CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-794

LABELING

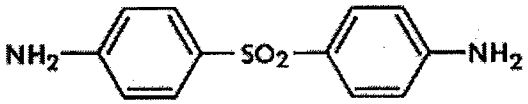
ACZONE™ Gel 5% PACKAGE INSERT

ACZONE™ (dapsone) Gel, 5%

FOR TOPICAL USE ONLY
NOT FOR ORAL, OPHTHALMIC, OR INTRAVAGINAL USE

DESCRIPTION

ACZONE™ Gel, 5%, contains dapsone, a sulfone, in an aqueous gel base for topical dermatologic use. ACZONE™ Gel is a gritty, translucent material with visible drug substance particles. Chemically, dapsone has an empirical formula of $C_{12}H_{12}N_2O_2S$. It is a white, odorless crystalline powder that has a molecular weight of 248. Dapsone's chemical name is 4,4'-diaminodiphenylsulfone and its structural formula is:



Each gram of ACZONE™ (dapsone) Gel, 5%, contains 50 mg of dapsone, USP, in a gel of carbomer 980; diethylene glycol monoethyl ether, NF; methylparaben, NF; sodium hydroxide, USP; and purified water, USP.

CLINICAL PHARMACOLOGY

Mechanism of Action:
The mechanism of action of dapsone gel in treating acne vulgaris is not known.

Pharmacokinetics:
An open-label study compared the pharmacokinetics of dapsone after ACZONE™ Gel, 5%, (110 ± 60 mg/day) was applied twice daily (~BSA 22.5%) for 14 days (n=18) with a single 100 mg dose of oral dapsone administered to a subgroup of patients (n=10) in a crossover design. On Day 14 the mean dapsone $AUC_{0\text{-}24\ h}$ was 415 ± 224 ng•h/mL for ACZONE™ Gel, 5%, whereas following a single 100 mg dose of oral dapsone the $AUC_{0\text{-}infinity}$ was 52,641 ± 36,223 ng•h/mL.

Special Populations: In a clinical study, periodic blood samples were collected up to 12 months to determine systemic exposure of dapsone and its metabolites in approximately 500 patients. Based on the measurable dapsone concentrations from 408 patients (M=192, F=216), obtained at month 3, neither gender, nor race appeared to affect the pharmacokinetics of dapsone. Similarly, dapsone exposures were approximately the same between the age groups of 12-15 years (N=155) and those greater than or equal to 16 years (N=253).

MICROBIOLOGY

In Vivo Activity: No microbiology or immunology studies were conducted during dapsone gel clinical trials.

Drug Resistance: No dapsone resistance studies were conducted during dapsone gel clinical trials. Therapeutic resistance to dapsone has been reported for *Mycobacterium leprae*, when patients have been treated with oral dapsone.*

*Matsuoka, M. A. Dec 2000. *Mycobacterium leprae* isolate resistant to dapsone, rifampin, ofloxacin and sparfloxacin. Int J Lepr Other Mycobact Dis. 68(4):452-5.

CLINICAL STUDIES

Two randomized, double blind, vehicle controlled, clinical studies were conducted to evaluate ACZONE™ Gel, 5%, for the treatment of patients with acne vulgaris (N=1475 and 1525). The studies were designed to enroll patients 12 years of age and older with 20 to 50 inflammatory and 20 to 100 non-inflammatory lesions at baseline. In these studies patients applied either ACZONE™ Gel, 5%, or vehicle control twice daily for up to 12 weeks. Efficacy was evaluated in terms of success on the Global Acne Assessment Score (no or minimal acne) and in the percent reduction in inflammatory, non-inflammatory, and total lesions.

The Global Acne Assessment Score was a 5-point scale as follows:

- 0 None: no evidence of facial acne vulgaris
- 1 Minimal: few non-inflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) may be present
- 2 Mild: several to many non-inflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) are present
- 3 Moderate: many non-inflammatory (comedones) and inflammatory lesions (papules/pustules) are present; no nodulo-cystic lesions are allowed
- 4 Severe: significant degree of inflammatory disease; papules/pustules are a predominant feature; a few nodulo-cystic lesions may be present; comedones may be present.

The success rates on the Global Acne Assessment Score (no or minimal acne) at Week 12 are presented in Table 1.

