

PRODUCT MONOGRAPH

Pr DIFFERIN®

adapalene topical cream

0.1%

adapalene topical gel

0.1%

Pr DIFFERIN® XP™

adapalene topical gel

0.3%

Acne Therapy

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Control No: 096223

Date of Preparation:
January 13, 1995

Date of Revision:
December 19, 2005

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
topical	cream 0.1%	None
	gel 0.1%, 0.3%	None
<i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>		

INDICATIONS AND CLINICAL USE

DIFFERIN (adapalene) topical cream and gel and DIFFERIN XP (adapalene) topical gel are indicated for:

- treatment of *acne vulgaris*

Geriatrics (> 65 years of age):

Safety and effectiveness in geriatric patients aged 65 years and above have not been established.

Pediatrics (< 12 years of age):

Safety and effectiveness in children below the age of 12 have not been established.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Patients with eczema or seborrheic dermatitis

WARNINGS AND PRECAUTIONS

General

For external use only. Avoid contact with the eyes, lips, angles of the nose, mucous membranes and open wounds. Certain cutaneous signs and symptoms such as erythema, dryness, scaling, burning or pruritus are associated with the topical application of retinoids and can also be expected with the use of DIFFERIN (adapalene) topical cream or gel and with DIFFERIN XP (adapalene) topical gel. These treatment-related effects generally occur during the first two to four weeks of therapy and usually resolve as the skin undergoes adjustment with continued use. Depending on the degree of the side effects, patients can be directed to use the medication less frequently or temporarily discontinue use until the symptoms subside (see DOSAGE AND ADMINISTRATION).

Patients should be advised to use non-comedogenic cosmetics. Colour cosmetics such as blushers and powders are acceptable, however, make-up cosmetics should be water based only. Cosmetics must be removed by thorough cleansing before the area is treated.

As with any retinoid, exposure to excessive sunlight, including sunlamps, should be avoided while using the preparation, or a suitably effective sunscreen product and protective clothing over the treated areas is recommended when exposure cannot be avoided. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with adapalene. As with other retinoids, use of “waxing” as a depilatory method should be avoided on skin treated with adapalene.

Carcinogenesis and Mutagenesis

See TOXICOLOGY.

Special Populations

Pregnant Women: It is recommended that topical adapalene should not be used by pregnant women. Topical adapalene should be used by women of childbearing years only after contraceptive counselling.

There have been rare reports of birth defects among babies born to women exposed to topical retinoids during pregnancy. However, there are no well controlled prospective studies of the use of topical retinoids, including adapalene, in pregnant women. A retrospective study of mothers exposed to topical tretinoin during the first trimester of pregnancy found no increase in the incidence of birth defects.

Adapalene administered orally at doses of ≥ 25 mg/kg/day (38 times the Maximum Recommended Human Dose [MRHD] based on mg/m² comparisons for rats or 65 times MRHD for rabbits) has been shown to be teratogenic. No teratogenic effects were seen in rats at oral doses of up to 5.0 mg/kg/day adapalene (7.6 times the MRHD). Cutaneous teratology studies in rats and rabbits at doses of 0.6 (0.03 %), 2.0 (0.1 %) and 6.0 (0.3 %) mg/kg/day (17 times the MRHD for rats or 32 times the MRHD for rabbits) exhibited no teratogenicity. At 2 mg/kg/day (0.1% adapalene gel), no adverse events were observed in rabbits and only a marginal increase in the incidence of additional lumbar ribs was observed in rats. However, at 6 mg/kg/day (0.3% adapalene gel), in addition to the recorded increase in foetal rib numbers in the rat and rabbit, there were also other skeletal anomalies in both species (see TOXICOLOGY). There are no adequate and well-controlled studies in pregnant women.

Nursing Women: It is not known whether this drug is excreted in human milk. Animal pharmacology studies indicate that adapalene is excreted in milk at levels lower than plasma levels. Because many drugs are excreted in human milk, caution should be exercised when DIFFERIN topical cream or gel or DIFFERIN XP topical gel is administered to a nursing mother.

Pediatrics (12-16 years of age): No specific monitoring or hazards are associated with the use of the product in pediatric patients between the ages of 12 and 16 years. Safety and effectiveness in children below the age of 12 have not been established.

Geriatrics (> 65 years of age): Safety and effectiveness in geriatric patients age 65 and above have not been established.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Treatment-related adverse reactions typically associated with use of DIFFERIN and DIFFERIN XP include mild to moderate application site reactions, such as skin irritation characterized by scaling, dryness, erythema, burning and stinging. DIFFERIN XP results in a slightly greater incidence of these events, as would be expected with the higher concentration of adapalene. These reactions usually occur early in the treatment, and tend to resolve after 2 to 4 weeks of therapy (see WARNINGS AND PRECAUTIONS).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

DIFFERIN (adapalene) Topical Cream or Topical Gel:

In clinical trials with DIFFERIN topical gel and cream 0.1%, most of the reactions occurred within two to four weeks of initiation of therapy and were generally observed to resolve with continued use of the product or temporary adjustment of the treatment schedule. Contact allergy to topical adapalene was not reported during clinical trials. To date, all adverse effects of DIFFERIN topical cream or gel 0.1% have been reversible upon discontinuation of therapy.

DIFFERIN XP (adapalene) Topical Gel:

In a multi-centre, placebo- and active-controlled Phase III clinical trial, signs and symptoms of local cutaneous irritation were monitored in 258 adult acne patients who used DIFFERIN XP topical gel 0.3% once daily for 12 weeks. Of the patients who experienced cutaneous irritation (erythema, scaling, dryness, and/or burning/stinging), the majority of cases were mild to moderate in severity, occurred in the first week of treatment, and decreased thereafter.

In a one-year, open-label safety study of 551 patients with acne vulgaris who used DIFFERIN XP, the pattern of adverse events was similar to the 12-week controlled study. The percentage of subjects who experienced cutaneous irritation (scaling, erythema, dryness, and/or stinging/burning) greater than baseline was highest after one week of treatment and decreased thereafter, continuing to decrease during the one-year treatment period.

Table 1: Related Adverse Events From Open, and Vehicle- and Active-Controlled Studies

	DIFFERIN XP adapalene gel 0.3% n= 1087 (%)	DIFFERIN adapalene gel 0.1% n=1463 (%)	DIFFERIN adapalene cream 0.1% n=311 (%)	Gel Vehicle n=134 (%)
Total No. (%) of Subjects with Related ¹ Adverse Event(s)	267 (24.6%)	153 (10.5%)	16 (5.1%)	6 (4.5%)
Skin and Appendages	263 (24.2%)	164 (11.2%)	17 (5.5%)	6 (4.5%)
Skin dry	117 (10.8%)	58 (4.0%)	1 (0.3%)	2 (1.5%)
Erythema	27 (2.5%)	18 (1.2%)	0 (0%)	0 (0%)
Skin discomfort	70 (6.4%)	40 (2.7%)	1 (0.3%)	0 (0%)
Desquamation	28 (2.6%)	9 (0.6%)	0 (0%)	0 (0%)
Pruritus	18 (1.7%)	13 (0.9%)	0 (0%)	0 (0%)
Sunburn	21 (1.9%)	13 (0.9%)	3 (1.0%)	2 (1.5%)
Irritant dermatitis	59 (5.4%)	33 (2.3%)	0 (0%)	0 (0%)
Skin irritation	0 (0%)	4 (0.4%)	5 (1.6%)	0 (0%)

¹ Related = Possibly, probably, or definitely related

