# 第２号

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米国 FDA（食品医薬品局）が承認されている
メトロクリーム、メトロゲルについて

PDR®

55 EDITION

2001

# PHYSICIANS' DESK REFERENCE®

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PDR®

55

EDITION

2001

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# PHYSICIANS' DESK REFERENCE®

## Desowen—Cont.

nant woman or can affect reproduction capacity. D Cream, Ointment and Lotion should be given to a pregnant woman only if clearly needed.

**Nursing mothers:** Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when **DesOwen®** Cream, Ointment or Lotion is administered to a nursing woman.

**Pediatric use:** Safety and effectiveness in pediatric patients have not been established. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression when they are treated with topical corticosteroids. They are therefore also at greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing's syndrome while on treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

### ADVERSE REACTIONS

In controlled clinical trials, the total incidence of adverse reactions associated with the use of desonide was approximately 8%. These were: stinging and burning approximately 3%, irritation, contact dermatitis, condition worsened, peeling of skin, itching, intense transient erythema, and dryness/scaliness, each less than 2%.

The following additional local adverse reactions have been reported infrequently with other topical corticosteroids, and they may occur more frequently with the use of occlusive dressings, especially with higher potency corticosteroids. These reactions are listed in an approximate decreasing order of occurrence: folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, secondary infection, skin atrophy, striae, and miliaria.

### OVERDOSAGE

Topically applied **DesOwen®** (desonide cream, ointment, and lotion) Cream, Ointment and Lotion can be absorbed in sufficient amounts to produce systemic effects (See PRECAUTIONS).

### DOSAGE AND ADMINISTRATION

**DesOwen®** Cream, Ointment or Lotion should be applied to the affected areas as a thin film two or three times daily depending on the severity of the condition. SHAKE LOTION WELL BEFORE USING.

As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

**DesOwen®** Cream, Ointment and Lotion should not be used with occlusive dressings.

### HOW SUPPLIED

**DesOwen®** (desonide cream) Cream 0.05% is supplied in tubes containing:

15 g **NDC** 0299-5770-15
60 g **NDC** 0299-5770-60

**DesOwen®** (desonide ointment) Ointment 0.05% is supplied in tubes containing:

15 g **NDC** 0299-5775-15
60 g **NDC** 0299-5775-60

**DesOwen®** (desonide lotion) Lotion 0.05% is supplied in bottles containing:

2 fl oz **NDC** 0299-5765-02
4 fl oz **NDC** 0299-5765-04

**Storage Conditions:** Store between 2° and 30°C (36° and 86°F).

**CAUTION:** Federal law prohibits dispensing without prescription.

**225025-0395** Revised: March 1995

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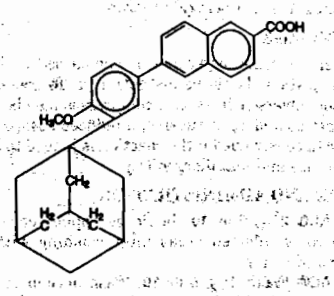
## DIFFERIN®
**(adapalene gel)**
**Gel, 0.1%**

### DESCRIPTION

**Differin®** Gel, containing adapalene, is used for the topical treatment of acne vulgaris. Each gram of **Differin®** Gel contains adapalene 0.1% (1mg) in a vehicle consisting of propylene glycol, carbomer 940, poloxamer 182, edetate disodium, methylparaben, sodium hydroxide, and purified water. May contain hydrochloric acid to adjust pH.

The chemical name of adapalene is 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. Adapalene is a white to off-white powder which is soluble in tetrahydrofuran, sparingly soluble in ethanol, and practically insoluble in water. The molecular formula is $C_{28}H_{28}O_3$ and molecular weight is 412.52. Adapalene is represented by the following structural formula:




### CLINICAL PHARMACOLOGY

Adapalene is a chemically stable, retinoid-like compound. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization, and inflammatory processes all of which represent important features in the pathology of acne vulgaris.

Mechanistically, adapalene binds to specific retinoic acid nuclear receptors but does not bind to the cytosolic receptor protein. Although the exact mode of action of adapalene is unknown, it is suggested that topical adapalene may normalize the differentiation of follicular epithelial cells resulting in decreased microcomedone formation.

***Pharmacokinetics:*** Absorption of adapalene through human skin is low. Only trace amounts (<0.25 ng/mL) of parent substance have been found in the plasma of acne patients following chronic topical application of adapalene in controlled clinical trials. Excretion appears to be primarily by the biliary route.

