifiable at Steady State</th>
<th>Most Exposed Subject</th>
<th>Safety Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adapalene 0.1% Gel (^a)</td>
<td>18254</td>
<td>Adults</td>
<td>6</td>
<td>5</td>
<td>C_{\text{max}} (ng/mL)</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adolescents (12-17)</td>
<td>18</td>
<td>17</td>
<td>AUC(_{0-24h}) (ng·h/mL)</td>
<td>2.90</td>
</tr>
</tbody>
</table>

\(^a\)LoQ = 0.02 ng/mL for Study 18254  
\(^b\)Ratio of lowest dermal systemic exposure in rat at the NOAEL for teratology to the highest individual human systemic exposure under maximized conditions in subjects with moderate to severe acne (\(C_{\text{max}}: 14.47 \text{ ng/mL}, \text{AUC}_{0-24h}: 204 \text{ ng.hr/mL}\))  
\(^c\)Day 15

- **Mean of all subjects at steady state:**  
  - Safety Margin = 234  
  - \(\text{AUC}_{0-24h} = 0.87 \pm 0.43 \text{ ng.h/mL}\)
Exposure During Pregnancy

- Data collected regarding exposure during pregnancy
  - Clinical studies and post-marketing surveillance
  - Two case types - prospective and retrospective

- 47 Retrospective cases identified
  - 15 in clinical studies
  - 32 in post-marketing surveillance

- 123 Prospective cases identified
  - 32 in clinical studies
  - 91 in post-marketing surveillance
Retrospective Cases of Exposure During Pregnancy

- 47 Retrospective cases of exposure identified
- Cases were identified due to reporting of:
  - 15 elective abortions
  - 16 miscarriages
  - 16 other abnormal outcomes/malformations
- One malformation, anophthalmia, has a known association with retinoids, but the overall range of malformations in the fetus were inconsistent with retinoid embryopathy
# Prospective Cases of Exposure to Adapalene During Pregnancy

## Pregnancy Outcome

<table>
<thead>
<tr>
<th>Pregnancy Outcome</th>
<th>Post-marketing Surveillance</th>
<th>Clinical Trials</th>
<th>Total</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective abortion</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>3.3</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>4</td>
<td>3</td>
<td>7</td>
<td>5.7</td>
</tr>
<tr>
<td>Among births</td>
<td>85</td>
<td>27</td>
<td>112</td>
<td></td>
</tr>
<tr>
<td>Healthy birth</td>
<td>83</td>
<td>26</td>
<td>109</td>
<td>97.3</td>
</tr>
<tr>
<td>Malformation</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1.8</td>
</tr>
<tr>
<td>Other abnormal outcome (abruption placenta and fetal death)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Total</td>
<td>91</td>
<td>32</td>
<td>123</td>
<td></td>
</tr>
</tbody>
</table>
Topical Application of Differin Gel Poses No Risk for Teratogenicity in Humans

- No teratogenicity observed in animals after topical application
  - Seen *only after high oral doses* in animals
- Systemic exposure in humans after topical application is very low
  - Safety margin of 70 using the dermal rat NOAEL AUC
- This safety margin is supported by the absence of human teratogenicity signals despite extensive marketed drug use
# AGENDA

<table>
<thead>
<tr>
<th>Session</th>
<th>Presenter</th>
</tr>
</thead>
</table>
| Dermatologist Perspective| Guy Webster, MD, PhD, FAAD  
Webster Dermatology and Professor of Clinical Dermatology at Jefferson Medical College, Philadelphia |
| Efficacy and Safety      | Matthew Meckfessel, PhD  
Medical Lead, Self-Medication, Galderma |
| Toxicology               | John DeSesso, PhD, DABFM, DABFE, FACFEI, DABCHS, Fellow ATS  
Director, Center for Toxicology and Mechanistic Biology, Exponent  
Professor of Biochemistry, Molecular & Cellular Biology, Georgetown University School of Medicine |
| Consumer Studies         | Julie Aker, MT (ASCP)  
President and CEO of Concentrics Research |
| Benefit-Risk Assessment  | Jonathan Wilkin, MD  
Director of Dermatology at Ohio State University (Retired)  
Founding Director of FDA Division of Dermatology & Dental Products (Retired) |
| Conclusion               | Howard Marsh, MD  
Vice President of Medical Affairs, Galderma |
Consumers Currently Self-Manage Acne

- Monograph is established and final for topical acne products
- Consumers know how to:
  - Self-diagnose
  - Self-treat
- The Differin Gel label is largely comprised of information from the monograph
- We focused our program primarily on new information on the Differin Gel label
OTC Development Program

Safety and Efficacy
- Clinical Trials, Post-Marketing, Maximal Use Study

Label Comprehension
- To evaluate if new information on the Drug Facts Label is understood

Actual Use
- To evaluate if the product is used according to the Drug Facts Label in an OTC environment

Targeted Self-Selection
- To evaluate self-selection based on the existing OTC pregnancy/breastfeeding warning
New Information on Differin Gel DFL

Contraindication
- Do not use on damaged skin (cuts, abrasions, eczema, sunburned)

Informational/Educational
- Irritation (redness, dryness, burning) is more likely to occur in the first few weeks of use
- Moisturizers may be used to relieve dry skin.
- During the early weeks of use, your acne may appear to worsen before it improves; this is not a reason to stop using the product
- Do not use wax to remove hair in areas where product has been applied.

