PRODUCT MONOGRAPH

PrNORITATE®
(metronidazole % w/w)

Topical Cream 1%

FOR TOPICAL USE ONLY

(NOT FOR OPHTHALMIC USE)

Anti-Rosacea Agent

Valeant Canada LP
4787 Levy St.
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H4R 2P9

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Submission Control No.: 153360

PRODUCT MONOGRAPH

PrNORITATE®
(metronidazole % w/w)

Topical Cream 1%

THERAPEUTIC CLASSIFICATION

Anti-Rosacea Agent

ACTIONS AND CLINICAL PHARMACOLOGY

NORITATE® (metronidazole) topical cream is particularly effective against the inflammatory papulopustular component of rosacea. The mechanisms by which NORITATE acts in reducing inflammatory lesions of rosacea are unknown, but may include an anti-bacterial and/or an anti-inflammatory effect.

INDICATIONS AND CLINICAL USE

NORITATE (metronidazole) is indicated for topical application in the treatment of inflammatory papules, pustules and erythema of rosacea.

CONTRAINDICATIONS

NORITATE (metronidazole) is contraindicated in individuals with a history of hypersensitivity to metronidazole, parabens or other ingredients of the formulation.

WARNINGS

Avoid contact with eyes.

Studies in rats and mice have provided some evidence that metronidazole may cause tumors in these species when administered orally for a long period at high doses. The relevance of these findings in humans undergoing topical treatment with metronidazole is not known.

The mutagenic potential of metronidazole was tested in two ways: the dominant lethal test in mammalian germ cells, which yielded negative results, and a test using a bacterial indicator strain, which yielded positive results. The inherent antimicrobial property of metronidazole complicates the interpretation of this result with respect to any possible risk to humans.

Use in Children
Safety and effectiveness in children have not been established.

Use in Pregnancy
There has been no experience to date with the use of NORITATE in pregnant patients. Systemically administered 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 the human response, this drug should be used during pregnancy only after careful assessment of the risk/benefit ratio.

Nursing Mothers
Even though metronidazole blood levels are significantly lower after topical than after oral administration, 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. After oral administration, metronidazole is secreted in breast milk in concentrations similar to those found in plasma.

PRECAUTIONS

Because of the minimal absorption of metronidazole and consequently its insignificant plasma concentration after topical administration, the adverse experiences reported with the oral form of the drug have not been reported with NORITATE (metronidazole).

General
NORITATE (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, discontinue use temporarily or discontinue use until further instructions. Metronidazole is a nitroimidazole and should be used with care in patients with evidence of, or a history of, blood dyscrasia. Although rosacea is a chronic disease, data on the long-term use of NORITATE in rosacea are not available. In controlled clinical trials, patients were treated for a maximum 2 months (see DOSAGE AND ADMINISTRATION).

Drug Interactions
Drug interactions are less likely with topical administration, but should be kept in mind when NORITATE is prescribed for patients who are receiving anticoagulant treatment. Oral metronidazole has been reported to potentiate the anticoagulant effect of coumarin and warfarin resulting in a prolongation of prothrombin time. Oral metronidazole also interacts with alcohol, producing a disulfiram-like reaction. Although this response has never been reported with topically applied metronidazole, an interaction with alcohol may be a possibility.

Dermatological Sensitivity

During clinical trials, there were 3 reports of possible contact dermatitis during treatment with NORITATE. Sensitivity to NORITATE was confirmed in only one of these patients by re-challenging with the product. In the other patients, a clear causal relationship could not be established. Nevertheless, physicians should be aware of the possibility of skin sensitivity reactions to NORITATE and/or of cross-sensitization with other imidazole preparations, such as clotrimazole and tioconazole.

ADVERSE REACTIONS

Adverse conditions reported included transient skin irritation, dryness and stinging, as well as 3 cases of possible contact dermatitis. The incidence of these dermatological effects was about 3-4% during clinical trials.

Gastrointestinal side effects (nausea, constipation, gastrointestinal upset) were reported in 7 patients (less than 2% of the total clinical experience with NORITATE).

The following table provides specific information about the adverse effects observed during the two controlled clinical trials in which a total of 99 patients received NORITATE.

Body System/ Adverse Effect	**Severity**	**Incidence (No. of patients)**	**Course of Action taken**
SKIN			
Burning sensation	Mild Moderate	1 1	None required None required
Pruritus	Mild	2	None required
Pruritus/erythema/ burning	Mild-Moderate	1	None required
Erythema	Mild	1	None required
Oily skin	Mild	1	None required
Photosensitivity	Moderate	1	None required
Papular rash	Mild	1	Drug discontinued
Contact dermatitis	Moderate Severe	1 2	Drug discontinued Drug discontinued
GASTROINTESTINAL			
Nausea	Mild Moderate	1 1	None required None required
Burping	Mild	1	None required
GI upset	Mild	1	None required

	Severe	2	Drug discontinued*
GI cramps/anorexia	Moderate-severe	1	Drug discontinued**

* One of these patients likely received an oral antibiotic
** Patient predisposed to stomach ailments

Post-Market Adverse Drug Reactions

Eye disorders: transient vision disorders such as diplopia, myopia, blurred vision, decreased visual acuity, changes in color vision. Optic neuropathy/neuritis has been reported.

