

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-741

FINAL PRINTED LABELING

DRAFT

DUAC Topical Gel

(clindamycin, 1% - benzoyl peroxide, 5%)

For Dermatological Use Only.

Not for Ophthalmic Use.

Rx Only

DESCRIPTION

DUAC Topical Gel contains clindamycin phosphate, (7(S)-chloro-7-deoxylincomycin-2-phosphate), equivalent to 1% clindamycin, and 5% benzoyl peroxide.

Clindamycin phosphate is a water soluble ester of the semi-synthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin.

Clindamycin phosphate is $C_{18}H_{34}ClN_2O_8PS$. The structural formula for clindamycin phosphate is represented below:

[insert structure]

Clindamycin phosphate has a molecular weight of 504.97 and its chemical name is methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-*threo*- α -D-*galacto*-octopyranoside 2-(dihydrogen phosphate).

Benzoyl peroxide is $C_{14}H_{10}O_4$. It has the following structural formula:

[insert structure]

Benzoyl peroxide has a molecular weight of 242.23.

Each gram of DUAC Topical Gel contains 10 mg (1%) clindamycin, as phosphate, and 50 mg (5%) benzoyl peroxide in a base consisting of carbomer 940, dimethicone, disodium lauryl sulfosuccinate, edetate disodium, glycerin, silicon dioxide, methylparaben, poloxamer, purified water, and sodium hydroxide.

CLINICAL PHARMACOLOGY

A comparative study of the pharmacokinetics of DUAC Topical Gel and 1% clindamycin solution alone in 78 patients indicated that mean plasma clindamycin levels during the four week dosing period were < 0.5 ng/ml for both treatment groups.

Benzoyl peroxide has been shown to be absorbed by the skin where it is converted to benzoic acid. Less than 2% of the dose enters systemic circulation as benzoic acid.

Microbiology:

Mechanism of Action

Clindamycin binds to the 50S ribosomal subunits of susceptible bacteria and prevents elongation

of peptide chains by interfering with peptidyl transfer, thereby suppressing protein synthesis. Benzoyl peroxide is a potent oxidizing agent.

In Vivo Activity

No microbiology studies were conducted in the clinical trials with this product.

In Vitro Activity

The clindamycin and benzoyl peroxide components individually have been shown to have *in vitro* activity against *Propionibacterium acnes*, an organism which has been associated with acne vulgaris; however, the clinical significance of this is not known.

Drug Resistance

There are reports of an increase of *P. acnes* resistance to clindamycin in the treatment of acne. In patients with *P. acnes* resistant to clindamycin, the clindamycin component may provide no additional benefit beyond benzoyl peroxide alone.

CLINICAL STUDIES

In five randomized, double-blind clinical studies of 1,319 patients, 397 used DUAC, 396 used benzoyl peroxide, 349 used clindamycin and 177 used vehicle. DUAC applied once daily for 11 weeks was significantly more effective than vehicle, benzoyl peroxide, and clindamycin in the treatment of inflammatory lesions of moderate to moderately severe facial acne vulgaris in three of the five studies (Studies 1, 2, and 5).

Patients were evaluated and acne lesions counted at each clinical visit: weeks 2, 5, 8, 11. The primary efficacy measures were the lesion counts and the investigator's global assessment evaluated at week 11. Patients were instructed to wash the face, wait 10 to 20 minutes, and then apply medication to the entire face, once daily, in the evening before retiring. Percent reductions in inflammatory lesion counts after treatment for 11 weeks in these five studies are shown in the following table:

Mean percent reduction in inflammatory lesion counts					
	Study 1 (n=120)	Study 2 (n=273)	Study 3 (n=280)	Study 4 (n=288)	Study 5 (n=358)
DUAC	65%	56%	42%	57%	52%
Benzoyl Peroxide	36%	37%	32%	57%	41%
Clindamycin	34%	30%	38%	49%	33%
Vehicle	19%	-0.4%	29%		29%

The DUAC group showed greater overall improvement in the investigator's global assessment than the benzoyl peroxide, clindamycin and vehicle groups in three of the five studies (Studies 1, 2, and 5).

