Supplemental New Drug Application for Over-the-Counter Marketing of Differin® (Adapalene 0.1%) Gel Galderma Laboratories, LP

FDA Introductory Remarks
FDA Nonprescription Drugs Advisory Committee Meeting for Differin® (Adapalene 0.1%) Gel
April 15, 2016

Theresa M. Michele, MD
Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
CDER, FDA

Adapalene Gel 0.1% (Differin Gel)

- Topical retinoid
- Approved Rx for topical treatment of acne vulgaris in adults and children 12 years of age and older
- Adapalene formulations

Single ingredient	Combinations with benzoyl peroxide
0.1% gel	**0.1%/2.5% gel (Epiduo)**
0.3% gel	**0.3%/2.5% gel (Epiduo Forte)**
0.1% solution (discontinued)	
0.1 % cream	
0.1% lotion	

OTC Development Program

- Relies on safety and efficacy of prescription product
- Treatment of acne indication same for Rx and OTC
- Post-marketing safety data
- Maximal use pharmacokinetic study (MUsT)
- Consumer studies

Study	Design	N	Population	Pertinent Endpoints
100544	Label comprehension	586 (130)	Adults and adolescents (Low Literacy)	Use once daily Do not use on damaged skin
103439	Self-selection	293 (112)	Pregnant and lactating women with acne (Low Literacy)	Consult a doctor before use
13049 *JUNO*	Actual Use	947 (125)	Adults and adolescents with acne (Low literacy)	Use once daily Use for acne only

Topics for Discussion

- Safety
  - Use by females of reproductive potential (teratogenic risk)
  - Pediatric use
  - Potential for misuse (excessive use or use for non-acne conditions)
- Drug Facts Label and Consumer Information Leaflet
- Benefit-risk profile for OTC use

Purpose of Proceedings Before an Advisory Committee (21 CFR 14.5)

- An advisory committee is utilized to conduct public hearing on matters of importance that come before FDA, to review the issues involved, and to provide advice and recommendations to the Commissioner
- The Commissioner has sole discretion concerning action to be taken and policy to be expressed on any matter considered by an advisory committee

Thank You!

Maximal Usage Trial (MUsT) Data

FDA Nonprescription Drugs Advisory Committee Meeting for

Differin® (Adapalene 0.1%) Gel

April 15, 2016

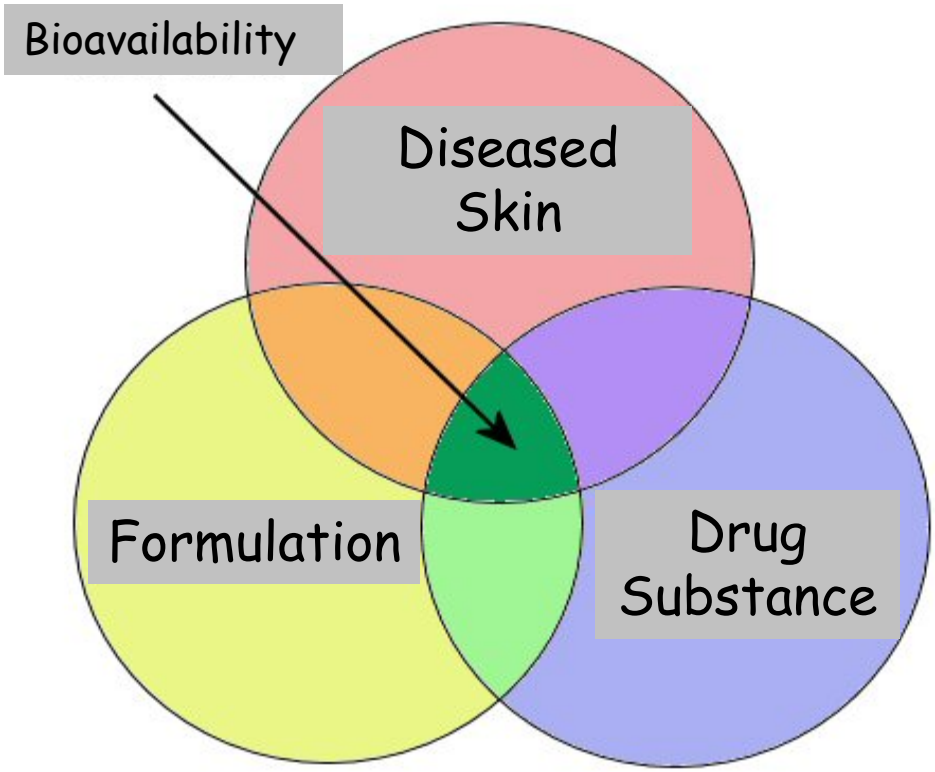
Chinmay Shukla, PhD
Clinical Pharmacologist
Division of Clinical Pharmacology III
Office of Clinical Pharmacology
CDER, FDA

Outline

- Factors influencing topical drug absorption and the concept of maximal usage
- Design of the maximal usage trial for Differin Gel, 0.1%
- Pharmacokinetic results
- Comparison of systemic exposure from the new maximal usage trial with other marketed products
- Observations and conclusions

Factors that Influence Topical Drug Absorption

- Dermatologic diseases are unique as topically applied drugs are delivered directly to the target tissues.
- Topical bioavailability is determined by the complex interaction of drug substance, formulation-dosage form, and the effect of the disease itself on the barrier function of the skin.
- These factors ultimately determine systemic drug exposure.



Why assess systemic exposure for topical products?

- For assessment of systemic safety

Why assess systemic exposure of adapalene following topical application of Differin Gel, 0.1%?

- Adapalene is a retinoid-like drug and there is a concern for teratogenicity based on animal toxicity data

How to evaluate the systemic exposure of Differin Gel, 0.1%?

- Maximal usage trial is currently recommended by the Agency

Reference: *Bashaw E.D. et al.; Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products; Therapeutic Innovation & Regulatory Science; 2015; 49(1); 108-115.*

What is a maximal usage trial?

A maximal usage trial is a pharmacokinetic (PK) trial designed to maximize the potential for topical drug absorption to occur by incorporating the following design elements:

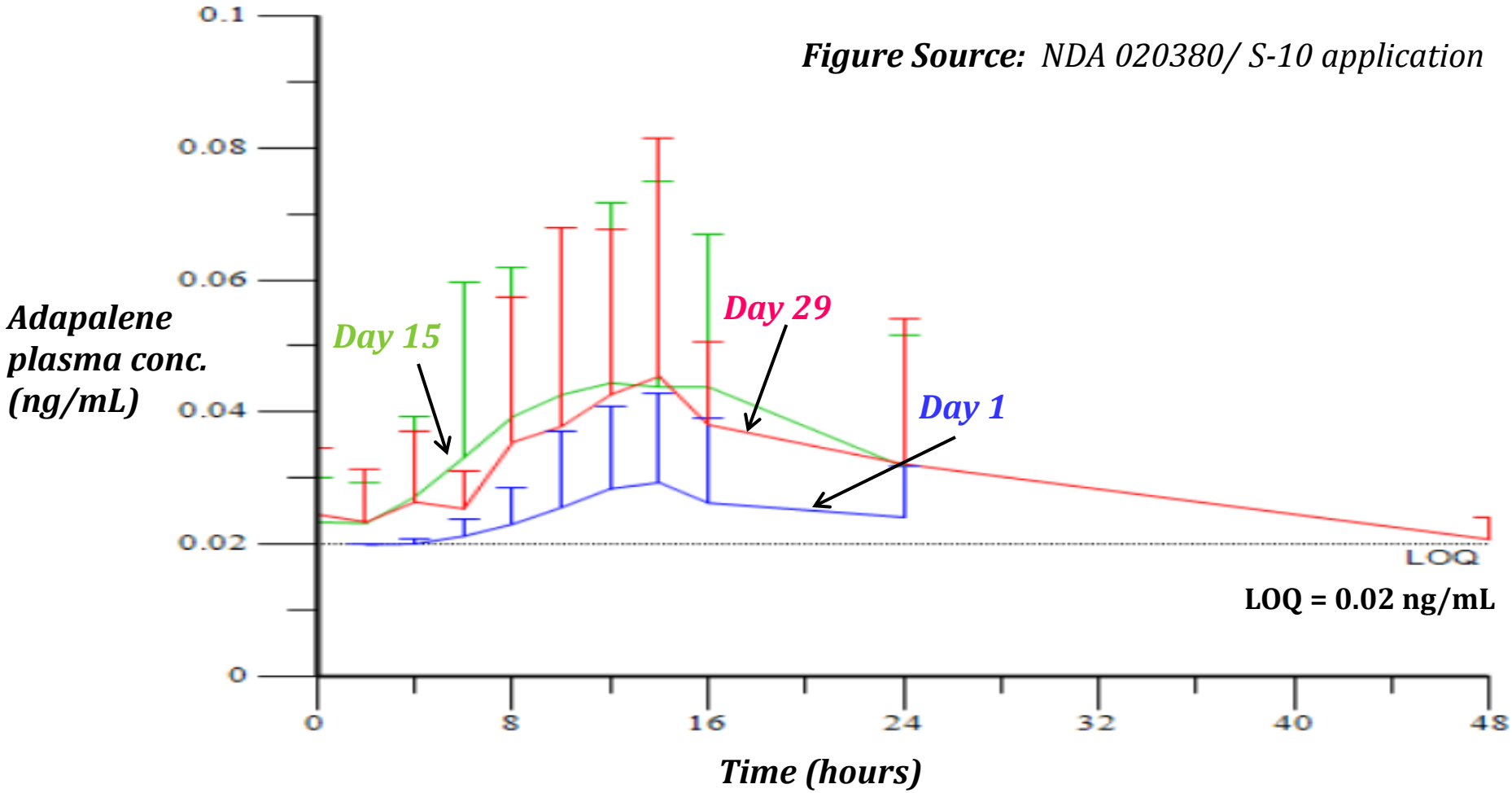
- Frequency and duration of dosing
- Amount applied per square centimeter
- Use of highest proposed strength
- Dermatological disease of interest at the upper range of severity
- Total involved surface area to be treated at one time
- Method of application/site preparation