Directions
- Ages 12 years and older
- Use once daily
- Under 12 years of age: Consult a physician
Various Study Populations Were Studied

<table>
<thead>
<tr>
<th>Studies</th>
<th>Study Populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualitative Label comprehension (iterative exploratory)</td>
<td>General population</td>
</tr>
<tr>
<td>Pivotal Label Comprehension</td>
<td>General population</td>
</tr>
<tr>
<td>Actual Use</td>
<td>All comers population</td>
</tr>
<tr>
<td>Targeted Self-selection</td>
<td>Pregnant/Breast-feeding women</td>
</tr>
</tbody>
</table>
OTC Development Program

Safety and Efficacy
Clinical Trials, Post-Marketing, Maximal Use Study

Label Comprehension
To evaluate if novel information on the Drug Facts Label is understood

Actual Use
To evaluate if the product is used according to the Drug Facts Label in an OTC environment

Targeted Self-Selection
To evaluate self-selection based on the common, OTC pregnancy/breastfeeding warning
Label Comprehension: Methodology

- Study Design based on FDA Guidance for Label Comprehension Studies
- 586 subjects recruited across United States and reviewed the Drug Facts Label
- 1:1 interviews with hypothetical scenarios posed
- Iterative testing was conducted to optimize the DFL and questionnaire prior to the pivotal study
- Thresholds represent defined success criteria
  - Not the same as a clinical trial threshold
  - The totality of the data and responses must be considered
Primary Endpoints

The primary endpoints reflect new important information

<table>
<thead>
<tr>
<th>Warning</th>
<th>Do not use on damaged skin (cuts, abrasions, eczema, sunburned)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Directions</td>
<td>Use once daily</td>
</tr>
</tbody>
</table>
Success Thresholds

- A 2-sided 95% confidence interval is calculated for objectives in consumer studies
  - The lower bound and upper bound are determined for the confidence interval
  - It is the lower bound of the 95% confidence interval that is recommended for evaluation
- A success threshold is defined for the primary endpoints
- For this study:
  - A lower bound of 85% was defined as the success threshold for the primary endpoints
## Primary Endpoints Exceeded the 85% Lower Bound Threshold

<table>
<thead>
<tr>
<th>Threshold &gt;85% Lower Bound</th>
<th>Cohort 1: General Population n=515</th>
<th>Cohort 2: Low Literacy n=130</th>
<th>Total Population n=586</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Score % CI (LB, UB)</td>
<td>Score % CI (LB, UB)</td>
<td>Score % CI (LB, UB)</td>
</tr>
<tr>
<td>Do not use on damaged skin (cuts, abrasions, eczema, sunburned)</td>
<td>97.5 (95.7, 98.7)</td>
<td>99.2 (95.8, 100.0)</td>
<td>97.8 (96.2, 98.8)</td>
</tr>
<tr>
<td>Directions: Use once daily</td>
<td>95.9 (93.8, 97.5)</td>
<td>86.9 (79.9, 92.2)</td>
<td>94.4 (92.2, 96.1)</td>
</tr>
</tbody>
</table>

- Do not use on damaged skin (cuts, abrasions, eczema, sunburned)
- Directions: Use once daily

Do not use on damaged skin (cuts, abrasions, eczema, sunburned)
### Secondary Endpoints 98-100% Correct

<table>
<thead>
<tr>
<th>Purpose: For the treatment of acne, clears up acne pimples and acne blemishes, helps prevent new acne pimples and acne blemishes from forming</th>
<th>Cohort 1: General Population n=515</th>
<th>Cohort 2: Low Literacy n=130</th>
<th>Total Population n=586</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>CI (LB, UB)</td>
<td>Score</td>
<td>CI (LB, UB)</td>
</tr>
<tr>
<td>100.0</td>
<td>(99.3, 100.0)</td>
<td>98.5</td>
<td>(94.6, 99.8)</td>
</tr>
</tbody>
</table>

| Directions: Age 12 and older | 99.0 | (97.8, 99.7) | 93.8 | (88.2, 97.3) | 99.7 | (98.8, 100.0) |

| When using this product: **Do not use wax** to remove hair in the areas where the product has been applied | 98.4 | (97.0, 99.3) | 96.9 | (92.3, 99.2) | 98.3 | (96.9, 99.2) |

| When using this product avoid unnecessary sun exposure, including tanning beds | 97.5 | (95.7, 98.6) | 95.4 | (90.2, 98.3) | 96.9 | (95.2, 98.2) |
## Secondary Endpoints 88-96% Correct

<table>
<thead>
<tr>
<th>No success thresholds required</th>
<th>Cohort 1: General Population n=515</th>
<th>Cohort 2: Low Literacy n=130</th>
<th>Total Population n=586</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Score</strong></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td><strong>CI (LB, UB)</strong></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>When using this product</td>
<td>95.7 (93.6, 97.3)</td>
<td>86.2 (79.0, 91.6)</td>
<td>94.7 (92.6, 96.4)</td>
</tr>
<tr>
<td>moisturizers may be used to</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>relieve dry skin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Directions: Under 12 years of</td>
<td>93.8 (91.3, 95.7)</td>
<td>85.4 (78.1, 91.0)</td>
<td>92.3 (89.9, 94.3)</td>
</tr>
<tr>
<td>age, consult a physician</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>When using this product</td>
<td>93.4 (90.9, 95.4)</td>
<td>86.2 (79.0, 91.6)</td>
<td>92.7 (90.2, 94.6)</td>
</tr>
<tr>
<td>irritation (redness, itching,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dryness, burning) is more</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>likely to occur in the first</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>few weeks or use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>When using this product</td>
<td>87.6 (84.4, 90.3)</td>
<td>75.4 (67.1, 82.5)</td>
<td>86.2 (83.1, 88.9)</td>
</tr>
<tr>
<td>during the early weeks of use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>your acne may appear to</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>worsen before it improves.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This is not a reason to stop</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>using the product.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Two Lowest Scoring Messages: Mitigated to ≥85% Acceptable/Correct (Both from Acne Monograph)

<table>
<thead>
<tr>
<th>Message</th>
<th>Cohort 1: General Population</th>
<th>Cohort 2: Low Literacy</th>
<th>Total Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop use and ask a doctor if irritation becomes severe. (monograph)</td>
<td>77.5 (73.6, 81.0)</td>
<td>71.5 (63.0, 79.1)</td>
<td>77.1 (73.5, 80.5)</td>
</tr>
<tr>
<td>Mitigated</td>
<td>9.5</td>
<td>10.0</td>
<td>9.4</td>
</tr>
<tr>
<td>Total Correct</td>
<td>87.0</td>
<td>81.5</td>
<td>86.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Message</th>
<th>Cohort 1: General Population</th>
<th>Cohort 2: Low Literacy</th>
<th>Total Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>When using this product irritation (redness, itching, dryness, burning) is more likely to occur if using more than one topical acne medication at a time. (monograph)</td>
<td>62.7 (58.4, 66.9)</td>
<td>51.5 (42.6, 60.4)</td>
<td>61.6 (57.5, 65.6)</td>
</tr>
<tr>
<td>Mitigated</td>
<td>22.0</td>
<td>27.7</td>
<td>23.0</td>
</tr>
<tr>
<td>Total Correct</td>
<td>84.7</td>
<td>79.2</td>
<td>84.6</td>
</tr>
</tbody>
</table>
Label Comprehension Summary: Consumers Comprehend the Drug Facts Label