### INDICATIONS AND USAGE

**Differin®** Gel is indicated for the topical treatment of acne vulgaris.

### CONTRAINDICATIONS

**Differin® Gel should not be administered to individuals who are hypersensitive to adapalene or any of the components in the vehicle gel.**

### WARNINGS

**Use of Differin® Gel should be discontinued if hypersensitivity to any of the ingredients is noted. Patients with sunburn should be advised not to use the product until fully recovered.**

### PRECAUTIONS

***General:*** **If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued. Exposure to sunlight, including sunlamps, should be minimized during the use of adapalene. Patients who normally experience high levels of sun exposure, and those with inherent sensitivity to sun, should be warned to exercise caution. Use of sunscreen products and protective clothing over 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.**

**Avoid contact with the eyes, lips, angles of the nose, and mucous membranes. The product should not be applied to cuts, abrasions, eczematous skin, or sunburned skin.**

**Certain cutaneous signs and symptoms such as erythema, dryness, scaling, burning, or pruritus may be experienced during treatment. These are most likely to occur during the first two to four weeks and will usually lessen with continued use of the medication. Depending upon the severity of adverse events, patients should be instructed to reduce the frequency of application or discontinue use.**

***Drug Interactions:*** **As Differin® Gel has the potential to produce local irritation in some patients, concomitant use of other potentially irritating topical products (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 approached with caution. Particular caution should be exercised in using preparations containing sulfur, resorcinol, or salicylic acid in combination with Differin® Gel. If these preparations have been used, it is advisable not to start therapy with Differin® Gel until the effects of such preparations in the skin have subsided.**

***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** **Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.3, 0.9, and 2.6 mg/kg/day and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day, approximately 4–75 times the maximal daily human topical dose. In the oral study, positive linear trends were observed in the incidence of follicular cell adenomas and carcinomas in the thyroid glands of female rats, and in the incidence of benign and malignant pheochromocytomas in the adrenal medullas of male rats.**

**No photocarcinogenicity studies were conducted. Animal studies have shown an increased tumorigenic risk with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or to sunlight. Although the significance of these studies to human use is not clear, patients should be advised**

exposure to either sunlight or arti
sources.

In a series of *in vivo* and *in vitro* studi
exhibit mutagenic or genotoxic activi

***Pregnancy:*** Teratogenic effects. Pregn
teratogenic effects were seen in rats
palene 0.15 to 5.0 mg/kg/day, up to 1
daily human topical dose. Cutaneous
ies conducted in rats and rabbits at d
mg/kg/day, up to 150 times the maxi
cal dose exhibited no fetotoxicity
creases in supernumerary ribs in r
quate and well-controlled studies in
palene should be used during p
potential benefit justifies the potenti

***Nursing Mothers:*** It is not known w
creted in human milk. Because many
human milk, caution should be exe
Gel is administered to a nursing wo

***Pediatric Use:*** Safety and effectivene
below the age of 12 have not been e

### ADVERSE REACTIONS

Some adverse effects such as eryth
pruritus, and burning will occur in 1
ritus or burning immediately after a
approximately 20% of patients. The
verse experiences were reported in a
of patients: skin irritation, burnin
sunburn, and acne flares. These ar
during the first month of therapy an
and severity thereafter. All adver
**Differin®** Gel during clinical trials w
continuation of therapy.

### OVERDOSAGE

**Differin®** Gel is intended for cutaneo
ication is applied excessively, no more
will be obtained and marked redness
may occur. The acute oral toxicity
and rats is greater than 10 mL/kg.
drug may lead to the same side effe
with excessive oral intake of Vitamin

### DOSAGE AND ADMINISTRATION

**Differin® Gel should be applied once**
after washing in the evening before
the gel should be applied, avoiding
membranes.

During the early weeks of therapy,
tion of acne may occur. This is due to
ication on previously unseen lesions
sidered a reason to discontinue thera
should be noticed after eight to twel

### HOW SUPPLIED

**Differin®** (adapalene gel) Gel, 0.1% is
ing sizes:

15 g laminate tube **NDC** 0299-59
45 g laminate tube **NDC** 0299-59

***Storage:*** Store at controlled room t
(68°–77°F).

**CAUTION:** Federal law prohibits dis
scription.

225022-0596
Revised: May 1996

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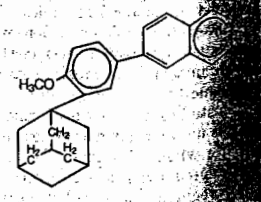
## DIFFERIN®
**(adapalene solution)**
**Solution, 0.1%**

### DESCRIPTION

DIFFERIN® Solution, containing ada
topical treatment of acne vulgaris. Ea
Solution contains adapalene 0.1% (1
sisting of polyethylene glycol 400 and
(w/v).