Design of the Maximal Usage Trial for Differin Gel, 0.1%

- This was a multicenter, open label PK study in 24 subjects 12 years and older with moderate to severe acne vulgaris.
- Drug was applied once daily for 29 days on the face, shoulders, upper chest and upper back.
- Mean amount of medication applied was 1.95 g/day (range 1.2 - 2.9 g/day) and the mean body surface area treated was 1865 cm^2 (range 1387 to 2894 cm^2).
- All 24 subjects completed the trial and this included 18 adolescent subjects (aged 12 to 17 years) and 6 adult subjects (aged 18 years and older).
- PK assessment was done via serial plasma sampling on Days 1, 15 and 29 and additional trough concentrations were assessed on Days 2, 10, 16 and 22 in adults and Days 2 and 16 in adolescent subjects.

Pharmacokinetic Profile of Adapalene

Figure Source: *NDA 020380/ S-10 application*



- By Day 29, plasma concentrations were quantifiable in all 24 subjects
- Steady state was reached by Day 15

Summary of PK Parameters of Differin Gel, 0.1%

	C_{max} (ng/mL)	AUC_{0-24} (ng*h/mL)
Day 1 (N=24 and N quantifiable = 15)		
Mean ± SD	0.033 ± 0.015	0.57 ± 0.14
Min, Max	< 0.020, 0.066	0.48, 0.96
Median	0.031	0.52
Day 15 (N =22 and N quantifiable = 21)		
Mean ± SD	0.054 ± 0.032	0.87 ± 0.43
Min, Max	< 0.020, 0.144	0.48, 1.99
Median	0.044	0.73
Day 29 (N = 24 and N quantifiable = 24)		
Mean ± SD	0.049 ± 0.030	0.83 ± 0.49
Min, Max	0.025, 0.171	0.50, 2.90
Median	0.042	0.68

Qualitative Assessment of Systemic Exposure of Adapalene from the New Maximal Usage Trial Compared to Other Products of 0.1% Strength

Trade name	PK data (N/C = Not Calculated)			LOQ (ng/mL)
	$N_{quantifiable}/N_{total}$	Mean C_{max} (ng/mL)	Mean AUC_{0-24} (ng*h/mL)	
New maximal usage trial with Differin Gel, 0.1%	24/24 (18 adolescents + 6 adults)	0.05 ± 0.03 (Range 0.025 – 0.17)	0.83 ± 0.49 (Range 0.50 – 2.90)	0.02
Differin Cream, 0.1%	N/C (adults)	N/C	N/C	0.35
Differin Lotion, 0.1%	2/14 (adults)	(Range 0.10 – 0.13)	N/C	0.1
	5/14 (adolescents)	0.13 ± 0.05 (Range 0.10 – 0.24)	3.07 ± 1.21 (Range 1.86 – 4.93)	0.1

LOQ: *Limit of quantification*

Observations and Conclusions

- Maximal usage trial was conducted in subjects 12 years of age and older with acne vulgaris.
- Adapalene concentrations were quantifiable in all 24 subjects and systemic concentrations were at steady state by Day 15.
- The mean ± SD $AUC_{0\text{-}24h}$ and C_{max} on Day 29 were 0.83 ± 0.49 ng*h/mL and 0.049 ± 0.030 ng/mL, respectively; and the highest value of $AUC_{0\text{-}24h}$ was 2.90 ng*h/mL.

Thank You

Nonclinical Summary

FDA Nonprescription Drugs Advisory Committee Meeting for

Differin® (Adapalene 0.1%) Gel

April 15, 2016

Cindy Li, PhD
Toxicologist
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
CDER, FDA

Outline

- Overview of Nonclinical Studies
- Review of Major Toxicology Studies
- Teratogenicity Associated with Adapalene
  - Findings in animal studies
  - Margin of exposure relative to human
  - Points to consider
- Conclusions

Overview of Nonclinical Studies

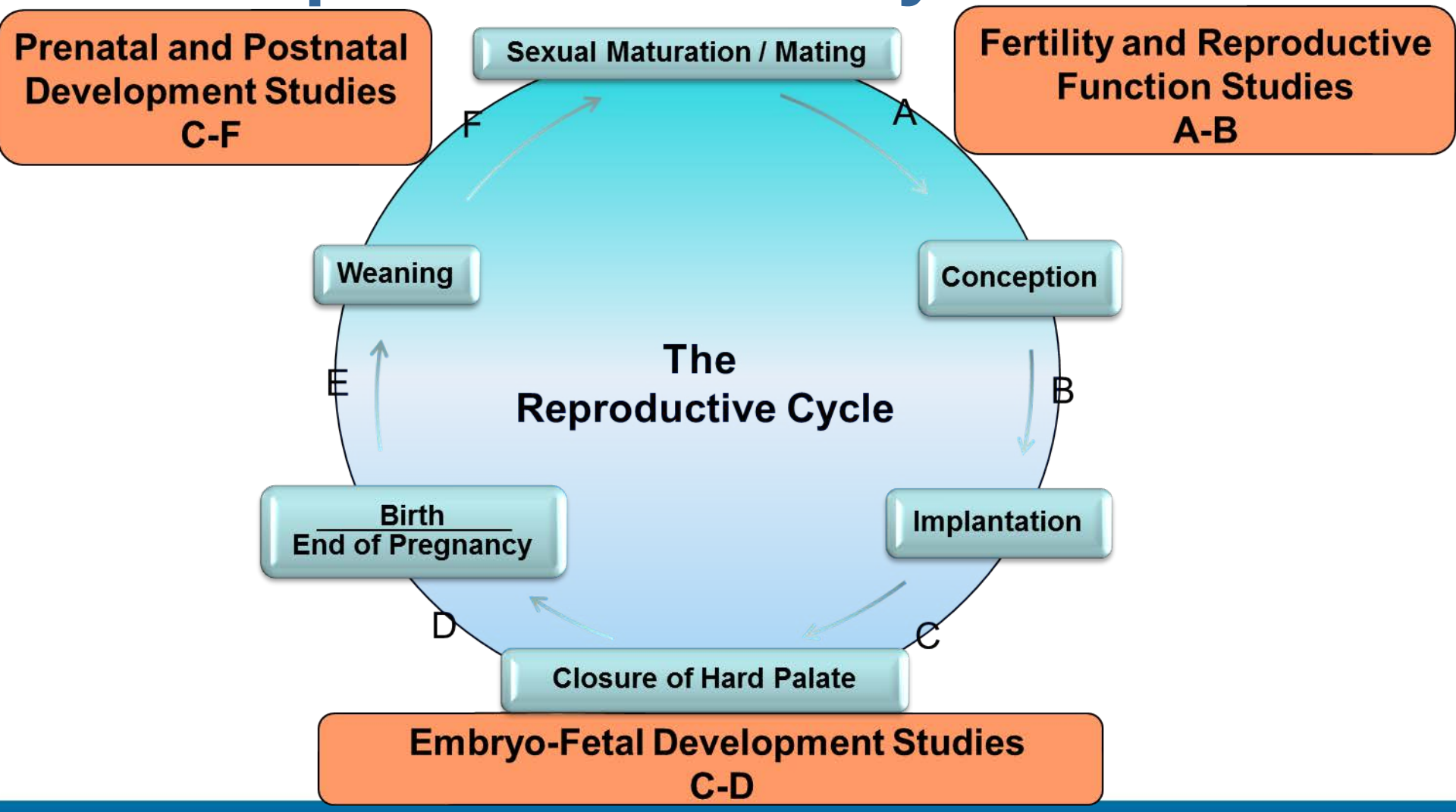
- Pharmacology
- Pharmacokinetics
- Toxicology
  - **Carcinogenicity**
  - **Reproductive/Developmental toxicity**
  - Genetic toxicity, general toxicity, local tolerance, etc.