- General Population
  - Primary endpoints exceeded threshold of >85% correct
  - Secondary endpoints:
    - 4 endpoints ≥98% correct
    - 4 endpoints ≥88% correct
    - 2 endpoints ≥85% correct/mitigated

- Scores were acceptable for adolescents and consumers of lower literacy
OTC Development Program

Safety and Efficacy
Clinical Trials, Post-Marketing, Maximal Use Study

Label Comprehension
To evaluate if novel information on the Drug Facts Label is understood

Actual Use
To evaluate if the product is used according to the Drug Facts Label in an OTC environment

Targeted Self-Selection
To evaluate self-selection based on the common, OTC pregnancy/breastfeeding warning
Goals of Actual Use Study

<table>
<thead>
<tr>
<th>To study how consumers will use the product in an OTC environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emulate, to the degree possible, a real-life experience</td>
</tr>
</tbody>
</table>

<p>| For this study, the objectives were to evaluate if consumers comply with |</p>
<table>
<thead>
<tr>
<th>3 new label messages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use once daily</td>
</tr>
<tr>
<td>Use for acne only (i.e. do not use off-label)</td>
</tr>
<tr>
<td>Use on correct body areas (not on damaged skin or on eyes, lips, mouth)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1 established label warning</th>
</tr>
</thead>
<tbody>
<tr>
<td>If pregnant or breastfeeding, ask a health professional before use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other areas of interest that were evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who used the product</td>
</tr>
<tr>
<td>Where they used the product</td>
</tr>
<tr>
<td>The quantity that was used</td>
</tr>
<tr>
<td>Con med use</td>
</tr>
</tbody>
</table>

|                          |
| Adverse events           |
| Use in subjects with eczema |
AUS Design

- Open-label, 6-week study in all-comers population of any age, race, gender
- 31 pharmacy sites, in 24 markets
- Not a self-selection study as acne is a well-established OTC condition
- Minimal screening criteria
- Actual use studies use advertising to reflect a real-life approach
## AUS Study Flow

<table>
<thead>
<tr>
<th>Recruitment</th>
<th>Visit 1 Enrollment</th>
<th>Home Use</th>
<th>Visit 2 End-of-Study</th>
</tr>
</thead>
</table>
| • All comers population  
• Minimal screening through call center | • CDA signed  
• Review of package labeling  
• Purchase decision  
• Informed Consent  
• Pregnancy test  
• Inclusion/exclusion  
• REALM Test  
• Product and diary dispensed  
• No coaching or instructions | • 6-week use at home  
• Ability to re-purchase  
• 24/7 adverse events coverage  
• Documented use in diary | • Collection of diary and product  
• Repeat pregnancy test  
• Investigation of any AEs  
• End-of-study questionnaire |
Subject Disposition

- **Screened from ad**
  - n=3234

- **Scheduled to pharmacy**
  - n=2037

- **Visit 1**
  - n=1277

- **Included in the actual use population**
  - n=947

- **Completers**
  - n=938

1,197 did not schedule due to convenience or screen failures.

760 No Shows

330 were not included in the actual use population primarily due to not choosing to purchase the drug or due to a screen failure.

9 Discontinued from Actual Use Period
### Demographics: Who Used the Product?

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total Population</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-17 years of age</td>
<td></td>
<td>203</td>
<td>21.4</td>
</tr>
<tr>
<td>18 years of age or older</td>
<td></td>
<td>744</td>
<td>78.6</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>304</td>
<td>32.1</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>643</td>
<td>67.9</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian/White</td>
<td></td>
<td>492</td>
<td>52.0</td>
</tr>
<tr>
<td>African American/Black</td>
<td></td>
<td>321</td>
<td>33.9</td>
</tr>
<tr>
<td>American Indian/Alaskan Native</td>
<td></td>
<td>12</td>
<td>1.3</td>
</tr>
<tr>
<td>Native Hawaiian or Pacific Islander</td>
<td></td>
<td>6</td>
<td>0.6</td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td>25</td>
<td>2.6</td>
</tr>
<tr>
<td>Refused</td>
<td></td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>88</td>
<td>9.3</td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td>113</td>
<td>11.9</td>
</tr>
</tbody>
</table>
PE1: Once Daily Use

- Proportion of subjects who used the product only once per day

- Success threshold = Lower bound >85% compliance

- Total correct include initial correct plus mitigations
  - Mitigations represent a reasonable response or a safe course of action
## PE1: Once Daily Use - 89% Compliance

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Score</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=947</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Threshold = Lower Bound &gt;85% Correct</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL CORRECT</strong></td>
<td>89.1</td>
<td>(87.0, 91.0)</td>
</tr>
<tr>
<td>Initially Correct</td>
<td>81.0</td>
<td>(78.3, 83.4)</td>
</tr>
<tr>
<td>Mitigated a priori (used &gt;1x only once)</td>
<td>6.4</td>
<td>(5.0, 8.2)</td>
</tr>
<tr>
<td>Mitigated post-study (schedule change/used late)</td>
<td>1.3</td>
<td>(0.7, 2.2)</td>
</tr>
<tr>
<td>Mitigated post-study (re-read directions)</td>
<td>0.4</td>
<td>(0.1, 1.1)</td>
</tr>
</tbody>
</table>
PE2: Use for Acne Only

- Proportion of subjects who used the product only for acne
- Success threshold ≥ 85% compliance
### PE2: Use for acne only - 99% Compliance

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Score</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=945</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Threshold = Lower Bound &gt;85% Correct</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL CORRECT</td>
<td>99.0</td>
<td>(98.5, 99.7)</td>
</tr>
<tr>
<td>Initially Correct</td>
<td>98.5</td>
<td>(97.8, 99.3)</td>
</tr>
<tr>
<td>Mitigated a priori (previously prescribed)</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Mitigated post-study (same area as acne)</td>
<td>0.5</td>
<td>(0.2, 1.2)</td>
</tr>
</tbody>
</table>
SE1: Use On Correct Body Area