Watering or tearing eyes may also occur if NORITATE (metronidazole) is applied too closely to this area.

Skin and subcutaneous tissue disorders: flushing, pustular eruptions, and urticaria.

DOSAGE AND ADMINISTRATION

Cleanse all affected areas of the skin. Then, squeeze out approximately 1/2 cm of NORITATE (metronidazole) cream and apply to the entire affected areas twice daily, morning and evening. Rub in lightly.

Significant therapeutic results should be evident within the first month of treatment and controlled clinical studies have demonstrated continuing improvement through 8 weeks of therapy. The dosage required for long-term administration is uncertain (see PRECAUTIONS).

Patients may use cosmetics after application of NORITATE.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There is no human experience with overdosage of topically applied NORITATE (metronidazole) cream.

Symptoms
Massive ingestion may produce vomiting and slight disorientation.

Treatment
There is no specific antidote. Ipecac syrup or gastric lavage; then activated charcoal followed by a saline cathartic is suggested. Treatment should include symptomatic and supportive therapy.

PHARMACEUTICAL INFORMATION

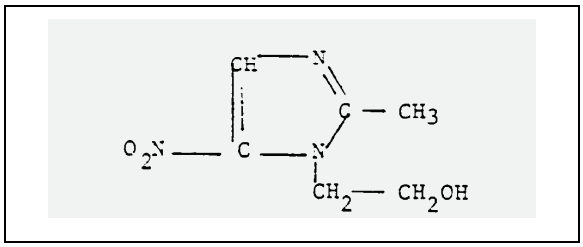
Trade Name: NORITATE

Drug Substance

Proper Name: Metronidazole

Chemical Name: 1-H-imidazole-1-ethanol, 2-methyl-5-nitro-
or
2-methyl-5-nitroimidazole-1-ethanol

Structural Formula:



Molecular Formula: $C_6H_9N_3O_3$

Molecular Weight: 171.16

Description:
Metronidazole is a white to pale yellow, odorless crystalline powder with a melting point of 159-163°C, and a bitter, metallic taste. It is sparingly soluble in water and alcohol at 20°C: 1.0g/100 mL in water and 0.5g/100 mL in ethanol. Slightly soluble in chloroform and ether (<0.05g/100 mL). Soluble in dilute acids. The pH of a saturated aqueous solution is 5.8.

Composition:
NORITATE (metronidazole) is a white to slightly off-white soft cream containing 10 mg metronidazole per g of cream (1% w/w).

Non-medicinal ingredients: stearic acid, glyceryl monostearate, glycerin, methyl paraben, propyl paraben, triethanolamine, purified water.

Stability and Storage Recommendations:
Store at room temperature (15 to 30°C).

AVAILABILITY OF DOSAGE FORMS

NORITATE (metronidazole) topical cream contains 1% metronidazole by weight and is supplied in aluminum tubes of 45 g.

PHARMACOLOGY

Clinical and experimental evidence suggests that rosacea presents through degenerative changes of the perivascular (and possibly vascular) collagen and elastic tissues. This dermal dystrophy leads to small vessel dilation resulting in telangiectasia, erythema and flushing. Eventually, this leads to small vessel incompetence with leakage of potentially inflammatory substances perivascularly which produce papules, pustules and lupoid nodules. Alternatively, a number of antigens, including the mite *Demodex folliculorum* or light-altered collagen and nuclear components could generate an immune response leading to the inflammatory changes.

Since metronidazole is particularly effective against the inflammatory papulopustular component of the disease, its mechanism of action may involve an anti-inflammatory effect. Evidence has been presented that metronidazole has a direct pharmacological effect on neutrophil cell function, inhibiting the generation of reactive oxygen species. Other investigators have provided evidence for an anti-inflammatory activity, modification of the granulocyte function and selective effects on some aspects of the humoral and cell-mediated immunity.

Pharmacokinetics:
Metronidazole is rapidly and nearly totally absorbed after oral administration. The drug is not significantly bound to serum proteins and distributes well to all body compartments with the lowest concentration found in fat. Metronidazole is excreted primarily in the urine as parent drug, oxidative metabolites and conjugates.

Percutaneous absorption of metronidazole from a 2% cream was studied in 16 healthy male volunteers following a single application of 100 mg of the cream to intact and stripped skin of the upper back. After 12 hours of exposure to the cream, there were no detectable levels of the drug in the plasma. An average of approximately 1.3% of the dose was recovered in the urine (intact and stripped skin) and 0.1-0.2% was recovered in the feces.