Review of Carcinogenicity Studies

- **Dermal** in Mice at ≤ 4.0 mg/kg
  - No drug-related neoplastic lesions
  - Up to 9.8X of maximal human dose*
- **Oral** in Rats at ≤ 1.5 mg/kg
  - ↑ pheochromocytomas in adrenal medullas in male rats at 1.5 mg/kg; findings not considered to represent a risk in humans
  - Up to 7.4X of maximal human dose*

* Based on body surface area

Reproductive / Developmental Toxicity Studies



Review of Reproductive / Developmental Toxicity Studies

- **Fertility and Reproductive Function**
  - No drug-related adverse effects at ≤ 20 mg/kg in rats
- **Embryo-fetal Development**
  - **Drug-related teratogenicity findings**
- **Prenatal and Postnatal Development**
  - No drug-related adverse effects at ≤ 15 mg/kg in rats

Findings in Embryo-Fetal Development Studies

- **Dermal** in Rats and Rabbits at 0.6, 2, 6 mg/kg
  - Minor variations observed
  - NOAEL: 6 mg/kg
- **Oral** in Rats and Rabbits at 5, 25, 60 mg/kg
  - **Teratogenic effects: ≥ 25 mg/kg**
  - NOAEL: 5 mg/kg

NOAEL: No-Observed-Adverse-Effect-Level

Animal Findings Relative to Human

- Dose Comparison Between Animal and Human
  - body weight (mg/kg)
  - body surface area (mg/m^2)
  - systemic exposure (e.g. $AUC_{0\text{-}24}$ as ng·h/mL)
- Margin of Exposure

$$\frac{\textbf{Animal Systemic Exposure at NOAEL}}{\textbf{Human Systemic Exposure Under Maximal Use}}$$

Margin of Exposure for Teratogenicity with Adapalene

	Dermal NOAEL (mg/kg)	Systemic Exposure $AUC_{0\text{-}24h}$ (ng·h/mL)	Margin of Exposure
Rat	6	204	204 / 2.9 = **70 X**
Rabbit	6	1036	1036 / 2.9 = 357 X
Human	-	2.9*	-

* highest value in the human maximal use trial with 0.1% adapalene gel

Points to Consider

- Factors that **Decrease** the Level of Concern
  - Animals: actual dermal NOAEL may be higher than the highest dose tested
  - Humans: highest individual systemic exposure, not the average, was used
- Factors that I**ncrease** the Level of Concern
  - Class of retinoids are known human teratogens
  - Human sensitivity to adapalene is unknown

Comparison with Other Topical Retinoids

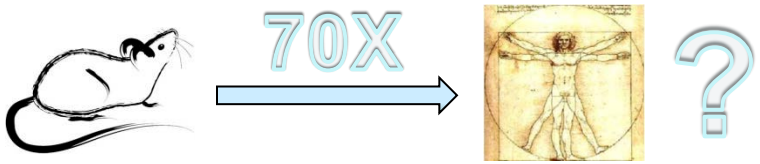
		Adapalene	Tretinoin	Tazarotene
First Approved in		1996	1971	1997
Route		Dermal	Dermal	Dermal
Indication		ACNE Vulgaris	ACNE Vulgaris	ACNE Vulgaris
Formulation		0.1% Gel	0.01-0.025% Gel	0.05-0.1% Gel
Pregnancy Contraindication		No	No	Yes
		Lowest Teratogenic Dose in mg/kg		
Oral	**Rat**	25	0.4	0.25
	Rabbit	25	2	0.2
Dermal	**Rat**	> 6	> 1	0.25
	Rabbit	> 6	> 0.2	0.25

Human Sensitivity to Adapalene

- The actual level of systemic exposure to cause an effect in humans may be different compared to animals
- Animal studies do not always predict effects in humans
- Well-controlled clinical studies in pregnant women are not available

Conclusions

- Adapalene, a retinoid-like compound, can induce teratogenicity in animals at sufficiently high systemic doses
- The margin is at least 70 fold for dermal application
- Animal studies do not always predict human effects



Label Comprehension and Self-Selection Studies

FDA Nonprescription Drugs Advisory Committee Meeting for
Differin® (Adapalene 0.1%) Gel
April 15, 2016

Barbara R. Cohen, MPA
Social Science Analyst
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
CDER, FDA

Outline

- What is a Label Comprehension Study?
- Label Comprehension Study #100544
  - Background: Regulatory Questions
  - Methodology
  - Results
- What is a Self Selection Study?
- Self Selection Study #103439
  - Background: Regulatory Questions
  - Methodology
  - Results
- Summary

What is a Label Comprehension Study?

- Conducted for most Rx to OTC switches
- Foundational study in OTC drug development program
- Addresses questions such as:
  - Is the wording understandable to the average consumer?
  - Does it convey the key concepts required for the safe use of the product?
- Phrasing used on other OTC products can and should be retested in LCS if it is more critical to the safe use of a particular new product
  - This can also optimize comprehension prior to proceeding with other consumer behavioral studies.

What is a Label Comprehension Study?

- Primary Objectives: Applicant identifies the most important label communication objectives from viewpoint of safety
- Target thresholds established a priori – based on clinical implications if consumers fail to adequately understand items
- Adequate comprehension is assessed by comparing the established threshold with the lower bound of the two sided 95% confidence interval
- Typically there is a general population cohort (assessed against the target threshold) and a low literacy cohort. FDA generally asks for 22-28% low literacy representation in the general population

What is a Label Comprehension Study?

- Secondary objectives – areas less critical to safe and appropriate use, yet clinically relevant
  - Typically not assessed against thresholds
- Generally recruit "all comers" – anyone should be able to read a label
- Participants go to a research facility and read the label at their own pace
- Then, the interviewer administers an "open book" test to assess whether they are aware of and can understand key elements of the label
- Typically scenario questions are employed

Label Comprehension Study #100544 - Objectives

- Primary objectives (as established by the Applicant):
  - Comprehension of "Use once daily"
  - Comprehension of "Do not use on damaged skin"
  - Assessed at 85% target threshold
- FDA had advised the Applicant during development that awareness of the labeled statement on pregnancy should be assessed as a primary objective
  - Applicant did not test this, saying that the statement already appears on other labels

Label Comprehension Study #100544 – Design and Conduct

- Conducted in April 2014 in eight geographically dispersed sites across the United States
- Total of 586 participants, males and females, ages 12-70.
- General population cohort only had 11% low literacy, so FDA looked at both cohorts in the analyses
- Both cohorts had good adolescent representation (282 adolescents in total) but poor representation among the 18-24 year old age group. Example:
  - 33 participants age 18-24
  - 78 participants age 45-54

Label Comprehension Study #100544 – Results

- Comprehension of "Use Once Daily":
  - General population: 95.9%, LCB 93.8%
  - NL: 96.5%, LL: 86.9%
  - No significant differences between genders or age groups
  - Significant difference between NL and LL comprehension, including adolescents
    - NL adolescent females: 96% (LCB 90.8%)
    - LL adolescent females : 83.9% (LCB 66.3%)
- Comprehension of "Do Not Use on Damaged Skin":
  - General population: 97.5%, LCB 95.7%
  - NL: 97.4%, LL: 99.2%
  - No significant difference between NL and LL comprehension

Label Comprehension Study #100544 – Results

- Ten secondary objectives assessed, including "Avoid unnecessary sun exposure, including tanning beds, and use sunscreen when going outdoors"
  - FDA had advised during the development process that this be assessed as a primary objective, and include the sunlight exposure component of the warning
  - Applicant declined to test as a primary objective and tested tanning bed comprehension only
  - Results:
    - 97.5% (Cohort 1, general population)
    - 97.4% NL, 95.4% LL
    - No significant differences between adults and adolescents

Label Comprehension Study #100544 – Results

- Secondary objectives: "Under 12 years of age, consult a physician"
  - 93.8% (Cohort 1, general Population)
  - NL 94.3%, LL 85.4%
  - No significant differences between adults and adolescents

What is a Self-Selection Study?

- Assesses whether consumer can apply understanding of the label to their own personal medical situation
- Typically required when a Rx to OTC switch represents a new OTC indication, or when there is a concern about a specific subpopulation using a product
- Target thresholds are established a priori based on the clinical implications of failure to correctly self-select
- Consumers are recruited for a specific contraindicated condition or medication, or another specific "do not use" category; subjects are blinded to why they are being recruited
- A consumer development program can encompass one or several self-selection studies. In total it can typically involve from 250-800 subjects, including low literacy recruitment

What is a Self-Selection Study?

- Subjects are given the product package, asked to look at it, and say whether the product would be appropriate for them personally to use
- Subjects are then probed to assess the reasons why they gave particular answers
- Typically self-selection decisions are validated through self-reported information, but increasingly physicians are involved in administering tests or obtaining detailed medical histories in order to validate decisions

Self-Selection Study #103439 - Objective

- Assesses whether pregnant or breastfeeding women would ask a health care professional prior to use, as per the directions on the DFL
  - During the development process, FDA had asked the Applicant to conduct self-selection research among pregnant women
- Target threshold established at 90%
  - No clinical rationale provided by Applicant, other than that it was asked for by FDA

Self-Selection Study #103439 - Methodology

- Conducted from November 2013-January 2014 among 293 pregnant/breastfeeding women ages 13-54*:
  - Cohort 1: General population, n=242 (181 NL, 61 LL)
    - 91 (37%) were pregnant; 11 of these women were also breastfeeding
    - The remainder of the cohort was breastfeeding only
    - LL – 25%
  - Cohort 2: Augmented LL Cohort, n=51

*Only two subjects were adolescents

Self-Selection Study #103439 - Methodology

- Adult female recruitment
  - Mall intercepts at 25 sites across the United States.
  - Women stopped if they appeared to be in at least one of four separate buckets: 1) between ages 18-50; 2) with noticeable acne; 3) visibly pregnant; 4) accompanied by baby appearing to be under 18 months old
  - Masked recruitment (asked about various medical conditions)
- Inclusion criteria: Pregnant/breastfeeding with acne, age 18+
- No data collected on pregnancy trimester

