

Labeling and Human Dermal Safety Testing

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Disclaimer and Conflict Statement

This presentation reflects the views of the speaker and should not be construed to represent FDA's views or policies.

I have no conflicts to disclose.

Outline

- Labeling basics
- Existing landscape

Caveats

- Descriptive
- Shared responsibility
- Change over time

Outline

- Labeling basics
- Existing landscape

Product labeling

- 4 components:
 - Professional labeling= package insert
 - Patient labeling
 - Carton/container labels
 - Commercial

- Professional labeling

General requirements

21 CFR 201.56(a)

- Essential scientific information needed for the safe and effective use of the drug
- Informative and accurate
- Not misleading in any particular
- Based whenever possible on data derived from human experience

Safety information

- 4-Contraindications
- 5-Warnings and Precautions
- 6-Adverse Reactions
- Specific situations
 - 7-Drug interactions
 - 8-Use in Specific Populations
 - 9-Drug Abuse and Dependence
 - 10-Overdosage
 - 12-Clinical Pharmacology
 - 13-Animal toxicology/pharmacology

Safety information

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Labeling Guidance

- Guidance for Industry: *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products—Content and Format*
- Negative finding acceptable for inclusion if “convincingly demonstrated in a trial of adequate design and power.”

Outline

- Labeling basics
- Existing landscape

Existing Landscape

- Dermal safety study results described PI
- Caveats
 - Descriptive
 - Shared responsibility
 - Change over time

Methods

- Used FDALabel—a labeling search tool
- Search professional labeling (PI) for topical prescription drug products
 - >200 unique topical products regulated by DDDP
 - PLR and old format
- August 2018
- Specific search terms
- Eliminated duplicates

Search terms

- Irritancy
- Contact sensitization
- Phototoxicity
- Photoallergenicity
- Local tolerability
- Cumulative irritancy
- Dermal safety
- Sensitization
- Repeat insult patch test

Dermal Safety Study Results in Labeling

- 29 products include DSS results
 - 16 products negative results
 - 13 products positive results
- Does not provide denominator

Dermal Safety Study Results in Labeling

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Product labeling--negative DSS results

- 16 products
- Discordant information elsewhere in labeling
 - Not a reason to exclude from labeling
- Two examples:
 - pimecrolimus cream
 - tazarotene cream

ELIDEL (pimecrolimus) Cream

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

No phototoxicity and no photoallergenicity were detected in clinical trials with 24 and 33 normal volunteers, respectively. In human dermal safety trials, ELIDEL Cream, 1% did not induce contact sensitization or cumulative irritation.

Table 1. Treatment Emergent Adverse Events (≥1%) in ELIDEL Cream, 1% Treatment Groups

	(6 weeks)		(20 weeks)	(1 year)		(1 year)
	ELIDEL Cream, 1%	Vehicle	ELIDEL Cream, 1%	ELIDEL Cream, 1%	Vehicle	ELIDEL Cream, 1%
General Disorders and Administration Site Conditions						
Application Site	28 (10.4%)	17 (12.5%)	5 (1.5%)	23 (8.5%)	5 (6.7%)	85 (25.9%)
Burning						
Pyrexia	20 (7.5%)	12 (8.8%)	41 (12.2%)	34 (12.5%)	4 (5.3%)	4 (1.2%)
Application Site Reaction NOS	8 (3.0%)	7 (5.1%)	7 (2.1%)	9 (3.3%)	2 (2.7%)	48 (14.6%)
Application Site Irritation	8 (3.0%)	8 (5.9%)	3 (0.9%)	1 (0.4%)	3 (4.0%)	21 (6.4%)
Influenza-Like Illness	1 (0.4%)	0	2 (0.6%)	5 (1.8%)	2 (2.7%)	6 (1.8%)
Application Site Erythema	1 (0.4%)	0	0	6 (2.2%)	0	7 (2.1%)

TAZORAC (tazarotene) cream

5 WARNINGS AND PRECAUTIONS

5.2 Local Irritation and Hypersensitivity Reactions

Local tolerability reactions (including blistering and skin desquamation) and hypersensitivity adverse reactions (including urticaria) have been observed with topical tazarotene. Application of TAZORAC

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in more detail in other sections of the labeling:

- Embryofetal toxicity [see Warnings and Precautions (5.1)]
- Photosensitivity and Risk of Sunburn [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In human dermal safety trials, TAZORAC Cream, 0.05% and 0.1% did not induce allergic contact sensitization, phototoxicity, or photoallergy.