- Two criteria evaluated:
  - Do not use on damaged skin (cuts, abrasions, eczema, sunburned)
  - Avoid contact with eyes, lips, mouth

- Scores were summarized; no success thresholds for secondary endpoints
## SE1: Use on Correct Body Area
97% Compliance

<table>
<thead>
<tr>
<th>Secondary Endpoint</th>
<th>Score</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=945</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL CORRECT</strong></td>
<td>97.3</td>
<td>(96.2, 98.4)</td>
</tr>
<tr>
<td>Initially Correct</td>
<td>95.9</td>
<td>(94.6, 97.2)</td>
</tr>
<tr>
<td>Mitigated a priori (Only 1-2 times)</td>
<td>1.0</td>
<td>(0.4, 1.8)</td>
</tr>
<tr>
<td>Mitigated post-study (used near area to treat acne)</td>
<td>0.3</td>
<td>(0.1, 0.9)</td>
</tr>
<tr>
<td>Mitigated post-study (side effect of product – dry skin)</td>
<td>0.1</td>
<td>(0.0, 0.6)</td>
</tr>
</tbody>
</table>
SE 2: Compliance with the Pregnancy/Breastfeeding Warning

- The codified pregnancy and breastfeeding warning was tested in this study
- It states that a health professional should be asked before use if pregnant or breastfeeding
### SE2: Compliance with Current OTC Warning

<table>
<thead>
<tr>
<th>Secondary Endpoint</th>
<th>Score n/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All comers population (on-site for Visit 1)</td>
<td>1277</td>
</tr>
<tr>
<td>Women of child-bearing potential (on-site for Visit 1)</td>
<td>561 (43.9%)</td>
</tr>
<tr>
<td>Pregnant or breastfeeding women who tried to enter the study</td>
<td>16 (1.25%)</td>
</tr>
<tr>
<td>Total correct</td>
<td>8 (50.0)</td>
</tr>
</tbody>
</table>
**Amount Purchased**

- The majority of subjects in the AUS purchased only 1 tube of product

<table>
<thead>
<tr>
<th>Counts of Purchased Tube(s)</th>
<th>All Subjects N=947</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>886 (93.6)</td>
</tr>
<tr>
<td>2</td>
<td>57 (6.0)</td>
</tr>
<tr>
<td>3</td>
<td>4 (0.4)</td>
</tr>
</tbody>
</table>

- 47 Subjects (5.0%) >1 tube at V1
- 14 Subjects (1.5%) returned for a repurchase
- Days between purchases:
  - 27.0 days (median)
  - 13 - 42 days (min – max)
- 2 subjects (0.2%) purchased additional tubes in the last week of the study

*Of the 4 subjects who reported using the most product, there were no adverse events.*
# Dermatologic AEs by Preferred Term

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>All Subjects N=947</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any TEAE</td>
<td>471 (49.7)</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dry Skin</td>
<td>100 (10.6)</td>
</tr>
<tr>
<td></td>
<td>Erythema</td>
<td>44 (4.6)</td>
</tr>
<tr>
<td></td>
<td>Skin Exfoliation</td>
<td>38 (4.0)</td>
</tr>
<tr>
<td></td>
<td>Skin Burning Sensation</td>
<td>37 (3.9)</td>
</tr>
<tr>
<td></td>
<td>Acne</td>
<td>30 (3.2)</td>
</tr>
<tr>
<td></td>
<td>Pruritus</td>
<td>19 (2.0)</td>
</tr>
<tr>
<td></td>
<td>Skin Irritation</td>
<td>17 (1.8)</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>14 (1.5)</td>
</tr>
<tr>
<td></td>
<td>Skin Fragility</td>
<td>9 (1.0)</td>
</tr>
<tr>
<td><strong>Injury, Poisoning and Procedural Complications</strong></td>
<td></td>
<td>79 (8.3)</td>
</tr>
<tr>
<td></td>
<td>Sunburn</td>
<td>28 (3.0)</td>
</tr>
<tr>
<td></td>
<td>Laceration</td>
<td>18 (1.9)</td>
</tr>
<tr>
<td></td>
<td>Skin Abrasion</td>
<td>10 (1.1)</td>
</tr>
</tbody>
</table>
Summary of AUS

• Consumers complied with new information on the Drug Facts Label:
  - ~90% used the product once daily
  - ~99% had no off-label product use
  - ~97% used the product on the correct body location

• The study results were similar for adolescents and low literate subjects

• The drug was used as instructed in the DFL and there were no potential safety concerns that would alter the known safety profile of the study product
OTC Development Program

Safety and Efficacy
Clinical Trials, Post-Marketing, Maximal Use Study

Label Comprehension
To evaluate if novel information on the Drug Facts Label is understood

Actual Use
To evaluate if the product is used according to the Drug Facts Label in an OTC environment

Targeted Self-Selection
To evaluate self-selection based on the common, OTC pregnancy/breastfeeding warning
Purpose

- Despite the confirmed minimal systemic availability of Differin Gel, and thus exposure of pregnant women not a safety concern,
  - A Targeted Self-Selection study was conducted based on principles outlined in the FDA Guidance for Self-Selection Studies.
  - Objective:
    - To provide self-selection data on the effectiveness of the codified (currently approved and used) warning statement
    - To evaluate the warning for women currently pregnant or breast-feeding
Targeted Self-Selection Recruitment