Table 1 - Success (No or Minimal Acne) on the Global Acne Assessment Score at Week 12

	Study 1*		Study 2*	
	ACZONE™ N=699	Vehicle N=687	ACZONE™ N=729	Vehicle N=738
Subjects with No or Minimal Acne	291 (42%)	223 (32%)	253 (35%)	206 (28%)

*Analysis excludes subjects classified with minimal acne at baseline

Table 2 presents the mean percent reduction in inflammatory, non-inflammatory, and total lesions from baseline to Week 12.

Table 2 - Percent Reduction in Lesions from Baseline to Week 12

	Study 1		Study 2	
	ACZONE™ N=745	Vehicle N=740	ACZONE™ N=761	Vehicle N=764
Inflammatory	46%	42%	48%	40%
Non-Inflammatory	31%	24%	30%	21%
Total	38%	32%	37%	29%

The clinical studies enrolled about equal proportions of male and female subjects. Female patients tended to have greater percent reductions in lesions and greater success on the Global Acne Assessment Score than males. The breakdown by race in the clinical studies was about 73% Caucasian, 14% Black, 9% Hispanic, and 2% Asian. Efficacy results were similar across the racial subgroups.

INDICATIONS AND USAGE

ACZONE™ Gel, 5%, is indicated for the topical treatment of acne vulgaris.

Glucose 6-phosphate dehydrogenase (G6PD) levels should be obtained prior to initiating therapy with ACZONE™ Gel, 5%. In patients with a history of anemia and predisposition to increased hemolytic effect with dapsone (e.g., glucose-6-phosphate dehydrogenase deficiency), closer follow-up for blood hemoglobin levels and reticulocyte counts should be implemented (see PRECAUTIONS). Alternatively, other therapies for acne than ACZONE™ Gel, 5%, may be considered.

CONTRAINDICATIONS

ACZONE™ Gel, 5%, is contraindicated in persons with a hypersensitivity to dapsone or any other component of the formulation.

PRECAUTIONS

General

Glucose 6-phosphate dehydrogenase levels should be obtained in all patients prior to initiating therapy with ACZONE™ Gel, 5%. Baseline complete blood counts, including a reticulocyte count, should be obtained in patients who are G6PD deficient or with a history of anemia. Routine follow-up for complete blood count and reticulocyte count

should be implemented for patients at risk. If signs, symptoms or laboratory evidence of anemia develop during treatment, use of ACZONE™ Gel, 5%, should be discontinued. Dose-related hemolysis is the most common adverse event seen in patients treated with oral Dapsone (with or without glucose-6-phosphate dehydrogenase deficiency). Hemolysis may be exaggerated in individuals with G6PD deficiency, methemoglobin reductase deficiency, or hemoglobin M.

While clinical studies conducted did not demonstrate evidence of clinically significant anemia, an increased reticulocyte count and a decreased hemoglobin level were noted to be associated in a G6PD deficient patient treated with ACZONE™ Gel, 5%, for acne vulgaris who had a complete blood count performed. Only 25 patients with low plasma glucose 6-phosphate dehydrogenase activity treated with ACZONE™ Gel, 5%, were included in the clinical study program. Safety of ACZONE™ Gel, 5%, has not been fully evaluated in patients with G6PD deficiency.

Although not observed in the clinical trials with topical dapsone, serious adverse reactions have been reported with oral use of dapsone, including agranulocytosis, hemolytic anemia, peripheral neuropathy (motor loss and muscle weakness), and skin reactions (toxic epidermal necrolysis, erythema multiforme, morbilliform and scarlatiniform reactions, bullous and exfoliative dermatitis, erythema nodosum, and urticaria).

In the clinical trials, a total of 12 out of 4032 patients were reported to have depression (3 of 1660 treated with vehicle and 9 of 2372 treated with ACZONE™ Gel, 5%). Psychosis was reported in 2 of 2372 patients treated with ACZONE™ Gel, 5%, and in 0 of 1660 patients treated with vehicle.

Information for Patients

1. Patients should use ACZONE™ Gel, 5%, as directed by the physician. ACZONE™ Gel, 5%, is for external topical use only. ACZONE™ Gel, 5%, is not for oral, ophthalmic or intravaginal use.
2. Patients should not use this medication for any disorder other than that for which it was prescribed.
3. Patients should tell their physician if they have any history of anemia or an enzyme deficiency (such as G6PD deficiency).
4. Patients should be informed as to the need for laboratory evaluation prior to starting ACZONE™ Gel, 5%.
5. Patients should report any signs of adverse reactions to their physician.
6. Protect ACZONE™ Gel, 5%, from freezing and light. Return to the original carton after application to protect from light.
7. See Patient Information for additional information on safety, efficacy, general use, and storage of ACZONE™ Gel, 5%.