Self-Selection Study #103439 - Methodology

- Adults
  - Qualified subjects directed to a research facility, where REALM (literacy) test was administered
  - Subjects asked to review principal display panel (PDP) and drug facts label (DFL) and then asked: "Is it ok for you to use this medication today or not", followed up by "why did you say that?"
  - All subjects who self reported pregnancy were administered urine pregnancy test to confirm pregnancy
  - All subjects who self selected incorrectly were then asked: "*Earlier you said that this product was ok for you to personally use. However, the warning on the package states that you should ask a health professional because you are pregnant or breastfeeding. Please tell me why you thought it would be ok to use this product even though you are pregnant or breastfeeding.*"

Self-Selection Study #103439 - Methodology

- Adolescents
  - Recruited from pregnancy centers and support groups
  - Initial target of nine adolescents in total
  - IRB approval issues led to delay in recruiting; only two recruited.
  - Subjects were administered an online questionnaire in a private room, instead of face to face interview, to ensure maximal privacy and sensitivity
  - Online questionnaire ended at the self-selection question; the clarification probe was not asked

Self-Selection Study #103439 – Results

- Applicant was not able to demonstrate that pregnant and/or breastfeeding women could adequately follow the labeled instructions to ask a healthcare professional before use
  - Cohort 1 (general population): 74.4% correct, LCB 68.4%
  - LCB over 20 percentage points below target threshold of 90%
  - This is evidence that the correct self-selection rate is statistically significantly lower than the target 90% threshold

Self-Selection Study #103439 – Results

- Across Cohort 1 (general population) and Cohort 2 (low literacy):
  - NL: 78.5% correct, LCB 71.7%
  - LL: 70.5% correct, LCB 61.2%
  - Correct self-selection rates do not differ significantly between literacy groups

Self-Selection Study #103439 – Pregnant Women

- Applicant was not able to demonstrate that pregnant women could adequately self-select to use the product:
  - Cohort 1 (general population): 70.0% correct, LCB 58.7%
  - Over 30 percentage points below target threshold of 90%
  - This is evidence that the correct self-selection rate is statistically significantly lower than the 90% threshold
- In Cohort 1, correct self selection *did not* differ significantly across the age groups
  - However, the small number of pregnant women in the study led to low statistical power to detect these differences

Self-Selection Study #103439 – Pregnant Women

- Across the two cohorts, for low literacy women under age 45, correct self selection did differ significantly across age groups:
  - Age 18-24: 55% (11/20)
  - Age 25-34: 87.5% (14/16)
  - Age 35-44: 100% (3/3)

Self-Selection Study #103439 – Results - Verbatims for Incorrect Self-Selection

- *"Ingredients…don't seem harmful…I don't have sensitive skin..I don't see what it has to do with me being pregnant."*
- *"Literally everything has that warning on it and after repeatedly asking a doctor you learn it's usually ok as long as it doesn't say "Do not take".*
- *"..this is over the counter".*
- *"Because I put it on my face, not on the baby and I put it on my skin, not in my blood so it wouldn't affect the baby"*
- *"What does my face have to do with my pregnancy?"*

- 15 subjects explicitly stated that they hadn't seen the warning on the label

Conclusions

Potential Pediatric Use/Misuse

- The Applicant did demonstrate that the following labeled items tested well for comprehension among participants ages 12-70:
  - Use once daily
  - Ask a doctor under age 12

Conclusions

Potential Use in Pregnant Women:

- There is no evidence provided on whether pregnant adolescents would know to ask a healthcare professional before use
- Correct self-selection for pregnant and/or breastfeeding women as a whole was over 20 percentage points below the target threshold of 90%
  - Correct self-selection for pregnant-only women was over 30 percentage points below the target threshold
- Pregnancy warning was not tested in label comprehension for overall comprehension and awareness, as a means of optimizing the label prior to self-selection

Thank you!

Actual Use Trial & Clinical Perspective

FDA Nonprescription Drugs Advisory Committee Meeting for
Differin® (Adapalene 0.1%) Gel
April 15, 2016

Ryan Raffaelli, MD
Medical Officer
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
CDER, FDA

Outline

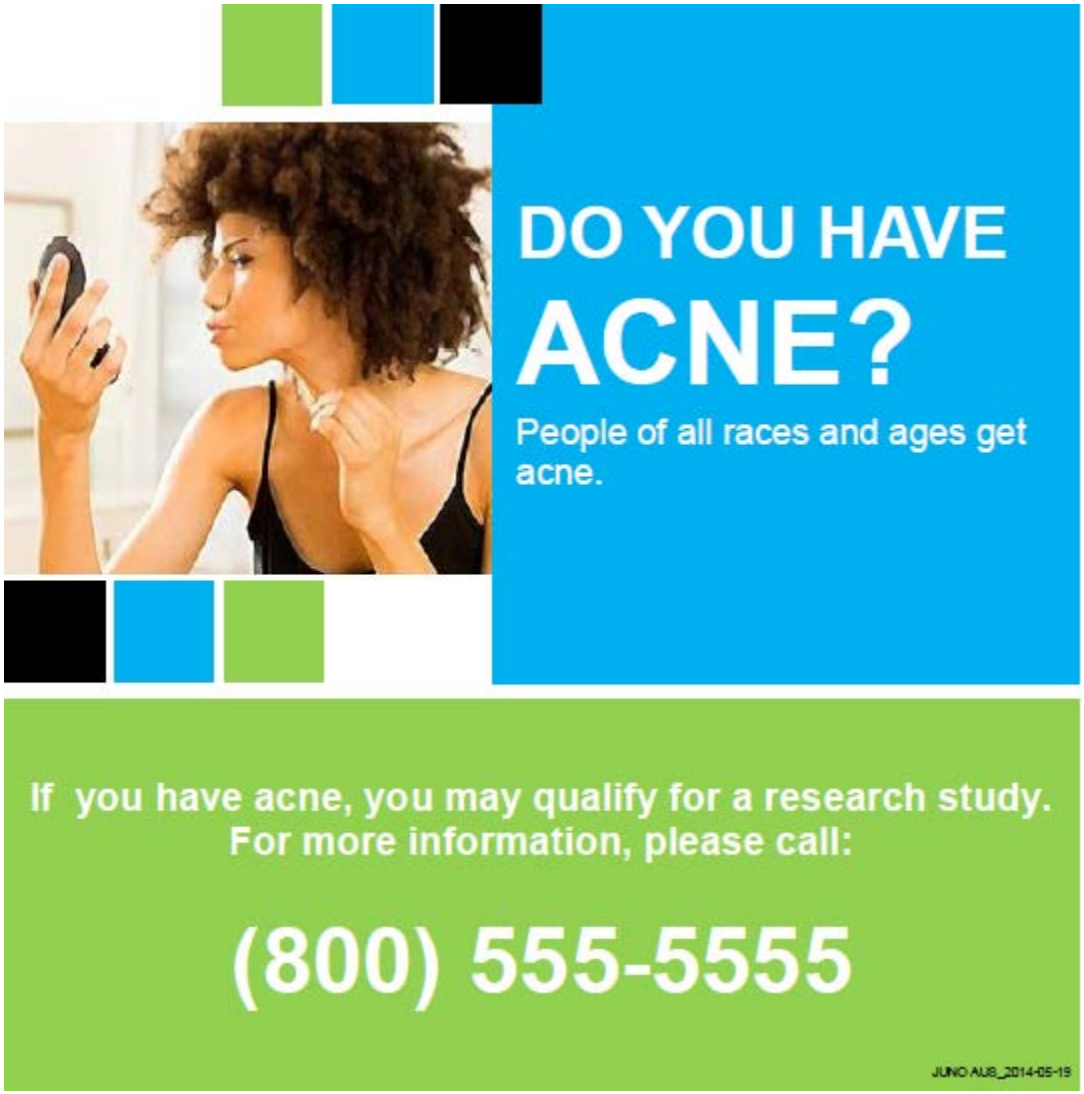
- Actual Use Trial (AUT)
  - "Juno" trial
  - Present
    - Brief introduction to AUTs
    - Purchase decisions
    - Primary and main secondary endpoints
- Safety Data and Pregnancy Issues
  - Maximal Usage Trial (MUsT) and AUT
- Prescription Differin® Postmarketing Experience

Design of Juno Trial

- Open-label, Single-arm, Multi-site Trial (31 pharmacy sites)
  - Duration: 6-week use phase
- Purpose: Assess, in a "naturalistic" over-the-counter (OTC) setting, how consumers ("all comers") might use the drug
  - 4 major endpoints: Assess correct use proportion (typical of AUTs)
    - Primary: Once daily use at same acne location
    - Primary: Use for acne only

    Success threshold: > 85% correct users
    - Secondary: Use on correct body areas (avoid damaged skin and eye/lip/mouth contact)
    - Secondary: Do pregnant or breastfeeding women ask HCP before use?