Clinical studies have not adequately demonstrated the effectiveness of DUAC versus benzoyl peroxide alone in the treatment of non-inflammatory lesions of acne.

INDICATIONS AND USAGE

DUAC Topical Gel is indicated for the topical treatment of inflammatory acne vulgaris

DUAC Topical Gel has not been demonstrated to have any additional benefit when compared to benzoyl peroxide alone in the same vehicle when used for the treatment of non-inflammatory acne.

CONTRAINDICATIONS

DUAC Topical Gel is contraindicated in those individuals who have shown hypersensitivity to any of its components or to lincomycin. It is also contraindicated in those having a history of regional enteritis, ulcerative colitis, pseudomembranous colitis, or antibiotic-associated colitis.

WARNINGS

ORALLY AND PARENTERALLY ADMINISTERED CLINDAMYCIN HAS BEEN ASSOCIATED WITH SEVERE COLITIS WHICH MAY RESULT IN PATIENT DEATH. USE OF THE TOPICAL FORMULATION OF CLINDAMYCIN RESULTS IN ABSORPTION OF THE ANTIBIOTIC FROM THE SKIN SURFACE. DIARRHEA, BLOODY DIARRHEA, AND COLITIS (INCLUDING PSEUDOMEMBRANOUS COLITIS) HAVE BEEN REPORTED WITH THE USE OF TOPICAL AND SYSTEMIC CLINDAMYCIN. 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. ENDOSCOPIC EXAMINATION MAY REVEAL PSEUDOMEMBRANOUS COLITIS. STOOL CULTURE FOR *Clostridium difficile* AND STOOL ASSAY FOR *Clostridium difficile* TOXIN MAY BE HELPFUL DIAGNOSTICALLY. WHEN SIGNIFICANT DIARRHEA OCCURS, THE DRUG SHOULD BE DISCONTINUED. LARGE BOWEL ENDOSCOPY SHOULD BE CONSIDERED TO ESTABLISH A DEFINITIVE DIAGNOSIS IN CASES OF SEVERE DIARRHEA. ANTIPERISTALTIC AGENTS SUCH AS OPIATES AND DIPHENOXYLATE WITH ATROPINE MAY PROLONG AND/OR WORSEN THE CONDITION. DIARRHEA, COLITIS AND PSEUDOMEMBRANOUS COLITIS HAVE BEEN OBSERVED TO BEGIN UP TO SEVERAL WEEKS FOLLOWING CESSATION OF ORAL AND PARENTERAL THERAPY WITH CLINDAMYCIN.

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General: For dermatological use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

The use of antibiotic agents may be associated with the overgrowth of nonsusceptible organisms, including fungi. If this occurs, discontinue use of this medication and take appropriate measures.

Avoid contact with eyes and mucous membranes.

Clindamycin and erythromycin containing products should not be used in combination. *In vitro* studies have shown antagonism between these two antimicrobials. The clinical significance of this *in vitro* antagonism is not known.

Information for Patients: Patients using DUAC Topical Gel should receive the following information and instructions:

1. DUAC Topical Gel is to be used as directed by the physician. It is for external use only. Avoid contact with eyes, and inside the nose, mouth, and all mucous membranes, as this product may be irritating.
2. This medication should not be used for any disorder other than that for which it was

prescribed.

3. Patients should not use any other topical acne preparation unless otherwise directed by their physician.
4. Patients should report any signs of local adverse reactions to their physician.
5. DUAC Topical Gel may bleach hair or colored fabric.
6. DUAC Topical Gel can be stored at room temperature up to 25°C (77°F) for up to 2 months. Do not freeze. Keep tube tightly closed. Keep out of the reach of small children. Discard any unused product after 2 months.
7. Before applying DUAC Topical Gel to affected areas, wash the skin gently, rinse with warm water, and pat dry.
8. Excessive or prolonged exposure to sunlight should be limited. To minimize exposure to sunlight, a hat or other clothing should be worn.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. The clinical significance of this is unknown.

Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice per week induced squamous cell skin tumors in transgenic TgAC mice in a study using 20 weeks of topical treatment.