Laboratory Tests

Glucose 6-phosphate dehydrogenase levels should be obtained in all patients prior to initiating therapy with ACZONE™ Gel, 5%. Baseline complete blood counts, including a reticulocyte count, should be obtained in patients who are G6PD deficient or with a history of anemia. Routine follow-up for complete blood count and reticulocyte count should be implemented for patients at risk.

Drug Interactions

A drug-drug interaction study evaluated the effect of the use of ACZONE Gel, 5%, in combination with double strength (160 mg/800 mg) trimethoprim/sulfamethoxazole (TMP/SMX). During co-administration, systemic levels of TMP and SMX were essentially unchanged. However, levels of dapsone and its metabolites increased in the presence of TMP/SMX. Systemic exposure (AUC_{0-12}) of dapsone and N-acetyl-dapsone (NAD) were increased by about 40% and 20% respectively in presence of TMP/SMX. Notably, systemic exposure (AUC_{0-12}) of dapsone hydroxylamine (DHA) was more than doubled in the presence of TMP/SMX. Exposure from the proposed topical dose is about 1% of that from the 100 mg oral dose, even when co-administered with TMP/SMX.

Certain concomitant medications (such as rifampin, anticonvulsants, St. John's wort) may increase the formation of dapsone hydroxylamine, a metabolite of dapsone associated with hemolysis. With oral dapsone treatment, folic acid antagonists such as pyrimethamine have been noted to possibly increase the likelihood of hematologic reactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Dapsone was not mutagenic in a bacterial reverse mutation assay (Ames test) using *S. typhimurium* and *E. coli*, with and without metabolic activation and was negative in a micronucleus assay conducted in mice. Dapsone increased both numerical and structural aberrations in a chromosome aberration assay conducted with Chinese hamster ovary (CHO) cells.

In studies conducted for ACZONE Gel, 5%, dapsone was not carcinogenic to rats when orally administered to females for 92 weeks or males for 100 weeks at dose levels up to 15 mg/kg/day (approximately 160 times the systemic exposure observed in human males and 300 times the systemic exposure observed in human females as a result of use of the maximum recommended topical dose, based on AUC comparisons).

No evidence of potential to induce carcinogenicity was obtained in a dermal study in which dapsone gel was topically applied to Tg.AC transgenic mice for approximately 26 weeks. Dapsone concentrations of 3%, 5%, and 10% were evaluated; 3% material was judged to be the maximum tolerated dosage.

ACZONE Gel, 5%, did not increase the rate of formation of ultra violet light-induced skin tumors when topically applied to hairless mice in a 12-month photocarcinogenicity study.

The effects of dapsone on fertility and general reproduction performance were assessed in male and female rats following oral (gavage) dosing. Dapsone reduced sperm motility at dosages of 3 mg/kg/day or greater (approximately 17 times the systemic exposure observed in human males as a result of use of the maximum recommended topical dose, based on AUC comparisons). The mean numbers of embryo implantations and viable embryos were significantly reduced in untreated females mated with males that had been dosed at 12 mg/kg/day or greater (approximately 70 times the systemic exposure observed in human males as a result of use of the maximum recommended topical dose, based on AUC comparisons), presumably due to reduced numbers or effectiveness of sperm, indicating impairment of fertility. Dapsone had no effect on male fertility at dosages of 2 mg/kg/day or less (approximately 13 times the systemic exposure observed in human males as a result of use of the maximum recommended topical dose, based on AUC comparisons). When administered to female rats at a dosage of 75 mg/kg/day (approximately 800 times the systemic exposure observed in human females as a result of use of the maximum recommended topical dose, based on AUC comparisons) for 15 days prior to mating and for 17 days thereafter, dapsone reduced the mean number of implantations, increased the mean early resorption rate, and reduced the mean litter size. These effects were probably secondary to maternal toxicity.