The chemical name of adapalene is
methoxyphenyl]-2-naphthoic acid. A
off-white powder which is soluble in
ingly soluble in ethanol, and practica
The molecular formula is $C_{28}H_{28}O_3$ a
412.52. Adapalene is represented by
tural formula:




### CLINICAL PHARMACOLOGY

Adapalene is a chemically stable, re
Biochemical and pharmacological pro
onstrated that adapalene is a modula
tiation, keratinization, and inflamma
which represent important features i
vulgaris. Mechanistically, adapalene

rs but does not bind to the cytoso- ough the exact mode of action of is suggested that topical ada- e differentiation of follicular epi- decreased microcomedone forma-

rption of adapalene through hu- e amounts (< 0.25 ng/mL) of par- found in the plasma of acne pa- ical application of adapalene in secretion appears to be primarily

SAGE

dicated for the topical treatment

uld not be administered to indi- itive to adapalene or any of the solution.

tion should be discontinued if hy- the ingredients is noted. Patients vised not to use the product until

ggesting sensitivity or chemical ir- medication should be discontin- nt, including sunlamps, should be e of adapalene. Patients who nor- vels of sun exposure, and those o sun, should be warned to exer- creen products and protective cloth- recommended when exposure can xtremes, such as wind or cold, also ents under treatment with ada-

yes, lips, angles of the nose, and product should not be applied to is skin, or sunburned skin.

and symptoms such as erythema, or pruritus may be experienced s most likely to occur during the nd will usually lessen with contin- . Depending upon the severity of should be instructed to reduce the or discontinue use.

DIFFERIN® Solution has the poten- ation in some patients, concomitant irritating topical products (medicat- nd cleansers, soaps and cosmetics g effect, and products with high con- stringents, spices, or lime) should be . Particular caution should be exer- ons containing sulfur, resorcinol, or ation with DIFFERIN® Solution. If been used, it is advisable not to FERIN® Solution until the effects of skin have subsided.

*enesis, Impairment of Fertility:* Car- h adapalene have been conducted in 0.3, 0.9, and 2.6 mg/kg/day and in s, 0.5, and 1.5 mg/kg/day, approxi- maximal daily human topical dose. ve linear trends were observed in the cell adenomas and carcinomas in the le rats, and in the incidence of benign mocytomas in the adrenal medullas

y studies were conducted. Animal increased tumorigenic risk with the ly similar drugs (e.g., retinoids) when iation in the laboratory or to sunlight. ance of these studies to human use is should be advised to avoid or minimize sunlight or artificial UV irradiation

and *in vitro* studies, adapalene did not genotoxic activities.

ic effects. Pregnancy Category C. No re seen in rats at oral doses of ada- /kg/day, up to 120 times the maximal dose. Cutaneous route teratology stud- and rabbits at doses of 0.6, 2.0, and 6.0 times the maximal daily human topi- rm fetotoxicity and only minimal in- numerary ribs in rats. There are no ade- rolled studies in pregnant women. Ada- ised during pregnancy only if the ifies the potential risk to the fetus.

it is not known whether this drug is ex- ilk. Because many drugs are excreted in ion should be exercised when DIFFERIN® ered to a nursing woman.

ety and effectiveness in pediatric pa- e of 12 have not been established.

ACTIONS

cts such as erythema, scaling, dryness, ning will occur in 30–60% of patients. Pru- mediately after application also occurs in % of patients. The following additional ad- were reported in approximately 1% or less of patients: skin irritation, burning/stinging, erythema, sunburn, and acne flares. These are most commonly seen during the first month of therapy and decrease in frequency and severity thereafter. All adverse effects with use of DIFFERIN® Solution during clinical trials were reversible upon discontinuation of therapy.

## OVERDOSAGE

DIFFERIN® Solution is intended for cutaneous use only. If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur. The acute oral toxicity of DIFFERIN® Solution in mice and rats is greater than 10 mL/kg. Chronic ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

## DOSAGE AND ADMINISTRATION

1. DIFFERIN® Solution should be applied once a day to affected areas.
2. Before retiring in the evening, wash and dry areas to be treated.
3. Apply a thin film of medication to the affected areas. Avoid the eyes, lips, and mucous membranes.

**Pledget:** Remove pledget from foil just before using. Discard pledget after single use. Do not use if seal is broken.
**Glass bottle:** Replace cap after each use.
During the early weeks of therapy, an apparent exacerbation of acne may occur. This is due to the action of the medication on previously unseen lesions and should not be considered a reason to discontinue therapy. Therapeutic results should be noticed after eight to twelve weeks of treatment.