TAZORAC (tazarotene) cream

5.3 Photosensitivity and Risk for Sunburn

Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) should be avoided unless deemed medically necessary, and in such cases, exposure should be minimized during the use of TAZORAC Cream. Patients must be warned to use sunscreens and protective clothing when using TAZORAC Cream. Patients with sunburn should be advised not to use TAZORAC Cream until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using TAZORAC Cream.

TAZORAC Cream should be administered with caution if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

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Dermal Safety Study Results in Labeling

- 29 products include DSS results
 - 16 products negative results
 - 13 products positive results
- Does not provide denominator

Product labeling—positive DSS results

- 13 products
- Concordance varies
 - Not a reason for inclusion or exclusion
- Two examples:
 - Ketaconazole foam
 - Sinocatechins ointment

EXTINA (ketaconazole) foam

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Table 1: Adverse Reactions Reported by > 1% Subjects in Clinical Trials

Adverse Reactions	EXTINA Foam N = 672 n (%)	Vehicle Foam N = 497 n (%)
Subjects with an Adverse Reaction	188 (28%)	122 (25%)
Application site burning	67 (10%)	49 (10%)
Application site reaction	41 (6%)	24 (5%)

6.2 Dermal Safety Studies

In a photoallergenicity study, 9 of 53 subjects (17%) had reactions during the challenge period at both the irradiated and non-irradiated sites treated with EXTINA Foam. EXTINA Foam may cause contact sensitization.

VEREGEN (sinecatechins) ointment

6 ADVERSE REACTIONS

In clinical trials, the incidence of patients with local adverse events leading to discontinuation or dose interruption (reduction) was 5% (19/397). These included the following events: application site reactions (local pain, erythema, vesicles, skin erosion/ulceration), phimosis, inguinal lymphadenitis, urethral meatal stenosis, dysuria, genital herpes simplex, vulvitis, hypersensitivity, pruritus, pyodermitis, skin ulcer, erosions in the urethral meatus, and superinfection of warts and ulcers.

Table 1: Local and Regional Adverse Reactions During Treatment (% Subjects)

	Veregen® (N = 397)	Vehicle (N = 207)
Erythema	70	32
Pruritus	69	45
Burning	67	31
Pain/discomfort	56	14
Erosion/Ulceration	49	10
Edema	45	11
Induration	35	11
Rash vesicular	20	6

In a dermal sensitization study of Veregen® in healthy volunteers, hypersensitivity (type IV) was observed in 5 out of 209 subjects (2.4%) under occlusive conditions.

Summary

- DSS results included in labeling for 29 unique topical prescription drug products
- Negative results often discordant with other information in labeling
- Positive results vary in relationship to other information

Reminder

- Discordance not reason to exclude information
- Concordance not reason to include information
- Standard:
 - Essential information needed for safe/effective use
 - Informative, accurate
 - Not misleading in any particular



Acknowledgement

- Nancy Xu, MD



Questions?

ZOVIRAX (acyclovir) cream

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in practice.

In five double-blind, placebo-controlled trials, 1124 patients were treated with ZOVIRAX Cream and 1161 with placebo (vehicle) cream. Local application site reactions were reported by 5% of patients receiving ZOVIRAX Cream and 4% of patients receiving placebo. The most common adverse reactions at the site of topical application were dry lips, desquamation, dryness of skin, cracked lips, burning skin, pruritus, flakiness of skin, and stinging on skin; each adverse reaction occurred in less than 1% of patients receiving ZOVIRAX Cream and placebo. Three patients on ZOVIRAX Cream and one patient on placebo discontinued treatment due to an adverse event.

An additional study, enrolling 22 healthy adults, was conducted to evaluate the dermal tolerance of ZOVIRAX Cream compared with vehicle using single occluded and semi-occluded patch testing methodology. Both ZOVIRAX Cream and placebo showed a high and cumulative irritation potential. Another study, enrolling 251 healthy adults, was conducted to evaluate the contact sensitization potential of ZOVIRAX Cream using repeat insult patch testing methodology. Of 202 evaluable subjects, possible cutaneous sensitization reactions were observed in the same 4 (2%) subjects with both ZOVIRAX Cream and placebo, and these reactions to both ZOVIRAX Cream and placebo were confirmed in 3 subjects upon rechallenge. The sensitizing ingredient(s) has not been identified.

ZOVIRAX (acyclovir) cream

6.2 Postmarketing Experience

In addition to adverse events reported from clinical trials, the following events have been identified during postapproval use of acyclovir cream. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to acyclovir cream.

General: Angioedema, anaphylaxis.

Skin: Contact dermatitis, eczema.

5.2 Contact Sensitization

ZOVIRAX Cream has a potential for irritation and contact sensitization [see *Adverse Reactions (6.1)*].