Dapsone was assessed for effects on perinatal/postnatal pup development and postnatal maternal behavior and function in a study in which dapsone was orally administered to female rats daily beginning on the seventh day of gestation and continuing until the twenty-seventh day postpartum. Maternal toxicity (decreased body weight and food consumption) and developmental effects (increase in stillborn pups and decreased pup weight) were seen at a dapsone dose of 30 mg/kg/day (approximately 500 times the systemic exposure observed in human females as a result of use of the maximum recommended topical dose, based on AUC comparisons). No effects were observed on the viability, physical development, behavior, learning ability, or reproductive function of surviving pups.

Pregnancy:
Teratogenic Effects: Pregnancy Category C

Dapsone has been shown to have an embryocidal effect in rats and rabbits when given in doses of 75 mg/kg/day and 150 mg/kg/day (approximately 800 and 500 times the systemic exposure observed in human females as a result of use of the maximum recommended topical dose, based on AUC comparisons), respectively. These effects were probably secondary to maternal toxicity. There are no adequate and well controlled studies in pregnant women. ACZONE Gel, 5%, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers:

Although systemic absorption of dapsone following topical application of ACZONE™ Gel, 5%, is minimal relative to oral dapsone administration, it is known that dapsone is excreted in human milk. Because of the potential for oral dapsone to cause adverse

reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue ACZONE™ Gel, 5%, taking into account the importance of the drug to the mother.

Pediatric Use:

Safety and efficacy was evaluated in 1169 children aged 12-17 years old treated with ACZONE Gel, 5%, in the clinical studies. The adverse event rate for ACZONE™ Gel, 5%, was similar to the vehicle control group. Safety and efficacy was not studied in pediatric patients less than 12 years of age, therefore ACZONE™ Gel, 5%, is not recommended for use in this age group.

Geriatric Use:

Clinical studies of ACZONE™ Gel, 5%, did not include sufficient number of patients aged 65 and over to determine whether they respond differently from younger patients.

ADVERSE REACTIONS

While clinical studies conducted with ACZONE Gel, 5%, for acne vulgaris did not demonstrate evidence of clinically significant anemia, an increased reticulocyte count and a decreased hemoglobin level were found in a G6PD deficient patient who had a complete blood count performed. Only 25 patients with low plasma glucose 6-phosphate dehydrogenase activity treated with ACZONE Gel, 5%, were included in the clinical study program.

Serious adverse events reported in patients treated with ACZONE Gel, 5%, during clinical trials included but were not limited to the following:
Nervous system/Psychiatric – Suicide attempt, tonic clonic movements.
Gastrointestinal – Abdominal pain, severe vomiting, pancreatitis.
Other – Severe pharyngitis

Combined contact sensitization/irritation studies with ACZONE Gel, 5%, in 253 healthy subjects resulted in at least 3 subjects with moderate erythema. ACZONE™ Gel, 5%, did not induce phototoxicity or photoallergy in human dermal safety studies.

ACZONE™ Gel, 5%, was evaluated for 12 weeks in four controlled studies for local cutaneous events in 1819 patients. The most common events reported from these studies include oiliness/peeling, dryness, and erythema. These data are shown by severity in Table 3 below.

Table 3 - Application Site Adverse Events by Maximum Severity from Four 12-Week, Vehicle-Controlled Studies

Application Site Event	ACZONE™ (N=1819)			Vehicle (N=1660)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	9%	5%	<1%	9%	6%	<1%
Dryness	14%	3%	<1%	14%	4%	<1%
Oiliness/Peeling	13%	6%	<1%	15%	6%	<1%

There were no significant differences in the adverse event rates between ACZONE™ Gel, 5%, and vehicle control treated patients. The adverse events occurring in at least 1% of patients in either arm in the four vehicle controlled studies are presented in Table 4.

Table 4 – Adverse Events Occurring in at least 1% of Patients in Four Vehicle Controlled Studies

	ACZONE™ N=1819	Vehicle N=1660
Application Site Reaction NOS	18%	20%
Application Site Dryness	16%	17%
Application Site Erythema	13%	14%
Application Site Burning	1%	2%
Application Site Pruritus	1%	1%
Pyrexia	1%	1%
Nasopharyngitis	5%	6%
Upper Respiratory Tract Inf. NOS	3%	3%
Sinusitis NOS	2%	1%
Influenza	1%	1%
Pharyngitis	2%	2%
Cough	2%	2%
Joint Sprain	1%	1%
Headache NOS	4%	4%

One patient treated with topical dapsone in the clinical trials had facial swelling which led to discontinuation of medication.