- **Intercept Process**
  - The interceptors at the mall approached the following types of consumers in the mall:
    - Females who appeared to be between the ages of 18 and 50
    - Females with visible acne
    - Females who are visibly pregnant
    - Females with children who appear to be under 18 months old
  - 25 mall sites and 1 specialty clinic for pregnant teens
  - Over 19,000 women were intercepted in order to find the required study population
If pregnant or breastfeeding, ask a health professional before use.
## Targeted SS Demographics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=293</td>
</tr>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Age: 13-17 years of age</td>
<td>2</td>
</tr>
<tr>
<td>18 – 24 years of age</td>
<td>111</td>
</tr>
<tr>
<td>25 – 34 years of age</td>
<td>124</td>
</tr>
<tr>
<td>35 – 44 years of age</td>
<td>51</td>
</tr>
<tr>
<td>45 – 54 years of age</td>
<td>5</td>
</tr>
<tr>
<td>Race:</td>
<td></td>
</tr>
<tr>
<td>Caucasian/White</td>
<td>168</td>
</tr>
<tr>
<td>African American/Black</td>
<td>60</td>
</tr>
<tr>
<td>American Indian/Alaskan Native</td>
<td>5</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>54</td>
</tr>
<tr>
<td>Hispanic</td>
<td>57</td>
</tr>
</tbody>
</table>
# Targeted SS Demographics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total Study Population</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=293</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Pregnant</td>
<td></td>
<td>96</td>
<td>32.8</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td></td>
<td>184</td>
<td>62.8</td>
</tr>
<tr>
<td>Both Pregnant &amp; Breastfeeding</td>
<td></td>
<td>13</td>
<td>4.4</td>
</tr>
<tr>
<td>Literacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal Literacy</td>
<td></td>
<td>181</td>
<td>61.8</td>
</tr>
<tr>
<td>Low Literacy</td>
<td></td>
<td>112</td>
<td>38.2</td>
</tr>
</tbody>
</table>
## Self-selection by Cohort

<table>
<thead>
<tr>
<th>Threshold &gt;90% Lower Bound</th>
<th>Cohort 1: General Population</th>
<th>Cohort 2: Low Literacy</th>
<th>Total Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Score %</td>
<td>CI %</td>
<td>Score %</td>
</tr>
<tr>
<td>Correct Self-Selection</td>
<td>74.4 (68.4, 79.8)</td>
<td></td>
<td>70.5 (61.2, 78.8)</td>
</tr>
<tr>
<td>Correct initially</td>
<td>73.1 (67.1, 78.6)</td>
<td></td>
<td>68.8 (59.3, 77.2)</td>
</tr>
<tr>
<td>Mitigated</td>
<td>1.2 (0.3, 3.6)</td>
<td></td>
<td>1.8 (0.2, 6.3)</td>
</tr>
</tbody>
</table>
Self-Selection Summary

- About three-quarters (74%) of pregnant or breastfeeding women who self-reported acne stated that they would ask a health professional prior to using Differin Gel.

- The endpoint was not met and not all women may comply with the warning, but as previously presented:
  - Large margins of safety exist to ensure that Differin Gel does not pose a risk of teratogenicity in a nonprescription environment.
Overall Summary for Consumer Studies

- Consumers understand the DFL
- Consumers can use Differin Gel, according to the DFL in an unsupervised OTC environment
  - Consumers will use the product once daily
  - On the correct body areas
  - And for the indication of acne
- None of the incorrect responses or behaviors posed any clinically relevant safety concerns
# AGENDA

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologist Perspective</td>
<td>Guy Webster, MD, PhD, FAAD</td>
</tr>
<tr>
<td></td>
<td>Webster Dermatology, P.A.</td>
</tr>
<tr>
<td>Efficacy and Safety</td>
<td>Matthew Meckfessel, PhD</td>
</tr>
<tr>
<td></td>
<td>Medical Lead, Self-Medication, Galderma</td>
</tr>
<tr>
<td>Toxicology</td>
<td>John DeSesso, PhD, DABFM, DABFE, FACFEI, DABCHS, Fellow ATS</td>
</tr>
<tr>
<td></td>
<td>Director, Center for Toxicology and Mechanistic Biology, Exponent</td>
</tr>
<tr>
<td></td>
<td>Professor of Biochemistry, Molecular &amp; Cellular Biology, Georgetown University School of Medicine</td>
</tr>
<tr>
<td>Consumer Studies</td>
<td>Julie Aker, MT (ASCP)</td>
</tr>
<tr>
<td></td>
<td>President and CEO of Concentrics Research</td>
</tr>
<tr>
<td>Benefit-Risk Assessment</td>
<td>Jonathan Wilkin, MD</td>
</tr>
<tr>
<td></td>
<td>Director of Dermatology at Ohio State University (Retired)</td>
</tr>
<tr>
<td></td>
<td>Founding Director of FDA Division of Dermatology &amp; Dental Products (Retired)</td>
</tr>
<tr>
<td>Conclusion</td>
<td>Howard Marsh, MD</td>
</tr>
<tr>
<td></td>
<td>Vice President of Medical Affairs, Galderma</td>
</tr>
</tbody>
</table>
Benefit-risk Assessment Framework

Decision factors

- Therapeutic area considerations
  1. Analysis of Condition
  2. Current Treatment Options

- Drug specific considerations
  1. Benefit
  2. Risk
  3. Risk Management
Analysis of Condition

- Well-recognized inflammatory skin condition
- Can lead to scarring
- High emotional and psychological impact
- Self-diagnosed and self-treated by consumers OTC for decades
Decision Factors

• Therapeutic area considerations
  1. Analysis of condition
  
  **2. Current treatment options**

• Drug specific considerations
  1. Benefit
  2. Risk
  3. Risk management
Single active ingredient topical products permitted:

- Benzoyl peroxide (30%)
- Salicylic acid (69%)
- Sulfur (<1%)

Combination active ingredient topical products permitted include resorcinol and resorcinol monoacetate in combination with sulfur (<1%)

Only OTC ingredient recommended in AAD Guideline’s (2016) treatment algorithm is benzoyl peroxide

AAD guidelines recommend as first line therapy, topical retinoids, currently not available for all severities of acne
Decision Factors

- **Therapeutic area considerations**
  1. Analysis of condition
  2. Current treatment options

- **Drug specific considerations**
  1. Benefit
  2. Risk
  3. Risk management
The Benefits of Differin Gel are Well Characterized

- Two distinct MOAs to treat acne
  - “Retinoids are the core of topical therapy for acne because they are comedolytic, resolve the precursor microcomedo lesion, and are anti-inflammatory” – 2016 AAD Guideline

- Once-daily use for Differin Gel

- Clinical efficacy proven in studies conducted to support FDA approval

- Labeling proposed is consistent with existing OTC acne labeling and new information is well understood

- Additional, valuable OTC acne medication option
Decision Factors

- Therapeutic area considerations
  1. Analysis of condition
  2. Current treatment options