Genotoxicity studies were not conducted with DUAC Topical Gel. Clindamycin phosphate was not genotoxic in *Salmonella typhimurium* or in a rat micronucleus test. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *Salmonella typhimurium* tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells. Studies have not been performed with DUAC Topical Gel or benzoyl peroxide to evaluate the effect on fertility. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 2.5 g DUAC Topical Gel, based on mg/m²) revealed no effects on fertility or mating ability.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Animal reproduction studies have not been conducted with DUAC Topical Gel or benzoyl peroxide. It is also not known whether DUAC Topical Gel can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. DUAC Topical Gel should be given to a pregnant woman only if clearly needed.

Developmental toxicity studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (240 and 120 times the amount of clindamycin in the highest recommended adult human dose based on mg/m², respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (100 and 50 times the amount of clindamycin in the highest recommended adult human dose based on mg/m², respectively) revealed no evidence of teratogenicity.

Nursing Women: It is not known whether DUAC Topical Gel is secreted into human milk after topical application. 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.

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

ADVERSE REACTIONS

During clinical trials, all patients were graded for facial erythema, peeling, burning, and dryness on the following scale: 0=absent, 1=mild, 2=moderate, and 3=severe. The percentage of patients that had symptoms present at baseline and during treatment were as follows:

Local reactions with use of DUAC Topical Gel % of patients using DUAC Topical Gel with symptom present Combined results from 5 studies (n=397)						
	Baseline			During Treatment		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	28%	3%	0	26%	5%	0
Peeling	6%	<1%	0	17%	2%	0
Burning	3%	<1%	0	5%	<1%	0
Dryness	6%	<1%	0	15%	1%	0

(Percentages derived by # subjects with symptom score/# enrolled DUAC subjects, n=397).

DOSAGE AND ADMINISTRATION

DUAC Topical Gel should be applied once daily, in the evening or as directed by the physician, to affected areas after the skin is gently washed, rinsed with warm water and patted dry.

HOW SUPPLIED

DUAC (clindamycin, 1% - benzoyl peroxide, 5%) Topical Gel is available in a 45 gram tube - NDC 0145-2371-05.

Store in a cold place, preferably in a refrigerator, between 2°C and 8°C (36 °F and 46°F Do not freeze.

To the Pharmacist: Dispense with a 60 day expiration date and specify "Store at room temperature up to 25°C (77°F). Do not freeze."