In addition, 486 patients were evaluated in a 12 month safety study. The adverse event profile in this study was consistent with that observed in the vehicle-controlled studies.

OVERDOSAGE

ACZONE™ Gel, 5%, is not for oral use. If oral ingestion occurs, medical advice should be sought.

DOSAGE AND ADMINISTRATION

After the skin is gently washed and patted dry, apply approximately a pea-sized amount of ACZONE™ Gel, 5%, in a thin layer to the acne affected areas twice daily. Rub in ACZONE™ Gel, 5%, gently and completely. ACZONE™ Gel, 5%, is gritty with visible drug substance particles present. Wash hands after application of ACZONE™ Gel, 5%.

If there is no improvement after 12 weeks, appropriateness of treatment with ACZONE™ Gel, 5%, should be reassessed.

HOW SUPPLIED:

ACZONE™ (dapsone) Gel, 5%, is supplied in the following size tubes:

Professional Sample
5 % NDC 0469-5005-03 Product Code 500503
3 gram laminate tube

Commercially Available as:
5 % NDC 0469-5005-30 Product Code 500530
30 gram plastic tube

KEEP OUT OF THE REACH OF CHILDREN LESS THAN 12 YEARS OLD.

Storage conditions:
Store at controlled room temperature, 20-25 °C (68-76 °F), excursions permitted to 15–30 °C (59–86 °F). Protect from freezing and light. Return to the original carton after application.

Rx Only

Manufactured by QLT USA, Inc., Fort Collins, CO 80525

PATIENT INFORMATION

ACZONE™ (dapsone) Gel 5%

Read this important information before you start using ACZONE™ (AK-zōn) Gel and each time you refill your prescription. There may be new information that you need to know. This summary is not meant to take the place of your doctor's advice. If you have any questions or want more information about ACZONE™ Gel, ask your doctor or pharmacist.

What is ACZONE™ Gel?

ACZONE™ Gel is a prescription skin use (topical) medicine used to help treat acne in people 12 years and older.

ACZONE™ Gel has not been studied in children under 12 years of age.

Who should not use ACZONE™ Gel?

Do not use ACZONE™ Gel if you are allergic any of the ingredients in ACZONE™ Gel. Ask your doctor or pharmacist for a list of these ingredients. The active ingredient is dapsone. See the end of this leaflet for a complete list of ingredients in ACZONE™ Gel.

What should I tell my doctor before using ACZONE™ Gel?

Tell your doctor about all of your medical conditions, including if you:

- are pregnant or planning to become pregnant. It is not known if ACZONE Gel may harm your unborn baby.
- are breastfeeding. ACZONE™ Gel passes into your milk and may harm your baby. You should choose either to use ACZONE™ Gel, or breastfeed, but not both. Talk to you doctor about the best way to feed your baby while using ACZONE™ Gel.
- have a history of anemia or have been diagnosed with glucose-6-phosphate dehydrogenase deficiency

Tell your doctor about all the medicines you are taking including prescription and nonprescription medicines, vitamins and herbal supplements. Especially, tell your doctor if you are using any other medicines applied to the skin.

How do I use ACZONE™ Gel?

- Use ACZONE™ Gel exactly as prescribed by your doctor. ACZONE™ Gel is usually used on your affected skin twice a day, once in the morning and once in the evening.
- Wash the areas of your skin where you will apply ACZONE™ Gel. Gently pat your skin dry with a clean towel.
- Apply a thin layer of ACZONE™ Gel to the areas of your skin that have acne. A pea-sized amount of ACZONE™ Gel will usually be enough.

- Rub the medicine in gently and completely
- Make sure to put the cap back on the ACZONE™ Gel tube. Close it tightly and put the tube back in its original box.
- Wash your hands after applying ACZONE™ Gel.
- Keep ACZONE™ Gel away from your mouth and eyes. Do not swallow ACZONE™ Gel. If you swallow ACZONE™ Gel, call your doctor or poison control center right away.
- If your acne does not get better after using ACZONE™ for 12 weeks, talk to your doctor about other treatments for acne.

What are the possible side effects of ACZONE™ Gel?