## HOW SUPPLIED

DIFFERIN® (adapalene solution) Solution, 0.1% is supplied in the following sizes:
30 mL glass bottle with applicator – NDC 0299-5905-30
60-count unit-of-use pledget – NDC 0299-5905-16
The applicator is designed so that the solution may be applied directly to the involved skin.
***Storage:*** Store at controlled room temperature 20° – 25°C (68° – 77°F). Keep container tightly closed and store upright.
**CAUTION:** Federal law prohibits dispensing without prescription.
225050-0100
Revised: January 2000

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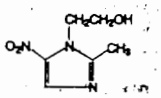
## METROCREAM®

**(metronidazole topical cream)**
*Topical Cream, 0.75%*
**FOR TOPICAL USE ONLY**
**(NOT FOR OPHTHALMIC USE)**

Rx

## DESCRIPTION

**MetroCream®** Topical Cream contains metronidazole, USP, at a concentration of 7.5 mg per gram (0.75%) in an emollient cream consisting of emulsifying wax, sorbitol solution, glycerin, isopropyl palmitate, benzyl alcohol, lactic acid and/or sodium hydroxide to adjust pH, and purified water. Metronidazole is a member of the imidazole class of antibacterial agents and is classified therapeutically as an antiprotozoal and antibacterial agent. Chemically, metronidazole is 2-methyl-5-nitro-1*H*-imidazole-1-ethanol. The molecular formula is $C_6H_9N_3O_3$ and molecular weight is 171.16. Metronidazole is represented by the following structural formula:




## CLINICAL PHARMACOLOGY

The mechanisms by which metronidazole acts in the treatment of rosacea are unknown, but appear to include an anti-inflammatory effect.

## INDICATIONS AND USAGE

**MetroCream®** (metronidazole topical cream) Topical Cream is indicated for topical application in the treatment of inflammatory papules and pustules of rosacea.

## CONTRAINDICATIONS

**MetroCream®** (metronidazole topical cream) Topical Cream is contraindicated in individuals with a history of hypersensitivity to metronidazole, or other ingredients of the formulation.

## PRECAUTIONS

**General:** Topical metronidazole has been reported to cause tearing of the eyes. Therefore, contact with the eyes should be avoided. If a reaction suggesting local irritation occurs, patients should be directed to use the medication less frequently or discontinue use. Metronidazole is a nitroimidazole and should be used with care in patients with evidence of, or history of blood dyscrasia.
**Information for patients:** This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
**Drug Interactions:** Oral metronidazole has been reported to potentiate the anticoagulant effect of warfarin and coumarin anticoagulants, resulting in a prolongation of prothrombin time. The effect of topical metronidazole on prothrombin time is not known.
**Carcinogenesis, mutagenesis, impairment of fertility:** Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats but not in studies involving hamsters. Metronidazole has shown evidence of mutagenic activity in several *in vitro* bacterial assay systems. In addition, a dose-response increase in the frequency of micronuclei was observed in mice after intraperitoneal injections and an increase in chromosome aberrations have been reported in patients with Crohn's disease who were treated with 200-1200 mg/day of metronidazole for 1 to 24 months. However, no excess chromosomal aberrations in circulating human lymphocytes have been observed in patients treated for 8 months.
**Pregnancy:** *Teratogenic effects: Pregnancy category B*
There are no adequate and well-controlled studies with the use of **MetroCream®** (metronidazole topical cream) Topical Cream in pregnant women. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity was observed after oral metronidazole in rats or mice. However, because animal reproduction studies are not always predictive of human response and since oral metronidazole has been shown to be a carcinogen in some rodents, this drug should be used during pregnancy only if clearly needed.
**Nursing Mothers:** After oral administration, metronidazole is secreted in breast milk in concentrations similar to those found in the plasma. Even though blood levels are significantly lower with topically applied metronidazole than those achieved after oral administration of metronidazole, 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 in pediatric patients have not been established.

## ADVERSE REACTIONS

In controlled clinical trials, the total incidence of adverse reactions associated with the use of **MetroCream®** Topical Cream was approximately 10%. Skin discomfort (burning and stinging) was the most frequently reported event followed by erythema, skin irritation, pruritus and worsening of rosacea. All individual events occurred in less than 3% of patients.
The following additional adverse experiences have been reported with the topical use of metronidazole: dryness, transient redness, metallic taste, tingling or numbness of extremities and nausea.

## DOSAGE AND ADMINISTRATION

Apply and rub in a thin layer of **MetroCream®** (metronidazole topical cream) Topical Cream twice daily, morning and evening, to entire affected areas after washing.
Areas to be treated should be washed with a mild cleanser before application. Patients may use cosmetics after application of **MetroCream®** Topical Cream.