- Drug specific considerations
  1. Benefit
  
  2. Risk
  3. Risk management
The Risks of Differin Gel are Well Understood and Low

- Clinical studies, including pharmacokinetic studies, and extensive post-marketing history confirm safety profile
- Phototoxicity and photoallergenic potential not a concern
- Risks associated with off-label use are low
The Risks of Differin Gel are Well Understood and Low

- **Teratogenicity**
  - Retinoids are currently available nonprescription in cosmetic creams and from dietary supplements
    - Differin Gel would be the first OTC retinoid approved under a New Drug Application
  - Properties of the drug and low systemic exposure lead to a large safety margin that ensures that topical Differin Gel does not pose a risk of teratogenicity
Decision Factors

- **Therapeutic area considerations**
  1. Analysis of condition
  2. Current treatment options

- **Drug specific considerations**
  1. Benefit
  2. Risk

  3. Risk management
Risk Management

- Side effects largely self-managed - dermatologic, mild, localized and reduced frequency over time

- Proposed nonprescription labeling incorporates important elements of:
  - Prescription labeling
  - OTC acne monograph labeling
  - Codified OTC pregnancy and breastfeeding warning

- Consumer development program has evaluated consumer behavior and confirmed appropriate use, expected for an existing OTC condition
Decision Factors for the Benefit-Risk Assessment are All Supportive

- **Therapeutic area considerations**
  1. Analysis of condition
  2. Current treatment options

- **Drug specific considerations**
  1. Benefit
  2. Risk
  3. Risk management
## AGENDA

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Founding Director of FDA Division of Dermatology & Dental Products (Retired) |
| Conclusion                      | Howard Marsh, MD  
Vice President of Medical Affairs, Galderma |
Differin Gel Meets Criteria for OTC Drugs

- The consumer must be able to self-diagnose the condition proposed to be treated
  - Consumers have self-diagnosed and self-treated their acne with topical OTC drugs for decades

- The consumer must be able to read and understand the product labeling to ensure proper usage
  - The proposed Differin Gel Drug Facts Label is similar to current OTC acne labeling, incorporates key elements of prescription label and consumer studies have demonstrated that it is well understood
Differin Gel Meets Criteria for OTC Drugs

- The product must be effective when used as recommended
  - Clinical studies have confirmed effectiveness

- The drug must be safe for self-use
  - No safety concerns due to potential misuse or if used by children under 12
  - Teratogenicity is not a concern when used topically
  - Adverse events are dermatologic in nature, local and generally mild
Differin Gel Should be Available Without a Prescription

- A once-daily, safe and effective treatment that consumers can use appropriately in an OTC setting
- Two MOAs in treating acne and differs from current OTC acne drugs
- An additional, first line treatment option for a condition that impacts the lives of millions of acne sufferers
# Drug Facts

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adapalene 0.1%</td>
<td>Acne Treatment</td>
</tr>
</tbody>
</table>

## Uses
- For the treatment of acne
- Clears up acne pimples and acne blemishes

## Warnings
For external use only.

- Do not use if on damaged skin (cuts, abrasions, eczema, sunburned)
- Do not use if pregnant or breast-feeding without consulting a health professional

When using this product:
- Avoid unnecessary sun exposure, including tanning beds, and use sunscreen when going outdoors.
- Avoid using more than one topical acne medication at a time.
- Moisturizers may be used to relieve dry skin.
- Avoid contact with eyes, lips and mouth. If contact occurs, immediately flush with water.
- During the early weeks of use, your acne may appear to worsen before it improves; this is not a reason to stop using the product.
- Do not use wax to remove hair in areas where product has been applied.

## Stop use and ask a doctor if
- Irritation becomes severe.

## Keep out of reach of children.
If swallowed, get medical help or contact a Poison Control Center right away.

## Directions
- Ages 12 years and older: Use once daily
- Under 12 years of age: Consult a physician

## Inactive Ingredients
- Carbomer 940,
- Edetate Disodium,
- Methylparaben,
- Poloxamer 182,
- Propylene Glycol,
- Purified Water
- Sodium Hydroxide. May contain Hydrochloric Acid to adjust pH.

## Questions?
1-866-735-4137
What is Differin and what is it used for?
- Differin is a once-a-day topical medication used for the treatment of acne in people age 12 and older.
- It works under the skin to unclog pores and clear up acne pimples and acne blemishes.

How long will it take for Differin to work?
- Results should start to appear after two weeks of daily usage.

What should I know before using the product?
- If pregnant or breast-feeding, ask a health professional before use.
- Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

How do I apply the product?
- Gently cleanse your entire face using a mild cleanser and pat dry.
- Differin should be applied as a thin layer to the entire face and any other affected areas of the skin once daily. Differin is not a spot treatment and should not be used to treat a single pimple or blemish.
- You should avoid contact with eyes, lips and mouth. If contact occurs, immediately flush with water.
- Do not apply product to damaged skin (cuts, abrasions, eczema, or sunburned skin).

How often do I apply the product?
- Apply this product once daily and you should try to apply the product at the same time each day if possible.

Can I use a moisturizer if my skin is dry?
- Yes.

What do I do if I need to be in the sun?
- When possible, avoid unnecessary sun exposure, including tanning beds.
- When going outdoors, use a sunscreen.

When is my skin most likely to become irritated? And what do I do?
- Irritation (redness, itching, dryness, burning) is more likely to occur:
  - In the first few weeks of use
  - If using more than one topical acne medication at a time.
- Moisturizers may be used.
- You may use a mild, non-comedogenic moisturizer (non-pore clogging).
- Irritation usually diminishes with use.

What do I do if my skin becomes severely irritated?
- If irritation becomes severe, stop use and ask a doctor before using the product again.

Can I remove unwanted facial hair by waxing while using this product?
- Do not use wax to remove hair in areas where product has been applied because skin is more sensitive after waxing.

What ingredients are used in Differin?
- Differin contains:
  - The active ingredient is adapalene 0.1%. The other ingredients are: Carbomer 940, Edetate Disodium, Methylparaben, Poloxamer 182, Propylene Glycol, Purified Water and Sodium Hydroxide.
- May contain Hydrochloric Acid to adjust the pH.
- Do not use Differin if you are allergic to any of these ingredients.