Recruitment for Juno Trial



Recruitment
↓
Early screening
↓
Enrollment
↓
Review package
↓
Make purchase decision

Source: Applicant's submission; Module 5.3.5.2, Protocol, Section 16.4

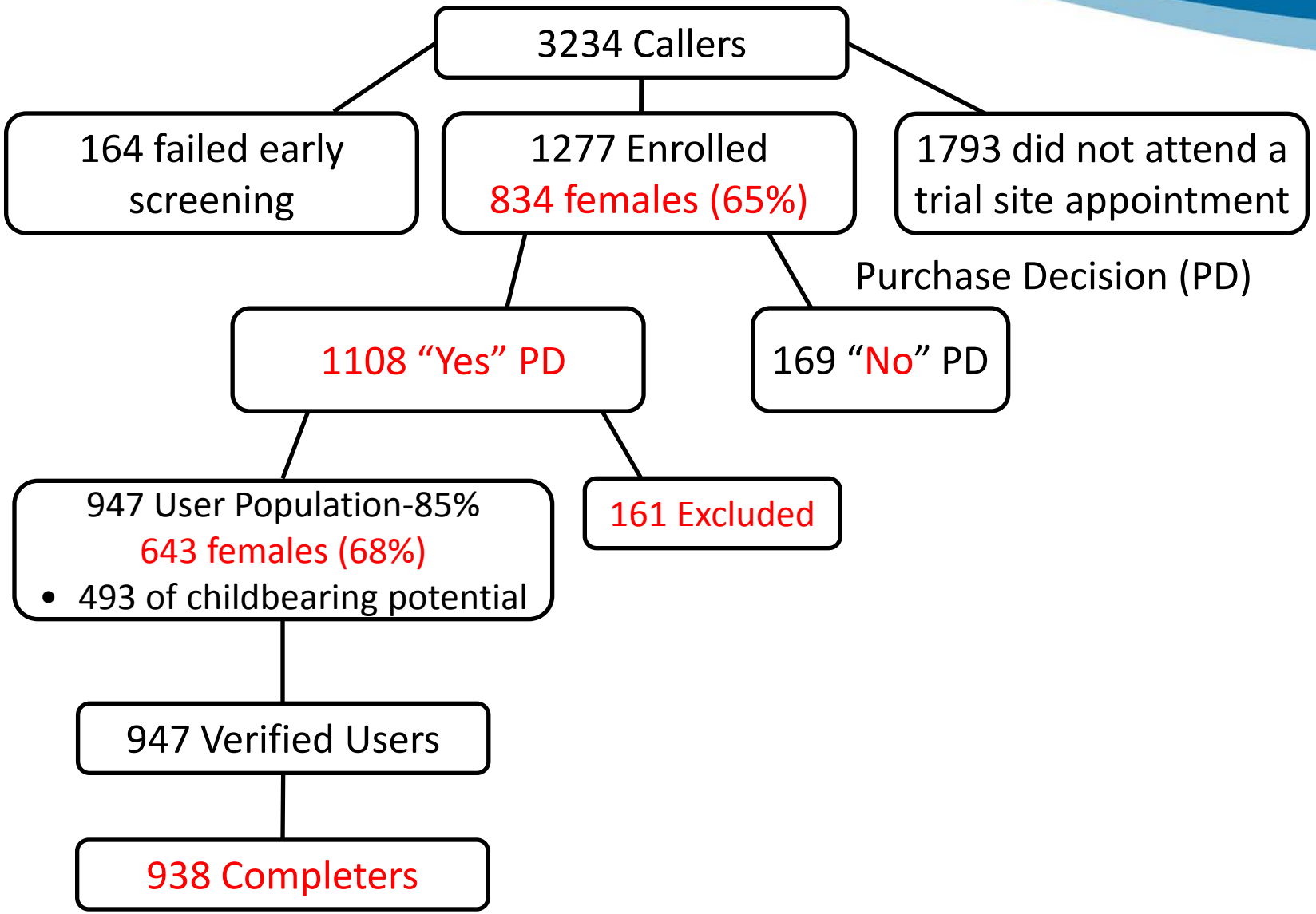
Design of Juno Trial

- Purchase decision is made
- Confirm eligibility to enter the "Use Phase"
- Urine pregnancy test
- REALM test (literacy)
- Use Phase - "At home"
- Evaluation/Endpoints
  - Diaries
  - Returned product (tubes)
  - Interviews (screening, End-of-Trial (EOT))
    - EOT interview: Greater than 99% of subjects completed this interview and returned their diaries and used tubes of product

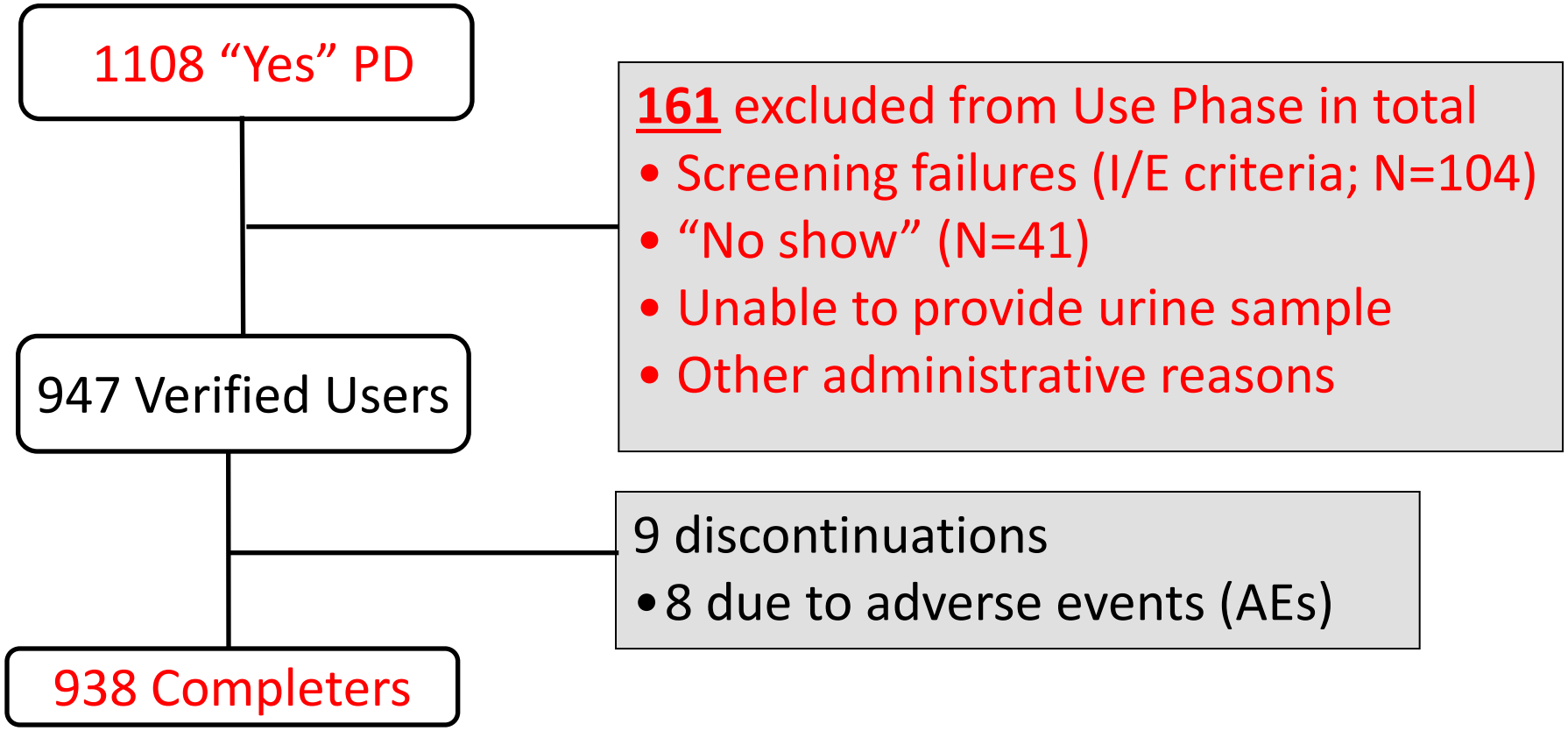
Clinical Exclusion Criteria:

- Does not self-report acne
- Under age 12 years
- Pregnant or breastfeeding
- Allergy to adapalene or ingredients
- In the investigator's judgment, is subject likely to be harmed or unlikely to follow trial procedures?