Like all medicines, ACZONE™ Gel can cause some side effects. These side effects are usually mild. The most common side effects of ACZONE™ Gel are dryness, redness, oiliness and peeling of the skin being treated.

Call your doctor if you have excessive tiredness or any side effects that do not go away or bother you. This is not a complete list of all the side effects. If you have any questions, ask your doctor or pharmacist.

How should I store ACZONE™ Gel?

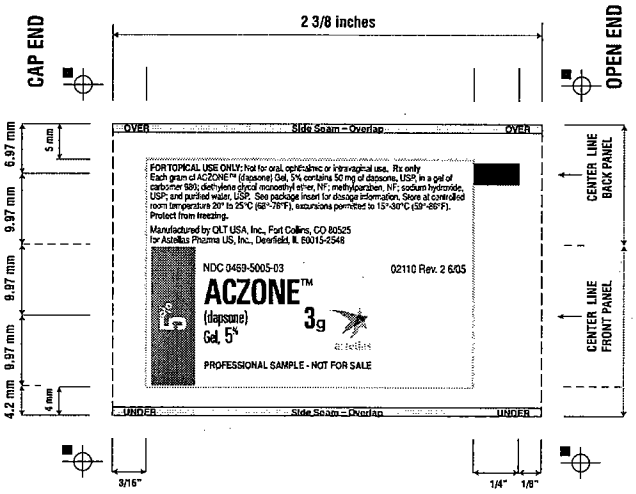
Store ACZONE™ Gel at room temperature 68 to 76 °F. Do not freeze ACZONE™ Gel. Protect ACZONE™ Gel tube from light. Store in original box after using it.

Keep ACZONE™ Gel out of the reach of children less than 12 years of age.

Where can I find more information about ACZONE™ Gel?

If you have any questions or want more information about ACZONE™ Gel, ask your doctor or pharmacist. Your doctor or pharmacist can also give you a copy of the ACZONE™ Gel Package Insert written for health professionals. Ask them to explain anything you do not understand.

You may call 1-800-727-7003 to obtain more information about ACZONE™ Gel.



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COMMUNICATIONS INC
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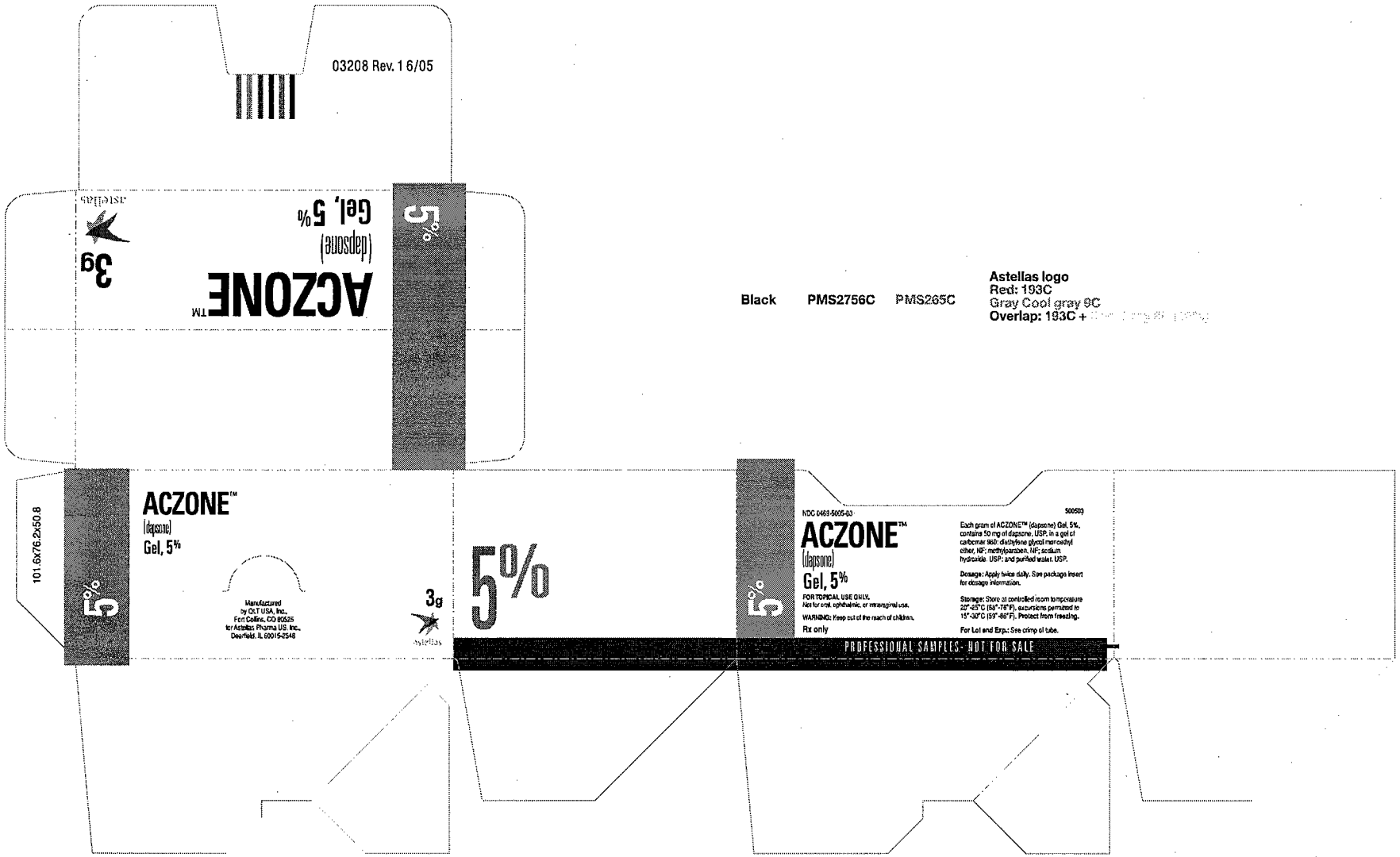