How should I store this product?
- Differin should be stored at room temperature [68° – 77°F]. Keep it from freezing.
- Do not use the product after the expiry date marked on the crimp of the tube.

Other Questions?
- Where can I get more information?
- Phone: 1-866-735-4137
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Other Questions?
- Where can I get more information?
- Phone: 1-866-735-4137
CLINICAL PHARMACOLOGY: Adapalene is a chemically stable, retinoid-like compound. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization, and inflammatory processes all of which represent important features in the pathology of acne vulgaris. Mechanistically, adapalene binds to specific retinoic acid nuclear receptors but does not bind to the cytosolic receptor protein. Although the exact mode of action of adapalene is unknown, it is suggested that topical adapalene may normalize the differentiation of follicular epithelial cells resulting in decreased microcomedone formation.

Pharmacokinetics: Absorption of adapalene through human skin is low. Only trace amounts (<0.25 ng/mL) of parent substance have been found in the plasma of acne patients following chronic topical application of adapalene in controlled clinical trials. Excretion appears to be primarily by the biliary route.
Gel until the effects of such preparations in the skin have subsided.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.3, 0.9, and 2.6 mg/kg/day and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day, approximately 4-75 times the maximal daily human topical dose. In the oral study, positive linear trends were observed in the incidence of follicular cell adenomas and carcinomas in the thyroid glands of female rats, and in the incidence of benign and malignant pheochromocytomas in the adrenal medullas of male rats.

No photocarcinogenicity studies were conducted. Animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or to sunlight. Although the significance of these studies to human use is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial UV irradiation sources.

In a series of in vivo and in vitro studies, adapalene did not exhibit mutagenic or genotoxic activities.

Pregnancy: Teratogenic effects. Pregnancy Category C. No teratogenic effects were seen in rats at oral doses of adapalene 0.15 to 5.0 mg/kg/day, up to 120 times the maximal daily human topical dose. Cutaneous route teratology studies conducted in rats and rabbits at doses of 0.6, 2.0, and 6.0 mg/kg/day, up to 150 times the maximal daily human topical dose exhibited no fetotoxicity and only minimal increases in supernumerary ribs in rats. There are no adequate and well-controlled studies in pregnant women. Adapalene should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN Gel is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS: Some adverse effects such as erythema, scaling, dryness, pruritus, and burning will occur in 10-40% of patients. Pruritus or burning immediately after application also occurs in approximately 20% of patients. The following additional adverse experiences were reported in approximately 1% or less of patients: skin irritation, burning/stinging, erythema, sunburn, and acne flares. These are most commonly seen during the first month of therapy and decrease in frequency and severity thereafter. All adverse effects with use of DIFFERIN Gel during clinical trials were reversible upon discontinuation of therapy.

OVERDOSAGE: DIFFERIN Gel is intended for cutaneous use only. If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur. The acute oral toxicity of DIFFERIN Gel in mice and rats is greater than 10 mL/kg. Chronic ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

DOSAGE AND ADMINISTRATION: DIFFERIN Gel should be applied once a day to affected areas after washing in the evening before retiring. A thin film of the gel should be applied, avoiding eyes, lips, and mucous membranes.

During the early weeks of therapy, an apparent exacerbation of acne may occur. This is due to the action of the medication on previously unseen lesions and should not be considered a reason to discontinue therapy. Therapeutic results should be noticed after eight to twelve weeks of treatment.

HOW SUPPLIED: DIFFERIN (adapalene gel) Gel, 0.1% is supplied in the following size:

45 g laminate tube - NDC 0299-5910-45


MARKETING INFORMATION:

GALDERMA LABORATORIES, L.P.
Fort Worth, Texas 76177 USA

Mfd. by:
G Production Inc.
Baie d’Urfé, QC, H9X 3S4 Canada

Made in Canada.

GALDERMA is a registered trademark.

P50045-1
Revised: April 2011
Backup Slides
**LC – Recruitment**

**Inclusion/Exclusion**

- **Inclusion was broad**
  - Ages 12+
  - Anyone who could potentially use the drug product regardless of age, sex, underlying medical conditions, and/or the use of concomitant medications
  - Agree to participate/parental permission to participate

- **Exclusions were minimal**
  - Participants were not required to have an interest in the drug product
  - Could not have participated in any clinical trial, product label study or marketing research study involving a healthcare product or topic in the previous twelve (12) months
  - Employment security

- **Qualified participants were invited to participate in the study and directed to a local facility for a one-on-one interview**
Inclusion Criteria

- Male or Female, of any race
- Self-report experiencing acne
- Able to read, speak, and/or understand English
- Read and sign the Health Insurance Portability and Accountability Act (HIPAA)/Confidentiality Agreement
- Read and sign the Informed Consent (ICF) – for subjects entering Use who are ages 18 and older
- Read and sign the Assent (for subjects entering Use who are ages 12-17) and parent to provide documented parental permission
Exclusion Criteria

- The subject or anyone in his/her household is currently employed by any of the following:
  - A marketing or clinical research company
  - An advertising agency or public relations firm
  - A pharmacy or pharmaceutical company
  - A manufacturer of medicines
  - A managed care or health insurance company as a healthcare professional
  - A healthcare practice
  - A public health agency such as Health and Human Services, or the Food and Drug Administration (FDA)

- The subject has ever been trained or employed as a healthcare professional. A healthcare professional is a physician, nurse practitioner, physician assistant or pharmacist
<table>
<thead>
<tr>
<th></th>
<th>Pregnant N=96</th>
<th>Breastfeeding N=184</th>
<th>Both N=13</th>
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<tr>
<td>Correct Self-Selection</td>
<td>72.9 %</td>
<td>76.6 %</td>
<td>76.9 %</td>
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<tr>
<td>Correct initially</td>
<td>72.9 %</td>
<td>74.5 %</td>
<td>69.2 %</td>
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<tr>
<td>Mitigated</td>
<td>-</td>
<td>2.2 %</td>
<td>7.7 %</td>
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Mitigation = 4 Breastfeeding and 1 Both
Proposed OTC Patient Leaflet (1 of 2)

Differin
0.1% Adapalene Gel

Frequently Asked Questions

What is Differin and what is it used for?
• Differin is a once-a-day topical medication used for the treatment of acne in people age 12 and older.
• It works under the skin to unclog pores and clear up acne pimples and acne blemishes.