Subject Disposition



Subject Disposition - Purchase Decision – "Yes"



HCP: Healthcare Professional; I/E: Inclusion and Exclusion

Impactful Demographics and Decisions

Purchase Decisions and Pregnant Subjects (Ages 23-45; mean 29.4 yrs)

- 5 of 9 incorrectly said "Yes;" 1 "No" was told pregnancy excluded
  - 2 stated they were pregnant despite negative urine tests
  - One subject did not see the warning to ask a healthcare provider first
  - One subject said her pregnancy did not change her decision
  - One subject - "all medications say ask a doctor…it shouldn't hurt my baby"

Actual Use Population (N=947)

- Mean age 29.9 years (12-73 years)
- Subjects 12-17 years (N=203; 21.4%); Female (N=643; 68%)
- Subjects with acne and eczema (N=14; 1.5%)
- REALM testing
  - Low Literacy: Adults - 13.8%; Adolescents - 10.8%

Actual Use Screening Failures (104 in total)

- 1108 Subjects - "Yes" to purchase*

Clinical Exclusion Criteria:

- Does not self-report acne (N=9)
- Under 12 years of age (N=6)
- Pregnant or breastfeeding (N=10; 5 were pregnant or reported pregnancy)
- Allergy to adapalene or ingredients (N=0)
- In the investigator's judgment, is subject likely to be harmed or unlikely to follow trial procedures? (N=25)

  – Other reasons to exclude: Incomplete administrative documentation (e.g., Informed Consent/Assent), or capacity to participate (e.g., visual impairment), or ineligible background (e.g., recent study participation)

* Some safety concerns with "Yes" decisions were mitigated

Endpoints	Correct use – Post-mitigation^
Primary Endpoints	
User applied the product no more than once daily at the same location (947 – 844 = 103 incorrect users)	**89.1% (87-91%;2-sided 95% CI*)** **844/947 (*a priori* threshold > 85%)**
User applied the product for acne treatment only (945-938 = 7 incorrect users)	**99.3% (98.5-99.7%;2-sided 95% CI)** **938/945[1] (*a priori* threshold > 85%)**
Secondary Endpoint	
User applied the product to undamaged skin and avoided use on or near eyes, lips or mouth	**97.5%**

^Misuse by all endpoints was mitigated by factors that were reasonably applied by the applicant

*95% CI= 95% Confidence Interval; [1]Two subjects had missing diary data

Pregnancy in Juno Trial

- Subjects who voluntarily reported becoming pregnant during the trial were to be withdrawn – None
  - No interval interviews during trial
  - No label warning to stop use and ask a doctor if pregnancy occurs
- 4 subjects became pregnant (Ages 18-34 years)
  - One subject discovered pregnancy only at EOT visit (+ test)
  - 3 visited a doctor during trial to confirm pregnancy
    - None discussed use of adapalene; 1 had applied her last dose
    - 2 continued using the product after confirming pregnancy
      - 1 chose to terminate pregnancy for unrelated, personal reasons
    - 1 healthy newborn

EOT: End-of-trial

Safety in MUsT and JUNO Trial

- MUsT – Approximately 56.5 g applied over estimated 10% body surface area
  - average 1.95 g/day applied over 1865.7 cm^2
  - duration: 29 days

- JUNO - Average total use = 24.3 g
  - up to 94% purchased (886/947) or used only 1 tube of adapalene (≤ 45 g)
  - 17% (12-17 years) vs. 12% (≥ 18 years) used > 40 g
- Mean treatment duration= 41.4 days
  - over 93% remained in the trial for ≥ 35 days
- Estimate 0.6 g/day applied

- Max recorded = 129.5 g; only 4 subjects bought 3 tubes (135 g total)
- 13 subjects (1.4%) used > 80 g (9 were 12-17 years)
- No major usage differences by age, gender or literacy

Safety in Clinical Trials

- Juno: Half of all users reported at least 1 adverse event (AE)
  - No serious events or deaths; 88% were mild; MUsT reporting similar
  - By age or gender, no major differences in reporting overall
  - Top 3 AEs :
    - Headache, 18% (N=179)
    - Dry skin, 10.5% (N=106)
    - Erythema, 4.5% (N=46)
  - 49% who used > once daily reported an AE
  - 7 highest users (> 91 g) – No skin-related AEs
  - 2% used on acne/damaged skin
  - 3% reported mild sunburn
  - 8 users (1.7% of all reporting AEs) discontinued (AEs); 3 were < 18 years
    - Most common reasons were skin-related events
    - None raised any safety issues

Postmarketing Safety Data

POSTMARKETING SAFETY DATABASES

NDA holder's pharmacovigilance database

FDA-Adverse Event Reporting System (FAERS)

World Health Organization (WHO)

- Applicant's focus: teratogenicity, fetotoxicity, carcinogenicity, skin-related AEs and drug interactions
- Over 40 million patients prescribed 0.1% or 0.3% since first approved
- 4176 AEs reported worldwide (1998-2014); 70 serious, unlabeled reports
  - Included in NDA holder's database
  - 70% of all reports are skin-related
  - 239 exposures in pregnancy – few varied malformations reported; no pattern

Postmarketing Safety Data

Findings Mirror that from Juno Trial

- Preferred Terms “dry skin” and “erythema” ~ 30% of all reported events
  - Skin-related events predominate in reports of overuse and when adapalene is used with other topical acne products containing ingredients, e.g., sulfur, resorcinol or salicylic acid
  - Risk for photosensitivity:
    - 48 reports of skin irritation/burn after sun exposure
    - 9 reports of concomitant use of tetracyline derivatives

Summary

- The Juno trial demonstrated high rates of correct usage by dosing regimen (once daily), for acne only, and on acceptable skin areas–findings consistent across subgroups
- Limitations of design and population–Juno Trial
  - General concerns with AUTs: OTC consumer market
  - Short 6-week trial duration (limited assessment of decisions with pregnancy)
  - Decisions by few pregnant subjects (likely to select for and continue using product)
  - Low literacy cohort was lower than recommended (13.8% overall)
  - Not a true assessment of “all comers;” recruitment of acne sufferers limited off-label usage assessment

Summary

- Use in Pregnancy
  - 5 of 9 pregnant subjects wished to purchase the product without advice from a learned intermediary
  - Four “on-treatment” pregnancies occurred during trial; no poor outcomes
  - No label warning to stop use if subjects become pregnant while using product
- Pediatrics: 21% of AUT users; 6 excluded due to age
  - No differences in endpoint assessments or safety reporting
  - More used > 40 g; 16 year old male had highest drug exposure in MUsT
- Trial and postmarketing safety data indicate that skin-related AEs are common, but most often mild and non-serious

Thank you

Post Marketing Prescription Safety Data

FDA Nonprescription Drugs Advisory Committee Meeting
for Differin® (Adapalene 0.1%) Gel
April 15, 2016

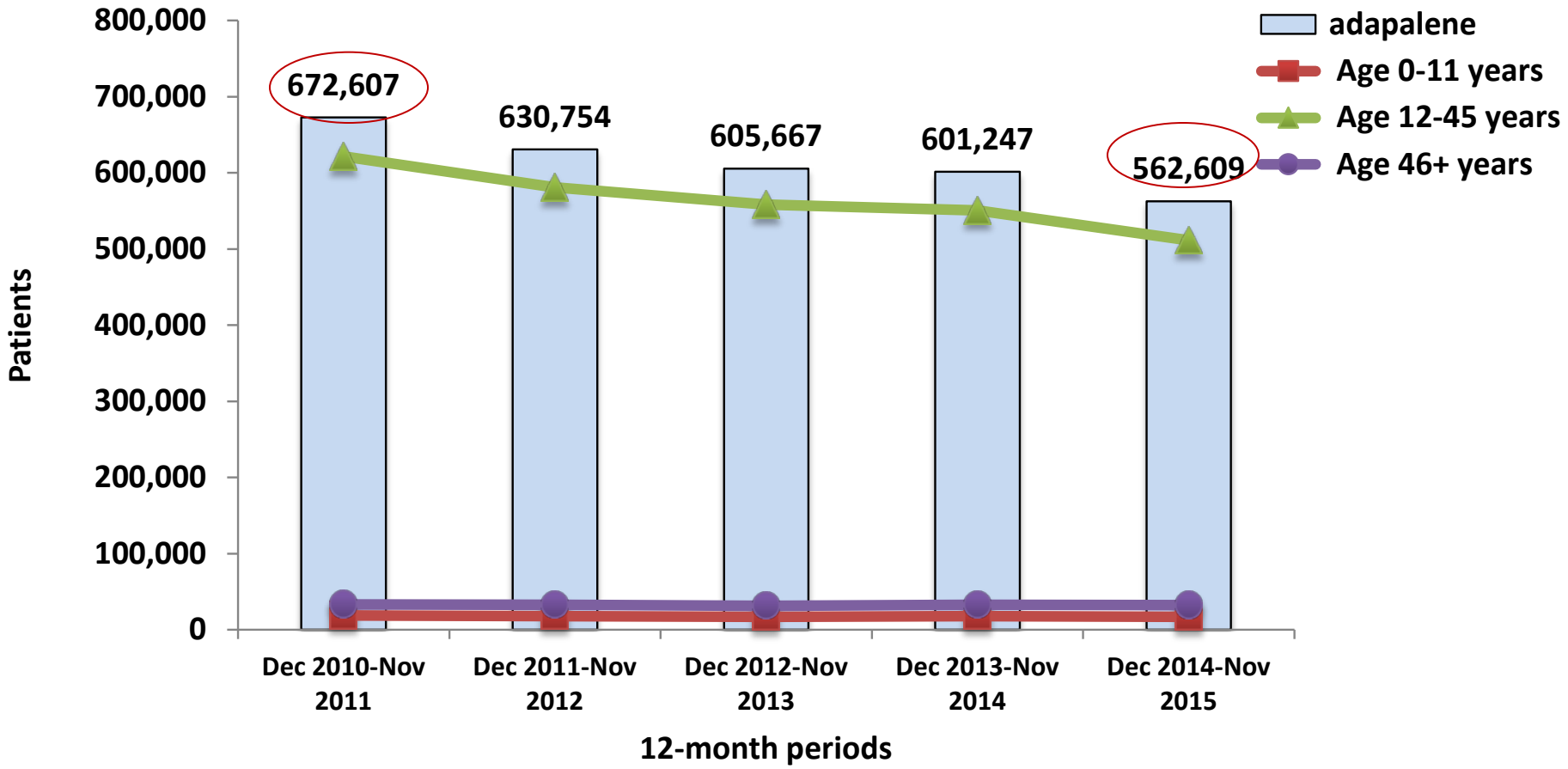
Lopa Thambi, PharmD
Safety Evaluator
Division of Pharmacovigilance II
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
CDER, FDA