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Astellas logo
Red: 193C
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Overlap: 193C +

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Aczone Gel 5%
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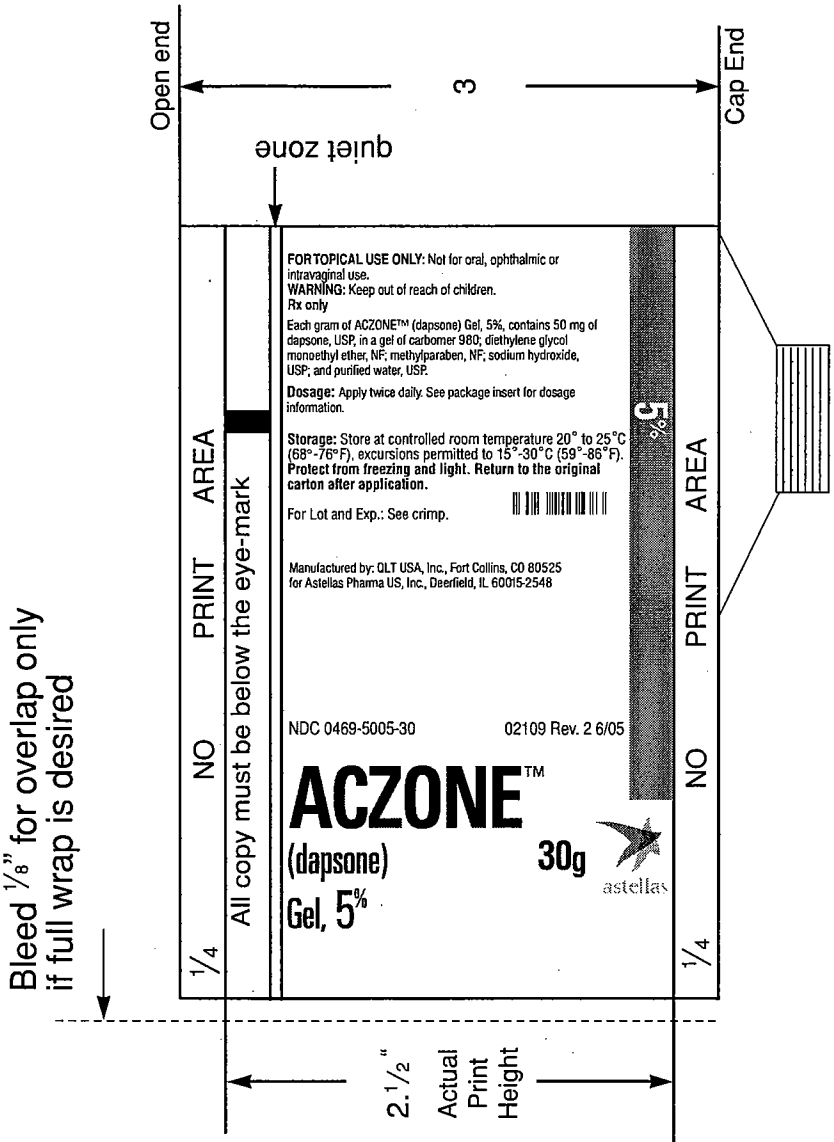
CrossTech
COMMUNICATIONS INC
312 382-0111 FAX 382-0004