How long will it take for Differin to work?
• Results should start to appear after two weeks of daily usage.

What should I know before using the product?
• If pregnant or breast-feeding, ask a health professional before use.
• Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

How do I apply the product?
• Gently cleanse your entire face using a mild cleanser and pat dry.
• Differin should be applied as a thin layer to the entire face and any other affected areas of the skin once daily. Differin is not a spot treatment and should not be used to treat a single pimple or blemish.
• You should avoid contact with eyes, lips and mouth. If contact occurs, immediately flush with water.
• Do not apply product to damaged skin (cuts, abrasions, eczema, or sunburned skin).

How often do I apply the product?
• Apply this product once daily and you should try to apply the product at the same time each day if possible.

Can I use a moisturizer if my skin is dry?
• Yes.

What do I do if I need to be in the sun?
• When possible, avoid unnecessary sun exposure, including tanning beds.
• When going outdoors, use a sunscreen.
Frequently Asked Questions (Continued)

When is my skin most likely to become irritated? And what do I do?
- Irritation (redness, itching, dryness, burning) is more likely to occur:
  - In the first few weeks of use
    - If using more than one topical acne medication at a time.
- Moisturizers may be used.
  - You may use a mild, non-comedogenic moisturizer (non-pore clogging)
- Irritation usually diminishes with use.

What do I do if my skin becomes severely irritated?
- If irritation becomes severe, stop use and ask a doctor before using the product again.

Can I remove unwanted facial hair by waxing while using this product?
- Do not use wax to remove hair in areas where product has been applied because skin is more sensitive after waxing.

What ingredients are used in Differin?
- Differin contains:
  - The active ingredient is adapalene 0.1%. The other ingredients are: Carbomer 940, Edetate Disodium, Methylparaben, Poloxamer 182, Propylene Glycol, Purified Water and Sodium Hydroxide.
  - May contain Hydrochloric Acid to adjust the pH.
- Do not use Differin if you are allergic to any of these ingredients.

How should I store this product?
- Differin should be stored at room temperature [68° - 77°F]. Keep it from freezing.
- Do not use the product after the expiry date marked on the crimp of the tube.

Other Questions?
- Where can I get more Information?
- Phone: 1-866-735-4137
Codified Pregnancy Warning

• 21 CFR 201.63
  • Rulemaking began Dec 3, 1982

• The labeling for all over-the-counter (OTC) drug products that are intended for systemic absorption, unless specifically exempted, shall contain a general warning under the heading "Warning" (or "Warnings" if it appears with additional warning statements) as follows: "if pregnant or breastfeeding, ask a health professional before use."

• The labeling of orally or rectally administered OTC aspirin and aspirin-containing drug products must bear a warning that immediately follows the general warning identified in paragraph (a) of this section. The warning shall be as follows:

  "It is especially important not to use" (select "aspirin" or "carbaspirin calcium," as appropriate) "during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery."
Three studies assessing systemic exposure from once-daily topical application of Adapalene 0.1% Gel (N=73)

1) SPR.18115\textsuperscript{a}
Adapalene 0.1% Gel
n = 25 adults
\textsuperscript{a}Study also included a treatment arm with Adapalene 0.3% Gel

2) SPR.18097
Arm 1:
Adapalene 0.1% Gel (Monad)
n = 12 adults
Arm 2:
Epiduo\textsuperscript{®} Gel (Fixed-dose combo)\textsuperscript{b}
n = 12 adults

\textsuperscript{b}Epiduo\textsuperscript{®} Gel is a fixed-dose combination of Adapalene and benzoyl peroxide (BPO) gel, 0.1%/2.5%

3) SPR.18254
Adapalene 0.1% Gel
N = 24
18 adolescents
6 adults
## Adapalene 0.1% Maximal Use Conditions: 3 Studies, Comparison of Systemic Exposure

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Subjects</th>
<th>Treatment Duration</th>
<th>Fixed Daily Dose</th>
<th>Fixed Surface Area</th>
<th>LOQ (ng/mL)</th>
<th>Most Exposed Subject: AUC&lt;sub&gt;0-24h&lt;/sub&gt; (ng.h/mL)</th>
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<td>4-week treatment</td>
<td>Fixed daily dose</td>
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<td>25 adult subjects</td>
<td>4-week treatment</td>
<td>Fixed daily dose</td>
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<tr>
<td><strong>Study SPR18254</strong></td>
<td>24 adult and adolescent subjects</td>
<td>4-week treatment</td>
<td>Variable daily dose</td>
<td>= 1.2 - 2.9 g</td>
<td>= 1387 - 2894 cm²</td>
<td>Most exposed subject: AUC&lt;sub&gt;0-24h&lt;/sub&gt; = 2.90 ng.h/mL</td>
</tr>
</tbody>
</table>
Pre-Clinical Reproductive Toxicology Studies

**ORAL**
- Teratology in rabbit by oral route
  - F.W. ROSS: Life Science Research Limited EYE Suffolk (England)
  - Final report 26 April 1989
- Teratology in rat by oral route
  - J.M. TESH: Life Science Research Limited EYE Suffolk (England)
  - Final report 24 January 1989

**DERMAL**
- Teratology in rabbit by dermal route
  - G.P. Bailey: Life science research Limited EYE Suffolk (England)
  - Final report 4 January 1990
- Teratology in rat by dermal route
  - T.J. Hall-Manning: Life science research Limited EYE Suffolk (England)
  - Final report 4 January 1990
Individual Pharmacokinetic Data: MUsT

- **Day 1**: adapalene quantifiable in 15 subjects (63%), with concentrations ranging from <0.02 ng/mL to 0.066 ng/mL.
- **Day 15**: adapalene quantifiable in 21 of 22 (95%), with concentrations ranging from < 0.02 ng/mL, up to 0.144 ng/mL.
- **Day 29**: adapalene quantifiable in all the subjects, with concentrations ranging from <0.02 ng/mL to 0.171 ng/mL.
Pregnancy and Breastfeeding

It is not recommended to use during pregnancy.

Differin may be used during breastfeeding. To avoid contact effects on the child, Differin should not be applied to the skin of the breast.