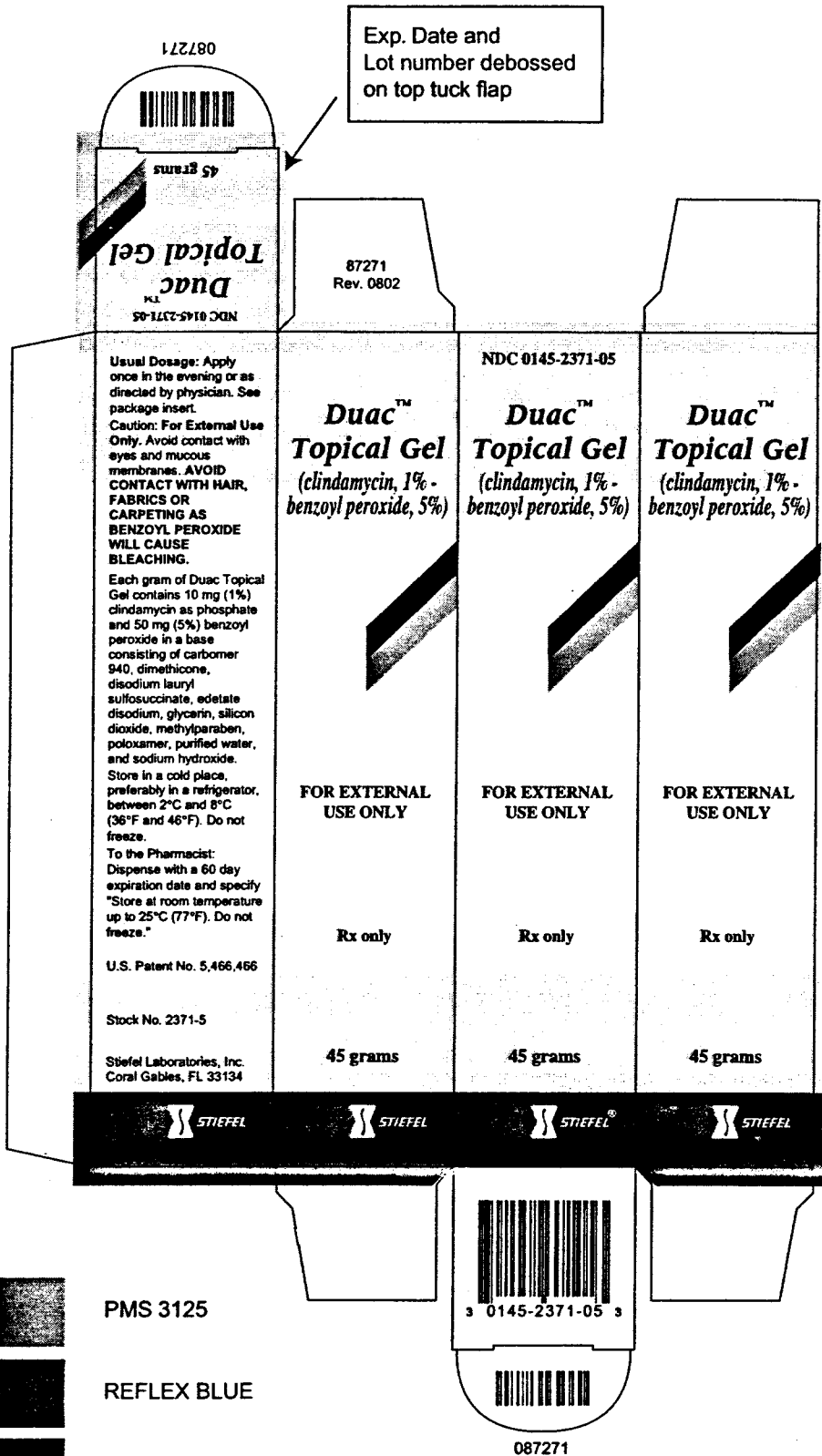
Keep tube tightly closed. Keep out of the reach of small children.