Outline

- Drug Utilization
  - Patient Demographics
  - Top Prescribing Specialties
  - Top Diagnoses Associated with Use
- Post Marketing
  - FDA Adverse Events Reporting System (FAERS)
  - Medical Literature
- Epidemiology

Patient Utilization: Single-Ingredient Adapalene

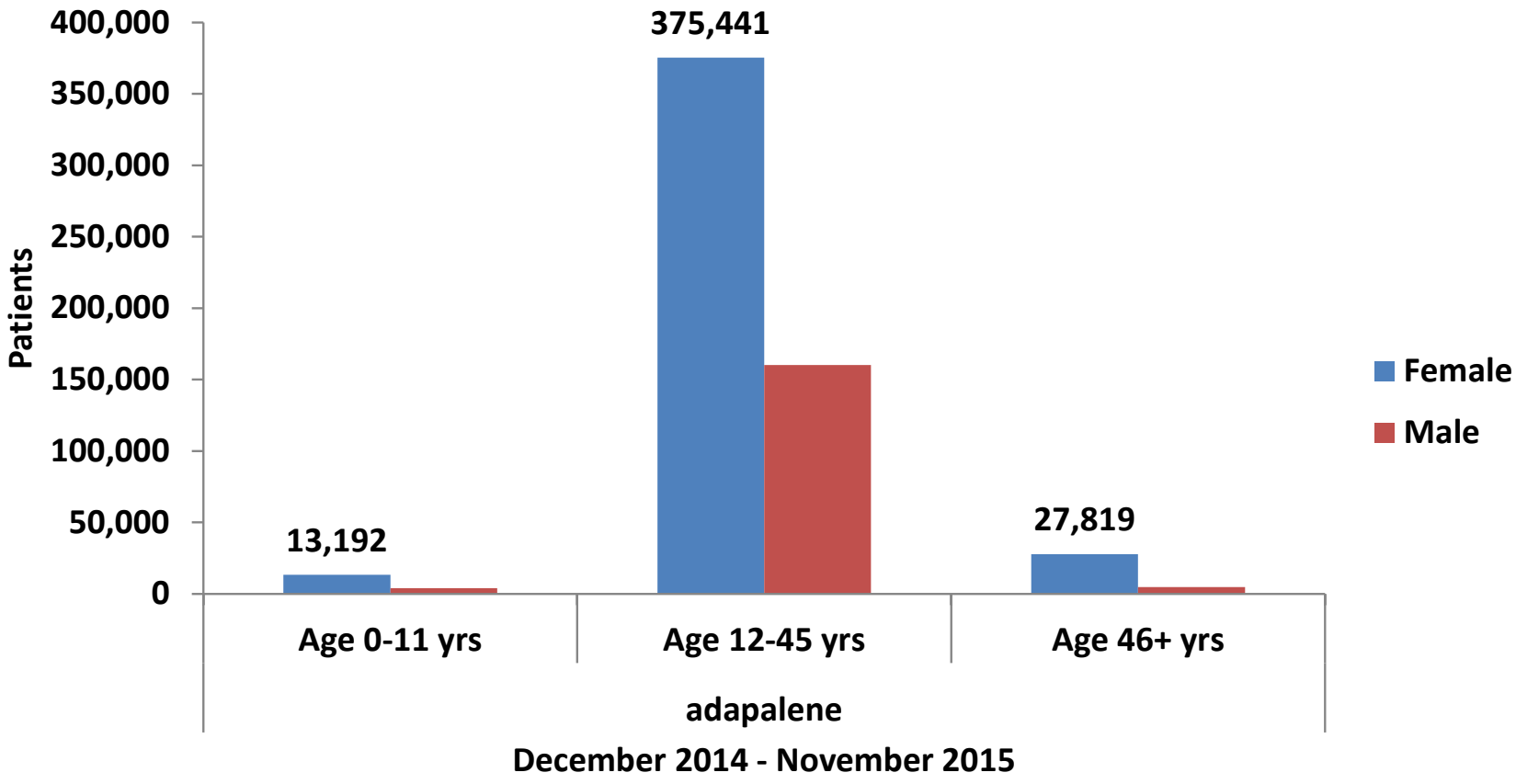
Nationally estimated number of patients with a dispensed prescription for adapalene, stratified by patient age (0-11, 12-45, 46+ years) from U.S. outpatient retail pharmacies, Dec 2010-Nov 2015



Source: IMS, Vector One®: Total Patient Tracker. Dec 2010 - Nov 2015. Extracted December 2015.

Patient Demographics: Single-Ingredient Adapalene

Nationally estimated number of patients with a dispensed prescription for adapalene, stratified by patient age and sex, from U.S. outpatient retail pharmacies, December 1, 2014 - November 30, 2015



Source: IMS, Vector One®: Total Patient Tracker. Dec 2010 - Nov 2015. Extracted December 2015. File:TPT 2015-2278 Adapalene total by gender 12-29-15.xls

Drug Utilization: Single-Ingredient Adapalene

❖ Top Prescribing Specialties[1]

- Dermatology (49% of prescriptions)
- Physician Assistant (15% of prescriptions)
- Pediatrics (10% of prescriptions)

❖ Top Diagnosis[2]

- Acne* was the top diagnosis reported in association with adapalene use as reported by office-based physician surveys

[1] Source: IMS National Prescription Audit (NPA). Dec 2010 - Nov 2015. Extracted December 2015.

[2]Source: Encuity Research, LLC., TreatmentAnswers™ with Pain Panel, Dec 2010 - Nov 2015. Extracted December 2015.

***"Acne, Not Elsewhere Classified" (ICD-9 code 706.1)**

Adapalene Post Marketing Safety Data

- FDA Adverse Event Reporting System (FAERS) Overview
  - Adapalene observed cases of congenital anomalies (FAERS and literature)
  - Adapalene observed cases of use on large body surface area (BSA) (FAERS and literature)
- Overall Summary

FDA Adverse Event Reporting System (FAERS)

FAERS Strengths

- Computerized database
- > 11 million reports since 1968
- Includes all U.S. marketed products
- Includes all uses (both approved and off-label use)
- Includes broad patient populations
- Detection of events not seen in clinical trials
- Detection of events with rare background rate
- Identification of reporting trends, possible risk factors, at risk populations

FAERS Limitations

- Causal relationship between a product and event is not required for reporting to the FDA
- Quality of reports is **variable** – information is limited in some reports
- **Under-reporting** – not every adverse event is reported
- FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population

FAERS Limitations and Teratogenicity

- *FDA Reviewer Guidance on Evaluating the Risks of Drug Exposure in Human Pregnancies* (FDA Guidance 2005)
  - Recommends epidemiological studies as the best method of evaluating a causal relationship between a drug exposure during pregnancy and congenital anomalies
  - Case reports can establish a signal for the need of further research
- Given the background rate of birth defects (2-4%) in the general population, it is typically not possible to establish causality for an isolated birth defect from a drug exposure
- Lack of spontaneous adverse event reports cannot establish that a drug is free of risk for any specific event, including teratogenicity

DPV Search Strategy

FAERS

Congenital Anomalies

- Product: single ingredient adapalene
- Date Searched: 1/1/1969-11/17/2015
- Serious* cases
- MedDRA Terms: Abnormal pregnancy outcomes

Adapalene use on large body surface area (BSA)

- Product: single ingredient adapalene
- 1/1/1969-11/17/2015
- Serious cases
- MedDRA Terms: All

*Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

DPV Search Strategy

Adverse Events of Interest in the Medical Literature

Searched for additional case reports of adapalene associated abnormal pregnancy outcomes or use on a large BSA

- Product: single ingredient adapalene
- 12/15/2015

Retinoic Acid Embryopathy

- Craniofacial anomalies (microtia, anotia, accessory parietal sutures, narrow sloping forehead, micrognathia, flat nasal bridge, cleft lip and palate, and ocular hypertelorism)
- Cardiac defects (primarily conotruncal malformations)
- Abnormalities in thymic development
- Alterations in central nervous system development

Lammer EJ, Chen DT, Hoar RM., et al. Retinoic acid embryopathy. N Engl J Med 1985;313:837-41.