## HOW SUPPLIED

**MetroCream®** (metronidazole topical cream) Topical Cream, 0.75% is supplied in a 45 g aluminum tube–**NDC** 0299-3836-45.
**Storage conditions:** STORE AT CONTROLLED ROOM TEMPERATURE: 59° to 86°F (15° to 30°C).
**Caution:** Federal law prohibits dispensing without prescription.
225029-0695
Revised: June 1995

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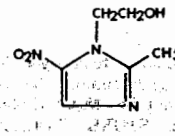
## METROGEL®

**(metronidazole topical gel)**
**Topical Gel, 0.75%**
**FOR TOPICAL USE ONLY**
**(NOT FOR OPHTHALMIC USE)**

Rx

## DESCRIPTION

**MetroGel®** Topical Gel contains metronidazole, USP, at a concentration of 7.5 mg per gram (0.75%) in a gel consisting of purified water, methylparaben, propylparaben, propylene glycol, carbomer 940, sodium hydroxide, and edetate disodium. Metronidazole is classified therapeutically as an antiprotozoal and antibacterial agent. Chemically, metronidazole is named 2-methyl-5-nitro-1*H*-imidazole-1-ethanol and has the following structure:




## CLINICAL PHARMACOLOGY

Bioavailability studies on the topical administration of 1 gram of **MetroGel®** Topical Gel (7.5 mg of metronidazole) to

***Continued on next page***

## Metrogel—Cont.

the face of 10 rosacea patients showed a maximum serum concentration of 66 nanograms per milliliter in one patient. This concentration is approximately 100 times less than concentrations afforded by a single 250 mg oral tablet. The serum metronidazole concentrations were below the detectable limits of the assay at the majority of time points in all patients. Three of the patients had no detectable serum concentrations of metronidazole at any time point. The mean dose of gel applied during clinical studies was 600 mg which represents 4.5 mg of metronidazole per application. Therefore, under normal usage levels, the formulation affords minimal serum concentrations of metronidazole. The mechanisms by which MetroGel® (metronidazole topical gel) Topical Gel acts in the treatment of rosacea are unknown, but appear to include an anti-inflammatory effect.

### INDICATIONS AND USAGE

MetroGel® Topical Gel is indicated for topical application in the treatment of inflammatory papules and pustules of rosacea.

### CONTRAINDICATIONS

MetroGel® Topical Gel is contraindicated in individuals with a history of hypersensitivity to metronidazole, parabens, or other ingredients of the formulation.

### PRECAUTIONS

**General:** MetroGel® Topical Gel has been reported to cause tearing of the eyes. Therefore, contact with the eyes should be avoided. If a reaction suggesting local irritation occurs, patients should be directed to use the medication less frequently or discontinue use. Metronidazole is a nitroimidazole and should be used with care in patients with evidence of, or history of blood dyscrasia.

**Information for patients:** This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.

**Drug interactions:** Oral metronidazole has been reported to potentiate the anticoagulant effect of coumarin and warfarin resulting in a prolongation of prothrombin time. The effect of topical metronidazole on prothrombin time is not known.

**Carcinogenesis, mutagenesis, impairment of fertility:** Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats but not in studies involving hamsters. Metronidazole has shown evidence of mutagenic activity in several *in vitro* bacterial assay systems. In addition, a dose-response increase in the frequency of micronuclei was observed in mice after intraperitoneal injections and an increase in chromosome aberrations have been reported in patients with Crohn's disease who were treated with 200–1200 mg/day of metronidazole for 1 to 24 months. However, no excess chromosomal aberrations in circulating human lymphocytes have been observed in patients treated for 8 months.

**Pregnancy:** ***Teratogenic effects: Pregnancy category B:*** There has been no experience to date with the use of MetroGel® (metronidazole topical gel) Topical Gel in pregnant patients. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity was observed after oral metronidazole in rats or mice. However, because animal reproduction studies are not always predictive of human response and since oral metronidazole has been shown to be a carcinogen in some rodents, this drug should be used during pregnancy only if clearly needed.

**Nursing mothers:** After oral administration, metronidazole is secreted in breast milk in concentrations similar to those found in the plasma. Even though MetroGel® Topical Gel blood levels are significantly lower than those achieved after oral metronidazole, 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 in pediatric patients have not been established.

### ADVERSE REACTIONS

The following adverse experiences have been reported with the topical use of metronidazole: burning, skin irritation, dryness, transient redness, metallic taste, tingling or numbness of extremities and nausea.

### DOSAGE AND ADMINISTRATION

Apply and rub in a thin film of MetroGel® Topical Gel twice daily, morning and evening, to entire affected areas after washing.

Areas to be treated should be cleansed before application of MetroGel® (metronidazole topical gel) Topical Gel. Patients may use cosmetics after application of MetroGel® Topical Gel.