U.S. Patent No. 5,466,466




Stiefel logo®
Stiefel Laboratories, Inc.
Coral Gables, FL 33134

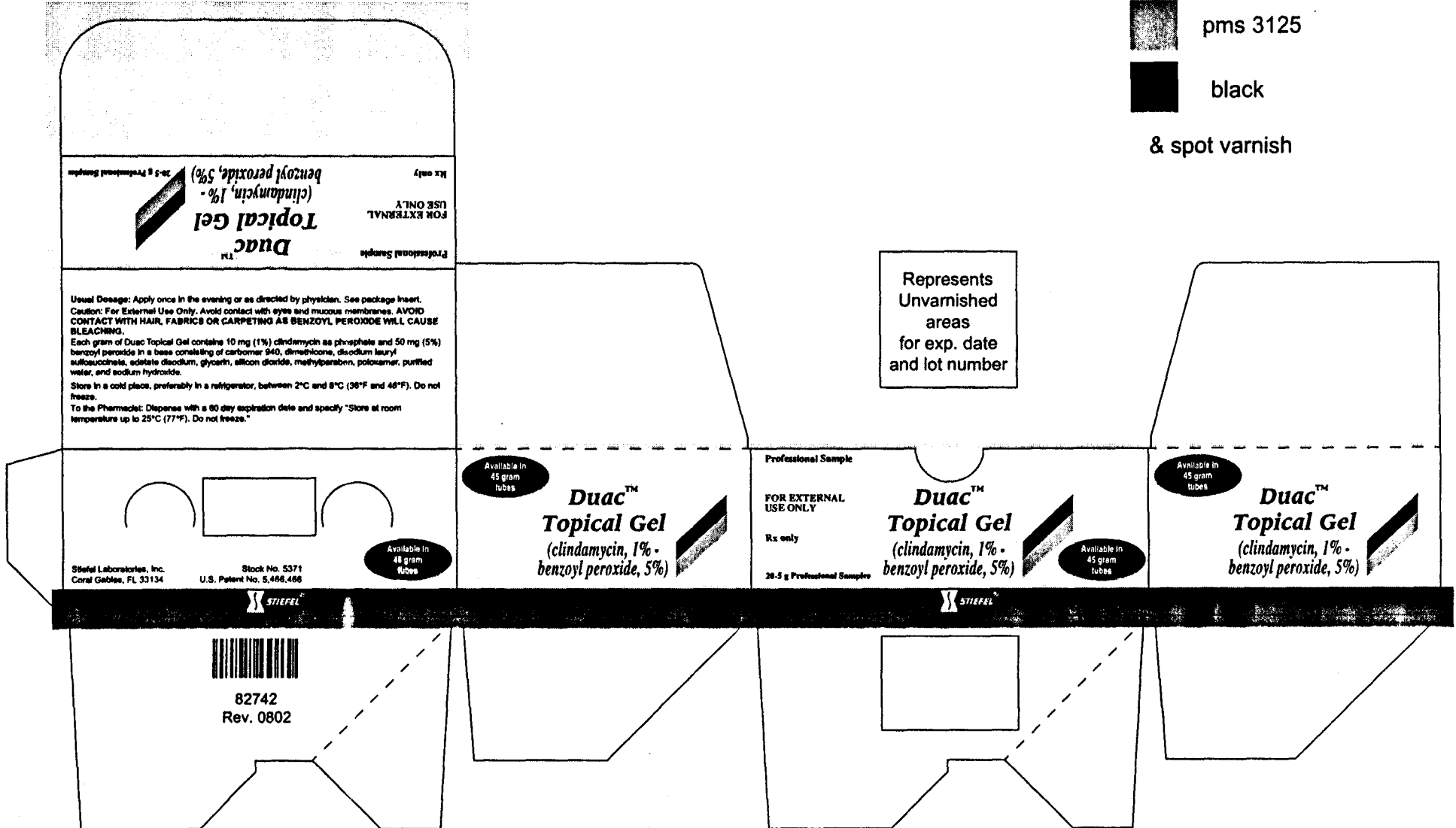
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Actual Size
1-3/8" x 1-3/8" x 6-1/4"



Actual size: 4-3/8" x 3-1/4" x 1-7/8" w/ 2" riser

-  reflex blue
 -  pms 3125
 -  black
- & spot varnish



Actual size
1" x 5-3/16"

SLEEVE LENGTH 5 7/32

CAP END

PRINT HEIGHT 4 7/32

OPEN END

NDC 0145-2371-05

Duac™
Topical Gel
(clindamycin, 1% -
benzoyl peroxide, 5%)

FOR EXTERNAL USE ONLY


Rx only

45 grams

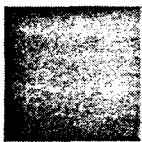
STIEFEL

Usual Dosage: Apply once daily in the evening or as directed by physician. See package insert.
Caution: For External Use Only. Avoid contact with eyes and mucous membranes. AVOID CONTACT WITH HAIR, FABRICS OR CARPETING AS BENZOYL PEROXIDE WILL CAUSE BLEACHING.
Each gram of Duac Topical Gel contains 10 mg (1%) clindamycin as phosphate and 50 mg (5%) benzoyl peroxide in a base consisting of carbomer 940, dimethicone, disodium lauryl sulfosuccinate, edetate disodium, glycerin, silicon dioxide, methylparaben, poloxamer, purified water, and sodium hydroxide.
Store in a cold place, preferably in a refrigerator, between 2°C and 8°C (36°F and 46°F). Do not freeze.
To the Pharmacist: Dispense with a 60 day expiration date and specify "Store at room temperature up to 25°C (77°F). Do not freeze."
See crimp of tube for lot number and expiration date.