DPV Search Results

- **<u>FAERS</u>**
  - Total serious reports associated with adapalene in FAERS **(n=237)**
- **<u>Congenital Anomalies</u>**
  - Cases of adapalene and congenital anomalies were observed in FAERS **(n=11)**
    - Includes case of congenital anomaly identified in FAERS ***AND*** published in medical literature **(n=1)**
- **<u>Adapalene Use on Large BSA in FAERS</u>**
  - Case of adapalene use on a large BSA in FAERS ***AND*** published in medical literature **(n=1)**

DPV Search Results

Descriptive characteristics of congenital anomalies reported with adapalene use received by FDA from January 1, 1969 –November 17, 2015 (n=11)	
Maternal Age (years)(n=6)	Mean: 30 Median: 30 Range: 22-34
FDA receive date	1996: 1 2001: 1 2008: 1 2014: 1 1997: 1 2003: 1 2009: 2 1998: 1 2006: 1 2010: 1
Source	Foreign: 9 US: 2
Indication (n=6)	Acne: 5 Mucinosis follicularis: 1
Trimester of exposure (n=9)	First: 7 Third: 1 First and second: 1
Adapalene strength/regimen (n=6)	0.1% BID: 1 0.3%: 1 0.1%: 1 BID: 1 0.1% QOD: 1 0.3 mg daily: 1
Elective abortion (n=5)	Abortion reported: 4 Abortion considered: 1

Congenital Anomaly Events (n=11)

#1	Brachydactyly/oligodactyly
#2	Clubbed foot
#3	VACTERL Syndrome (vertebral anomalies, anal atresia, cardiovascular anomalies, tracheoesophageal fistula, esophageal atresia, renal and/or radial anomalies, and limb defects)
#4	Dandy Walker Syndrome (congenital brain malformation involving cerebellum)
#5	Anophthalmia, optic chiasma (Literature case)
#6	Single kidney and single umbilical artery
#7	Aarskog's syndrome suspected (monogenic X-linked recessive disorder)
#8	Cleft lip, cleft palate, brain, gastric, cardiovascular, intestinal anomalies
#9	Scimitar syndrome, Dandy walker malformation, normal karyotype

Congenital Anomaly Events (n=11) (continued)

#10	Genetic 2q37 deletion
#11	Trampling of feet, swallowing absent, absent primitive reflex; clinical signs of serious brain damage

Adapalene Use on Large Body Surface Area (n=1)

- A 55-year-old female with Darier disease (keratosis follicularis) treated with acitretin (oral retinoid) long term. Her liver tests were normal
- Ten months later, acute mixed pattern hepatitis ALT 107 IU/L, AST 67 IU/L, alkaline phosphatase 319 IU/L gamma-glutamyltransferase 81 IU/L, and bilirubin 7.1 micromol/L
- *10 months later, treated with adapalene 0.1% cream daily* for the relapse of Darier disease
- 15 tubes of 30 g adapalene applied on 15% of her body surface (8 months)
- Adapalene discontinued, liver tests progressively improved and returned to near normal seven months later

Lerisson M, Ripault MP, Pageaux GP, Guillot B, Larrey D. Hepatitis after retinoid percutaneous administration. Clin Res Hepatol Gastroenterol 2014 Oct;38(5):e99-e101.

FAERS Summary

- DPV observed 11 cases which do not show a pattern consistent with retinoid embryopathy; isolated malformations
- Cases do not support a signal of adapalene associated congenital anomaly
- No additional safety signals

Epidemiological Data

- PubMed literature search performed using generic names for *all topical retinoids* and AE subheadings
- Identified 15 studies
  - Reproductive outcomes (N=4 original, 1 meta-analysis)
  - Other serious AEs (N=2)
  - Cutaneous AEs (N=8)
- **No studies of adverse reproductive outcomes or other serious events assessed adapalene specifically**
- Findings from studies of other topical retinoids are inconclusive

Summary

- Wide utilization of adapalene, with the majority of use in women of child bearing age
- In the 20 years since approval, approximately 11 cases of congenital anomalies observed with adapalene use
- No epidemiological study of reproductive outcomes or other adverse events assessed adapalene specifically. Findings from studies of other topical retinoids are inconclusive

Acknowledgements

Office of Surveillance and Epidemiology (OSE)

- Allen Brinker, MD
- Grace Chai, LCDR, PharmD
- Hongliu Ding, MD, PhD, MPH
- Rajdeep Gill, PharmD
- Patty Greene, PharmD
- Lynda McCulley, PharmD, BCPS
- Scott Proestel, MD
- S. Christopher Jones, PharmD, MS, MPH
- Lockwood Taylor, PhD
- Cunlin Wang, MD, PhD

Benefit Vs Risk

FDA Nonprescription Drugs Advisory Committee Meeting for Differin® (Adapalene 0.1%) Gel April 15, 2016

Jane Filie, MD
Lead Medical Officer
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
CDER, FDA

Background

- Adapalene 0.1% gel was approved in 1996, for the treatment of acne vulgaris in patients 12 years and older
- The condition affects 50 million individuals in the US:
  - 85% teenagers
  - 12% adult women
- No mortality, but physical and psychological morbidity: permanent scarring, poor self-image, depression, anxiety
- The potential for teratogenicity is a concern in pregnant women.
- The population likely to use the drug includes a large proportion of women of childbearing age
- *Does the benefit of this drug in the OTC setting outweigh any risks?*

Background

- Efficacy for the indication was established for prescription use.
- Similar efficacy is expected in the OTC setting
- Retinoids are often recommended in guidelines as first-line therapy for acne of all severities, alone or in combination with other agents
- OTC treatments available:
  - Benzoyl peroxide 2.5 to 10%, in gel, washes, creams
  - Salicylic acid 0.5% to 2%, washes, cream, lotion, gels
  - Resorcinol 2% combined with sulfur
  - Resorcinol monoacetate 3% combined with sulfur
  - Sulfur 3 to 10%
  - Sulfur 3 to 8% combined with resorcinol

Toxicology and Clinical Pharmacology

- Teratogenicity is a known toxicity with retinoids
- Congenital anomalies were seen in the animal studies, as observed with drugs of the retinoid class
- The MUsT showed systemic absorption: quantifiable plasma concentrations in all 24 subjects by Day 29
- The margin of exposure for adapalene based on the MUsT is estimated to be at least 70-fold
- *Caveat:*
  - *Animal studies do not always predict effects in humans*
  - *The human sensitivity to this drug is unknown*

Post-Marketing Safety Data

- The Applicant's 20-year post-marketing data: estimated 40 million patients prescribed adapalene gel (0.1 and 0.3%):
  - 8 reports with outcomes were identified; no patterns consistent with retinoid exposure or insufficient data to draw conclusions
- FAERS (approval-11/2015): 11 cases of congenital anomalies observed with adapalene
- Literature review: 5 publications with pregnancy outcomes, none assessed adapalene-related risk specifically

- *Limitations of post-marketing data:*
  - *Under-reporting, lack of clinical data, reporting biases*
  - *The postmarketing data of Rx use may not reflect the safety of this product in the OTC setting*

Label Comprehension and Self-Selection Studies

- The **Label Comprehension Study** had a significant deficiency:
  - The lack of assessment of the pregnancy statement, which was recommended by FDA
- The **Self-Selection Study (SSS)** failed to demonstrate that pregnant women would consult a healthcare professional before using the product:
  - The SSS was conducted mostly in breastfeeding women rather than pregnant women
  - Reasons for making an incorrect self-selection include:
    - The lack of perception that an OTC product could potentially cause harm to their babies
    - 15 women did not see the warning on the label

Actual Use Trial

- The **Actual Use Trial** (**AUT)** indicated that consumers will use per directions once daily and unlikely overuse the product
- However:
  - Of the 9 pregnant women who enrolled in the study, 5 incorrectly chose to purchase the product without first asking a healthcare provider
  - During a short period (6 weeks), 4 pregnancies occurred
- If available OTC, the product would be used by pregnant women

Benefit vs Risk Assessment

Factors to Consider:

- Potential teratogenicity (preclinical data, margin of exposure, human absorption)
- Post-marketing safety data related to pregnancy
- Potential use by women of childbearing age and pregnant
- Implications for the pediatric population

Thank you

Charge to Committee

FDA Nonprescription Drugs Advisory Committee Meeting for
Differin® (Adapalene 0.1%) Gel
April 15, 2016

Valerie Pratt, MD
Deputy Director for Safety
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
CDER, FDA

Key Points

Adapalene is a Retinoid-like Product

- Teratogenic effects were seen in animal studies
- Based on the MUsT, the margin of exposure is at least 70 fold
- However, the human sensitivity to this drug is unknown

Key Points

- Label Comprehension study
  - Did not assess the pregnancy statement
  - “Under 12 years of age consult a physician” tested well among males and females ages 12-70
- Self-Selection study failed to demonstrate that pregnant women would consult a health care professional (HCP) before use
- AUT demonstrated that most consumers with acne used the product as directed
  - The most common reason for discontinuation was mild skin-related adverse events, which resolved
  - 5 of 9 pregnant women inappropriately requested to use the product without seeking HCP advice
  - With the current labeling, it appears that pregnant women will not stop use and seek HCP advice
  - Seven children less than 12 years of age approached the pharmacy to access the product

Question 1

DISCUSSION: Discuss the safety profile of adapalene gel 0.1% in the over-the-counter (OTC) setting. In your discussion, please consider the following:

a. *use by females with reproductive potential (i.e., teratogenic risk),*
b. *pediatric use (i.e., use by adolescents and/or younger children), and*
c. *potential for misuse (e.g., excessive use or use for non-acne conditions) and the consequences of such use.*

Question 2

VOTE: Has the safety of adapalene gel 0.1% for OTC use for the treatment of acne been adequately demonstrated?

- *If not, what additional data, if any, should be obtained to demonstrate safety in the OTC setting?*

Question 3

DISCUSSION: Discuss the proposed Drug Facts Label and Consumer Information Leaflet.

- *If your review of the label and leaflet identifies concerns, please discuss ways in which the documents could be revised to encourage the safe and proper use of the product by consumers.*

Question 4

VOTE: The sponsor proposes OTC use of adapalene gel 0.1% for the treatment of acne in consumers ages 12 years and older. Does the totality of the data support the use of this product OTC?

a. *If yes, do you have additional comments or recommendations for labeling?*
b. *If not, what further data, if any, should be obtained to support such use?*

Thank you