### HOW SUPPLIED

MetroGel® (metronidazole topical gel) Topical Gel is supplied in a 1 oz (28.4 g) aluminum tube—NDC 0299-3835-28 and a 45 g aluminum tube—NDC 0299-3835-45.

**Storage conditions:** STORE AT CONTROLLED ROOM TEMPERATURE: 59° to 86°F (15° to 30°C).

**Caution:** Federal law prohibits dispensing without prescription.

225032-0895

Revised: August 1995

## METROLOTION®

(metronidazole lotion)

Topical Lotion, 0.75%

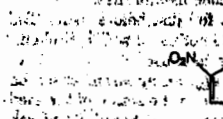
Rx only

FOR TOPICAL USE ONLY
(NOT FOR OPHTHALMIC USE)

### DESCRIPTION

MetroLotion® (metronidazole lotion) Topical Lotion contains metronidazole, USP at a concentration of 7.5 mg per gram (0.75% w/w) in a lotion consisting of benzyl alcohol, carbomer 941, cyclomethicone, glycerin, glyceryl stearate, light mineral oil, PEG-100 stearate, polyethylene glycol 400, potassium sorbate, purified water, steareth-21, stearyl alcohol, and sodium hydroxide and/or lactic acid to adjust pH.

Metronidazole is an imidazole and is classified therapeutically as an antiprotozoal and antibacterial agent. Chemically, metronidazole is 2-methyl-5-nitro-1*H*-imidazole-1-ethanol. The molecular formula is $C_6H_9N_3O_3$ and molecular weight is 171.16. Metronidazole is represented by the following structural formula:



### CLINICAL PHARMACOLOGY

The mechanisms by which metronidazole acts in the treatment of rosacea are unknown, but appear to include an anti-inflammatory effect.

***Pharmacokinetics:*** Absorption of metronidazole after topical application of MetroLotion® Topical Lotion is less complete and more prolonged than after oral administration. Detectable plasma levels were found in all subjects following the administration of a single 1 gram dose of MetroLotion® Topical Lotion (containing 7.5 mg of metronidazole) to the faces of 12 healthy volunteers. The highest concentration (64 ng/mL) seen was approximately 100 times lower than the peak concentrations produced by a single 250 mg tablet of metronidazole. The mean relative bioavailability of metronidazole from MetroLotion® Topical Lotion was 47.4%.

### INDICATIONS AND USAGE

MetroLotion® Topical Lotion is indicated for topical application in the treatment of inflammatory papules and pustules of rosacea.

### CLINICAL STUDIES

A controlled clinical study was conducted in 144 patients with moderate to severe rosacea, in which MetroLotion® Topical Lotion was compared with its vehicle. Applications were made twice daily for 12 weeks during which patients were instructed to avoid spicy foods, thermally hot foods and drinks, alcoholic beverages and caffeine. Patients were also provided samples of a soapless cleansing lotion and, if requested, a moisturizer. MetroLotion® Topical Lotion was significantly more effective than its vehicle in mean percent reduction of inflammatory lesions associated with rosacea and in the investigators' global assessment of improvement. The results of the mean percent reduction in inflammatory lesion counts from baseline after 12 weeks of treatment and the investigators' global assessment of improvement at week 12 are presented in the following table.

[See table below]

The scale is based on the following definitions:

Worse:
Exacerbation of either erythema or quantitative assessment of papules and/or pustules.

No Change:
Condition remains the same.

Minimal Improvement:
Slight improvement in the quantitative assessment of papules and/or pustules, and/or slight improvement in erythema.

Definite Improvement:
More pronounced improvement in the quantitative assessment of papules and/or pustules, and/or more pronounced improvement in erythema.

Marked Improvement:
Obvious improvement
papules and/or pust
in erythema.

Clear:
No papules or pustu
rythema.

### CONTRAINDICATION

MetroLotion® Topical
als with a history of hy
other ingredients of the

### PRECAUTIONS

*General:* Topical metro
ported to cause tearing
the eyes should be avo
irritation occurs, patient
cation less frequently
a nitroimidazole and
with evidence or history

*Information for Patient*
Topical Lotion should
instructions:
1. This medication is to
sician.
2. It is for external use
3. Avoid contact with
4. Cleanse affected ar
5. Patients should re
sician.

*Drug Interactions:* Or
to potentiate the anti
marin anticoagulant
thrombin time. The e
thrombin time is not k

*Carcinogenesis, Muta*
Metronidazole has sh
in a number of studies
tion in mice and rats
Neither carcinogenici
have been performed
tion® Topical Lotion
lations.

