



BY ALAN
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UNDER MY SKIN

Rational Actors

Thursday was quite illuminating. Some days are like that. Merle came by in the morning. She places skin care products in

health food stores. Merle can do this from anywhere, so last month she did it from

Hawaii. "I saw a black spot here that alarmed me," she said, pointing to the crook of her left arm. "It looked like this." Her picture looked like the kind of mask you wear to costume balls, with dark spots for eyes. "I couldn't get an appointment with a dermatologist for weeks," said Merle. "So I applied bloodroot—you know, the black salve."

Of course. The escharotic that's supposed to destroy cancers.

"But then I worried," she said. "How did I know what I was treating?"

How indeed? "Good point," I said.

Merle looked down at her antecubital space, with a patch of proud flesh shaped like her drawing. "I wonder if I drove it inside," she said. "Maybe the cancer is in my bloodstream."

"That's why we like to send moles we remove for biopsy confirmation, rather than just destroy them," I said.

Merle nodded in apparent understanding. "Well, I had to do something," she said. "I couldn't get an appointment with a dermatologist."

Then Brian came in the afternoon, looking haggard. Brian is in commercial real estate. He had scratch marks on his arms and back. "Under much stress?" I asked.

"I'll say," said Brian. "I've been divorced 5 years, and my wife is still coming after me." He then launched into the bitter tale.

"I filed an appeal in superior court," he said. "I brought the document myself and had them stamp it and make me a copy. Then they lost it and refused to hear the appeal. But my luck changed this week," said Brian, brightening a little.

"How's that?" I asked.

"I got a haircut," he said, "and I told my barber what was happening. He told me what to do. He said, 'Take a piece of paper and write your wife's name on it. Then wet the paper, put it in the freezer, and freeze her out of your life!'"

"I know it sounds ridiculous," said Brian, "but I did it. I mean, I'd tried everything else. And you know what? Tuesday, one of the court clerks was rummaging on the floor and found my appeal stapled in between two other different papers!"

Merle and Brian may sound a bit extreme, but they illuminate some ways people think and act when it comes to taking care of themselves:

► Patients do silly things, despite being quite capable of explaining why these things make no sense even by their own standards.

► They tend to act this way when they are fearful or frustrated enough, especially when other people advise it and so reduce any risk of embarrassment. Such advisers need no credentials.

Where health and livelihood are concerned, both Merle and Brian believe in consulting professionals such as doctors, lawyers, and accountants. When it suits them, however, they also take the advice of friends who recommend escharotics and of barbers who suggest sympathetic magic. The contradiction between what they profess and what they do—if they notice it at all—doesn't trouble them.

What makes this odd is that, according to those in and around my own profession, patients are rational actors who engage in health behaviors demonstrated to be in their best interest. Given data and access, they seek out appropriate treatments based on the best current evidence. Properly incentivized, they consult physicians who are objectively superior and more efficient.

All this is true, of course; it ought to be, it must be, and leading experts say it is.

The only problem is that these rational patients live on a planet different from the one I practice on. But I am optimistic that space travel will rapidly improve, so I can visit that planet soon. In the meantime, as they say nowadays, you treat the patients you have. ■

BRIEF SUMMARY

(see package insert for full prescribing information)

ZIANA™

(clindamycin phosphate 1.2% and tretinoin 0.025%) Gel

Rx only

For topical use only

INDICATIONS AND USAGE

ZIANA Gel is indicated for the topical treatment of acne vulgaris in patients 12 years or older.

CONTRAINDICATIONS

ZIANA Gel is contraindicated in patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis.

WARNINGS AND PRECAUTIONS

Colitis

Systemic absorption of clindamycin has been demonstrated following topical use of this product. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. When significant diarrhea occurs, ZIANA Gel should be discontinued.

Severe colitis has occurred following oral or parenteral administration of clindamycin with an onset of up to several weeks following cessation of therapy. Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen severe colitis. Severe colitis may result in death.

Studies indicate a toxin(s) produced by clostridia is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Stool cultures for *Clostridium difficile* and stool assay for *C. difficile* toxin may be helpful diagnostically.

Ultraviolet Light and Environmental Exposure

Exposure to sunlight, including sunlamps, should be avoided during the use of ZIANA Gel, and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight as a result of the use of tretinoin. Patients who may be required to have considerable sun exposure due to occupation and those with inherent sensitivity to the sun should exercise particular caution. Daily use of sunscreen products and protective apparel (e.g., a hat) are recommended. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with ZIANA Gel.

ADVERSE REACTIONS

Clinical Studies Experience

Because clinical trials are conducted under prescribed conditions, adverse reaction rates observed in the clinical trial may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse reactions that appear to be related to drug use for approximating rates.