STIEFEL • Stiefel Laboratories, Inc.
Coral Gables, FL 33134 U.S. Patent No. 5,466,466 Stock No. 2371-5 82101 Rev. 0802



REFLEX
BLUE



PMS
3125

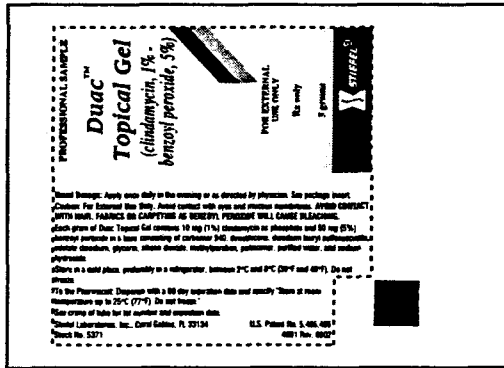
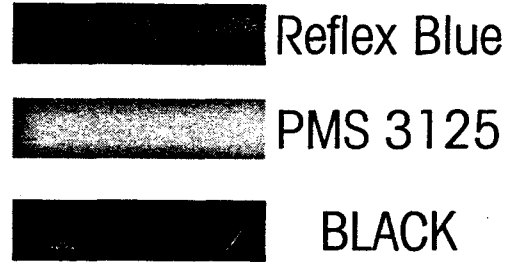
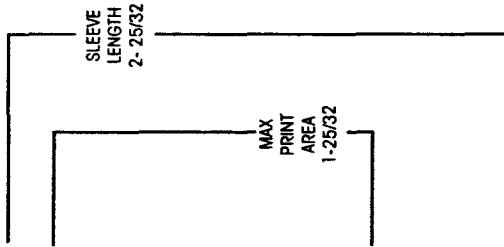


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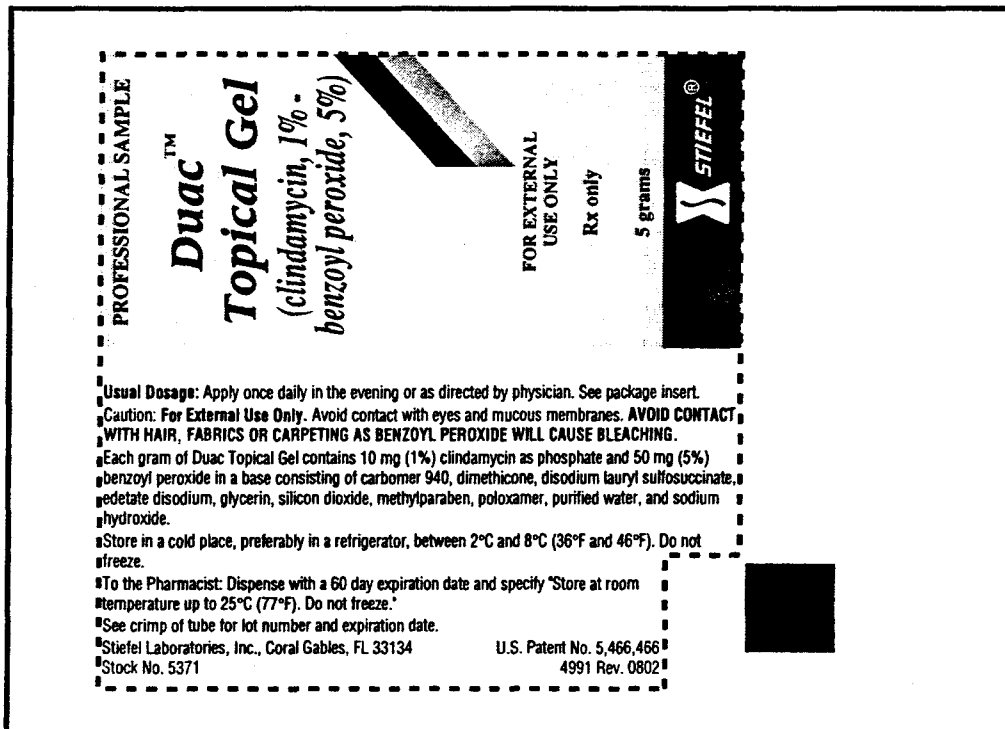
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BAR CODE
SHOULD
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ACTUAL SIZE
5/8" X 2-3/4



100%



200%

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jonathan Wilkin

8/26/02 10:16:30 AM

Per discussion with TL, there was no new information
in the safety update that had not been
reviewed previously.

**APPEARS THIS WAY
ON ORIGINAL**