In several long-term
mately 198 mg/m²/da
times the human top
ciated with an increa
lymphomas in fema
Several long-term st
shown statistically
hepatic tumors in
pituitary adenomas
1598 mg/m²/day or
the human topical
study (by gavage)
served with a dos
64 times the human
In a published
cinogenesis was
carcinogenic activity
shown by a decre
skin neoplasms
skin following the
determined. This
nidazole must be
radiation in prod
metronidazole could
isting ultraviolet
of these results
treatment of
Metronidazole has
several *in vitro* bac
response increase
served in mice after
in chromosome
was reported in
treated with 200–

**Efficacy Outcomes at Week 12**

**Mean Percent Reduction in Inflammatory Lesion Counts**

| | MetroLotion® Topical Lotion N=65 | Vehicle Lotion N=60 |
|---|---|---|
| | 55% | |

**Investigators' Global Assessment of Improvement (percent change from baseline)**

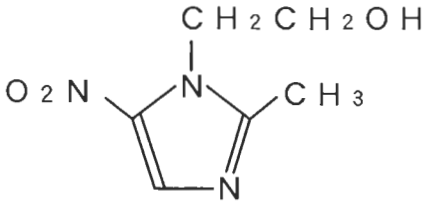
| | Worse | No Change | Minimal Improvement | Definite Improvement |
|---|---|---|---|---|
| MetroLotion® Topical Lotion N=65 | 5% | 13% | 11% | |
| Vehicle Lotion N=60 | 15% | 27% | 23% | |

**PDR®(PHYSICIANS' DESK REFERENCE) 55 edition 2001**

**MetroCream®**
(メトロニダゾール局所用クリーム)
局所用クリーム, 0.75%
局所用のみに限定
(目には使用しないこと)

説明
**MetroCream®**局所用クリームは、乳化ワックス、ソルビトール液、グリセリン、イソプロピールパルミチン酸、ベンジルアルコール、乳酸、精製水、必要に応じてpH調整の為の水酸化ナトリウムを加えた柔らかい軟膏基剤1g中に、メトロニダゾールUSP(米国薬局方)を7.5mg (0.75%) 含有するものである。メトロニダゾールは化学的にはニトロイミダゾールに属する抗菌化合物に分類され、治療剤としては抗原虫剤及び抗菌剤に分類されている。メトロニダゾールの化学名は2-メチル-5-ニトロ-1H-イミダゾール-1-エタノール、分子式は$C_6H_9N_3O_3$ 、分子量は171.16でであり、次の化学構造を有する。

化学構造式




**臨床薬理**
メトロニダゾールが、酒さを改善するメカニズムは不明であるが、恐らくはメトロニダゾールの抗炎症作用が関与しているものと考えられる。

**適応症と用法**
**MetroCream®**局所用クリームは、酒さの炎症性の丘疹、膿疱の治療の為に外用で使用する適応を有する。

**禁忌**
**MetroCream®**局所用クリームは、メトロニダゾールあるいはクリーム基剤中の成分に対して、過去に過敏性反応の既往を有する人に対しては禁忌である。

**注意事項**

**一般的事項：**局所用メトロニダゾールが催涙を起こしたという報告がある。従って、目に入らないように注意すること。もしも局所刺激作用を疑うような反応が見られた場合には、患者に対して薬剤の使用頻度を減らすか、使用を停止するよう指示を出す必要がある。メトロニダゾールは、ニトロイミダゾールに属する化合物であるので、血液障害の既往あるいは症状を有する患者には十分注意して使用すること。

**患者への説明：**この医薬品は臨床医の指示のもとに使用するものである。
適用法は外用。目に入らないように注意すること。

**薬剤の相互作用：**メトロニダゾールを経口投与した際に、ワルファリン及びクマリンの抗凝固作用が増強され、その結果プロトロンビン時間の延長することが報告されている。外用で用いたメトロニダゾールが、**プロトロンビン時間に影響**したという報告は知られていない。

**発癌性、変異原性、受精障害：**メトロニダゾールに発癌性のあることについては、マウス、ラットに長期経口投与した試験を含めて多くの研究が報告されている。しかし、ハムスターにおける検討結果は陰性であった。メトロニダゾールは、いくつかの細菌を用いた in vitro の試験で変異原性が示されている。加えて、マウスに腹腔内投与した試験で、用量依存性に小核を有する細胞の頻度が増加したとの報告、また、メトロニダゾールを 1 日 200－1200ｍｇ、１ヶ月から２４ヶ月投与されたクローン病患者で、染色体異常の頻度が増えたという報告がある。しかし、8 ヶ月間メトロニダゾールの治療を受けた患者の循環リンパ球の染色体異常の頻度に変化は観察されていない。