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Dark Red: Astellas Red+Astellas Gray (PMS 193C + Cool Gray 9C @40%)
Gray: Astellas Gray (PMS Cool Gray 9C)
Purple: PMS 265C
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CrossTech–46870–Proof A9
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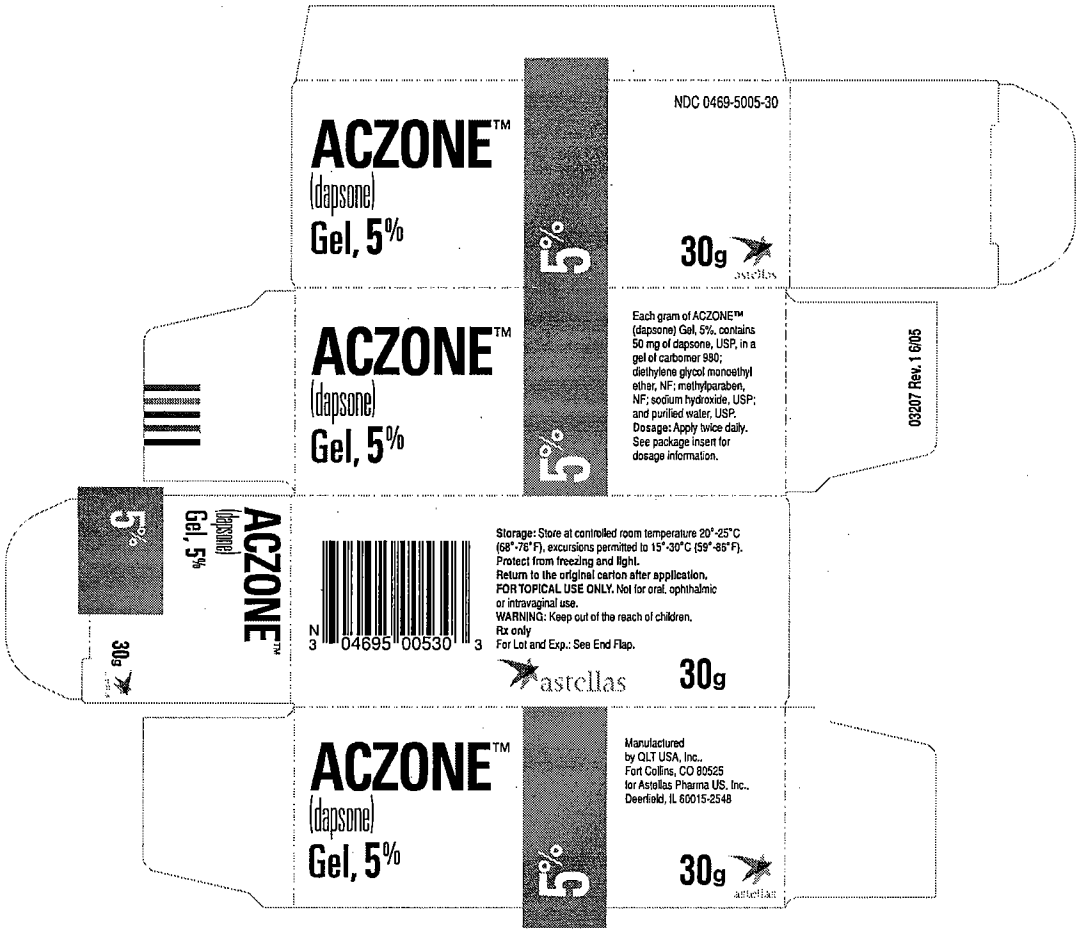

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CrossTech–46872–Proof A9
Form M01
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Aczone Gel 5%
6/30/05–am–Q4.11

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