The safety data presented in Table 1 (below) reflects exposure to ZIANA Gel in 1,853 patients with acne vulgaris. Patients were 12 years and older and were treated once daily for 12 weeks. Adverse reactions that were reported in ≥ 1% of patients treated with ZIANA Gel were compared to adverse reactions in patients treated with clindamycin phosphate 1.2% in vehicle gel, tretinoin 0.025% in vehicle gel, and the vehicle gel alone:

Table 1: Adverse Reactions Reported in at Least 1% of Patients Treated with ZIANA Gel: 12-Week Studies

	ZIANA Gel N=1853 N (%)	Clindamycin N=1428 N (%)	Tretinoin N=846 N (%)	Vehicle N=423 N (%)
PATIENTS WITH AT LEAST ONE AR	497 (27)	342 (24)	225 (27)	91 (22)
Nasopharyngitis	65 (4)	64 (5)	16 (2)	5 (1)
Pharyngolaryngeal pain	29 (2)	18 (1)	5 (1)	7 (2)
Dry skin	23 (1)	7 (1)	3 (<1)	0 (0)
Cough	19 (1)	21 (2)	9 (1)	2 (1)
Sinusitis	19 (1)	19 (1)	15 (2)	4 (1)

Note: Formulations used in all treatment arms were in the ZIANA vehicle gel.

Cutaneous safety and tolerance evaluations were conducted at each study visit in all of the clinical trials by assessment of erythema, scaling, itching, burning, and stinging:

Local Reaction	Baseline N=1835 N (%)	End of Treatment N=1614 N (%)
Erythema	636 (35)	416 (26)
Scaling	237 (13)	280 (17)
Itching	189 (10)	70 (4)
Burning	38 (2)	56 (4)
Stinging	33 (2)	27 (2)

At each study visit, application site reactions on a scale of 0 (none), 1 (mild), 2 (moderate), and 3 (severe), and the mean scores were calculated for each of the local skin reactions. In Studies 1 and 2, 1277 subjects enrolled with moderate to severe acne, 854 subjects treated with ZIANA Gel and 423 treated with vehicle. Analysis over the twelve week period demonstrated that cutaneous irritation scores for erythema, scaling, itching, burning, and stinging peaked at two weeks of therapy, and were slightly higher for the ZIANA-treated group, decreasing thereafter.

One open-label 12-month safety study for ZIANA Gel showed a similar adverse reaction profile as seen in the 12-week studies. Eighteen out of 442 subjects (4%) reported gastrointestinal symptoms.

DRUG INTERACTIONS

Concomitant Topical Medication

Concomitant topical medication, medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices or lime should be used with caution. When used with ZIANA Gel, there may be increased skin irritation.

Erythromycin

ZIANA Gel should not be used in combination with erythromycin-containing products due to its clindamycin component. *In vitro* studies have shown antagonism between these two antimicrobials. The clinical significance of this *in vitro* antagonism is not known.

Neuromuscular Blocking Agents

Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, ZIANA Gel should be used with caution in patients receiving such agents.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C. There are no well-controlled trials in pregnant women treated with ZIANA Gel. ZIANA Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ZIANA Gel was tested for maternal and developmental toxicity in New Zealand White Rabbits with topical doses of 60, 180 and 600 mg/kg/day. ZIANA Gel at 600 mg/kg/day

(approximately 12 times the recommended clinical dose assuming 100% absorption and based on body surface area comparison) was considered to be the no-observed-adverse-effect level (NOAEL) for maternal and developmental toxicity following dermal administration of ZIANA Gel for two weeks prior to artificial insemination and continuing until gestation day 18, inclusive. For purposes of comparisons of the animal exposure to human exposure, the recommended clinical dose is defined as 1 g of ZIANA Gel applied daily to a 60 kg person.

Clindamycin

Teratology (Segment II) studies using clindamycin were performed orally in rats (up to 600 mg/kg/day) and mice (up to 100 mg/kg/day) (583 and 49 times amount of clindamycin in the recommended clinical dose based on a body surface area comparison, respectively) or with subcutaneous doses of clindamycin up to 180 mg/kg/day (175 and 88 times the amount of clindamycin in the recommended clinical dose based on a body surface area comparison, respectively) revealed no evidence of teratogenicity.

Tretinoin

In oral Segment III studies in rats with tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (~ 78 times the recommended clinical dose assuming 100% absorption and based on body surface area comparison).

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty cases of temporally associated congenital malformations have been reported during two decades of clinical use of another formulation of topical tretinoin. Although no definite pattern of teratogenicity and no causal association have been established from these cases, 5 of the reports describe the rare birth defect category, holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

Dermal tretinoin has been shown to be fetotoxic in rabbits when administered in doses 40 times the recommended human clinical dose based on a body surface area comparison. Oral tretinoin has been shown to be fetotoxic in rats when administered in doses 78 times the recommended clinical dose based on a body surface area comparison.

Nursing Mothers

It is not known whether clindamycin is excreted in human milk following use of ZIANA Gel. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is not known whether tretinoin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZIANA Gel is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of ZIANA Gel in pediatric patients under the age of 12 have not been established. Clinical trials of ZIANA Gel included patients 12–17 years of age.

Geriatric Use

Clinical studies of ZIANA Gel did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Manufactured by:
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