**妊娠：催奇形性＝妊娠カテゴリー B**　妊婦を対象とした本剤の適切で十分にコントロールされた臨床試験は行われていない。メトロニダゾールは、血液胎盤関門を通過して胎児の循環の中へ速やかに移行する。ラット及びマウスに経口投与した試験では、胎児毒性は認められなかった。しかし、動物を使った生殖試験でヒトに起こる反応が全て予見できるとは限らないこと、また、本薬の**経口投与で齧歯類の一部に発癌性の見られ**たことを考慮すると、本剤の妊婦への使用は、本剤の使用が必要不可欠であることが明確な場合に限定すべきである。

**授乳中の婦人：**　メトロニダゾールは、経口投与後、血漿中濃度と同じ程度に乳汁中に分泌される。本剤の外用では、経口投与の場合に比較してメトロニダゾールの血中濃度ははるかに低いものであるが、本薬が母親にとってどれほど必要であるかを考慮して、授乳を止めるか、本剤の使用を止めるかの決断が必要である。

**小児における使用：**本剤の小児における安全性と有効性は確立されていない。

**副作用**

MetroCream®のコントロールされた臨床試験における副作用頻度の総計は約 10％であった。その内訳は、皮膚不快感（灼熱感、チクチク感）が最も多く、以下、紅斑、皮膚刺激感、

掻痒感、酒さの増悪であった。個々の症状の発現頻度はいずれも3%未満であった。メトロニダゾールの局所使用ではほかにも下記の副作用が報告されている：灼熱感、皮膚の刺激、皮膚の乾燥、一過性の発赤、金属のような味、四肢のピリピリ感及びシビレ感、悪心。

**用法・用量**

**MetroCream®**局所用クリームは朝夕の 2 回、洗ってきれいにした患部全体に薄くのばして擦り込む。

患部は塗布の前に必ず刺激の無い洗剤できれいに洗うこと。

本剤を塗布した後で化粧することは差し支えない。

**包装**

**MetroCream®**局所用クリームは、アルミチューブに45ｇ入り製品として供給。

**保管方法**　：15 度～30 度に保持された室内に保管すること。

**注意**

連邦法により処方箋なしでの販売は禁止されている。

発売元：GALDERMA　Laboratories, Inc.,　FortWorth, Texas　76133
　　USA

製造元：DPT　Laboratories, Inc.　San Antonio, Texas　78215
　　USA

GALDERMA は登録商標である。

改訂年月　：　1995 年 6 月

PDR®(PHYSICIANS' DESK REFERENCE) 55 edition 2001

**DR®(PHYSICIANS' DESK REFERENCE) 55 edition 2001**

**METROGEL®**
(メトロニダゾール局所用ゲル)
局所用ゲル, 0.75%
局所用のみに限定
(目には使用しないこと)

説明

**MetroGel®**局所用ゲルは、精製水、メチルパラベン、プロピルパラベン、プロピレングリコール、カルボマー940、水酸化ナトリウム、EDTA-2ナトリウムより成るゲルの中に1g中に、メトロニダゾールを7.5mg(0.75%)を含有する。
メトロニダゾールは、治療上、抗原虫剤及び抗菌剤として分類されている。
メトロニダゾールの化学名は、2－メチル-5-ニトロ-1H－イミダゾール－1－エタノールであり、次の化学構造を有する。

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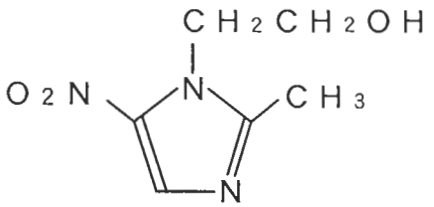


臨床薬理

**MetroGel®**局所用ゲル1g(メトロニダゾール7.5mg)を10名の酒さ患者の顔面に投与した生物学的利用能試験で、1名に最高血清中濃度66ng/mlが観察された。この濃度は、本薬250mg錠を単回経口投与後に得られる血中濃度の、約100分の1に相当する。いずれの患者においても、殆どの測定時間の血中薬物濃度は検出限界以下であった。3名では全く検出できなかった。臨床試験で適用された局所用ゲル剤の平均使用量は1回600mg、メトロニダゾールとしては4.5mgに相当する。従って、通常の使用条件下で起こる本薬の血中濃度の上昇はきわめて低いと思われる。**MetroGel®**が酒さの治療に際してどのような機作で作用しているかは不明であるが、恐らくはメトロニダゾールの有する抗炎症作用が関与しているものと考えられる。

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メトロニダゾールの局所使用により次の副作用が報告されている：灼熱感、皮膚の刺激、皮膚の乾燥、一過性の発赤、金属のような味、四肢のピリピリする感覚及びシビレ感、悪心。

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改訂年月　：　1995 年 8 月

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