In another study, metronidazole was applied to intact or stripped skin of volunteers as a 0.5%, 1% and 2% cream for 44 days. At the end of this period, plasma levels ranged from below the limit of detection (<20 ng/mL) in 6 of 24 subjects to a maximum of 58 ng/mL in one subject (mean for remaining subjects: 31 ng/mL). These concentrations are more than 100 times lower than those produced by a single 250 mg oral tablet. Therefore, with normal use, NORITATE affords minimal systemic concentrations of metronidazole.

CLINICAL STUDIES

Two randomized double-blind controlled studies were conducted in rosacea patients for a period of 8 weeks. One study employed a placebo control, while the other employed orally administered tetracycline (250 mg t.i.d.) as an active standard of comparison. In both studies NORITATE (metronidazole) cream was applied to the affected areas twice daily. The results are summarized in the following table:

Study #	**No. Patients Evaluated**	**% Patients with Substantial Reduction in Inflammatory Lesions**		**% Patients with Improvement in Erythema**	
CMT 1286	82	NORITATE	Placebo	NORITATE	Placebo
		77%* (32/42)	57% (23/40)	Mild erythema pre-treatment in both groups with slight improvement	
		*p<0.05 vs placebo (lesion count)			
CMT 1487	101	NORITATE	Tetracycline	NORITATE	Tetracycline
		86% (42/49)	87% (45/52)	Some improvement with both treatments	
		No significant difference between treatments			

Statistically significant differences were observed between NORITATE and placebo cream with respect to lesion counts, especially after the first month of treatment. NORITATE proved to be statistically and clinically comparable to orally administered tetracycline. None of the treatments had an effect on the telangiectatic component of the disease.

TOXICOLOGY

Acute Toxicity:

The LD_{50} values for metronidazole are given in the following table:

SPECIES	SEX	ROUTE	LD_{50} (mg/kg)
Mouse	--	p.o.	4350
	M	i.p.	3650
	M	i.v.	1170
	F	i.v.	1260

Rat	--	p.o.	5000
	M	i.p.	5000
	M	i.v.	1575
	F	i.v.	1575

Signs of toxicity following oral and intravenous administration of metronidazole were sedation, ataxia and death in mice, and sedation and death in rats. Single doses of 500, 750, 1000, 1500, 3000 or 5000 mg/kg metronidazole were administered to dogs by gastric intubation; severe vomiting ensued at all doses above 500 mg/kg, accompanied by ataxia, loss of spatial judgement, dozing, walking blindly and convulsions.

Subacute and Chronic Toxicity

The following table summarizes the results of subacute and chronic toxicity testing:

SPECIES	DOSE (mg/kg)	ROUTE	DURATION (months)	FINDINGS
Rat	0, 25, 50 100 1000	Oral Oral Oral	1 0.5 1	No abnormalities, except minor epithelial desquamation in the epididymus in 100 and 1000 mg/kg groups
Rat: 20M 20F	30	I.V.	1	Statistical decrease in body weight gain in males only
Dog	0, 25, 50	Oral	1	No abnormalities
Dog	75, 110, 225	Oral	6	Ataxia, muscle rigidity tremor
Dog: 2M 2F	37.5	I.V.	5 days/week x 1 month	Relative weights of thyroids below controls in 2 males and 1 female

Primary Eye Irritation

The ocular irritant effects of 0.5%, 1% and 2% topical metronidazole cream were tested in rabbits against a placebo control. An aliquot (0.1 mL) of one of the cream formulations was placed in the lower lid of one eye of each of three animals. The eyes were subsequently examined for the appearance and severity of ocular lesions after 1 hour and 1, 2, 3, 4 and 7 days after instillation. Mild conjunctival irritation was noted in several animals in both the active and placebo cream groups. The eyes of the animals in all treatment groups normalized within 1 to 3 days of instillation. None of the rabbits showed any corneal or iridial inflammation.

Cumulative Skin Irritation Studies in Humans:
Three strengths of metronidazole cream (0.5%, 1% and 2%) were tested daily in 24 healthy subjects over 44 days. Each strength (0.2g) was applied to a thin perforated non adherent polyester film and secured to the intact skin of the scapular region with a hypoallergenic adhesive dressing. In addition, the 2% cream was applied to an area of stripped skin, also in the scapular region. A placebo cream served as the control. The sites of application remained covered for 24 hours until the time of the next application.

There were random, mild irritations in both the test and placebo groups, but no systematic evidence of acute or cumulative irritation or of an allergic reaction to any formulation. After 44 days, there was no evidence of photosensitivity, except in 1 subject who exhibited a slight erythema at the stripped skin site following exposure to UV light. The erythema resolved in one day.

Mutagenicity Studies
The mutagenic potential of metronidazole has been measured in two test systems. In a study using a bacterial indicator strain to detect mutagenic effects, positive results were reported. The inherent anti-microbial property of metronidazole further complicates the interpretation respecting genetic and carcinogenic hazard to man. The other test system, the dominant lethal test, measured the effect of metronidazole on mammalian germ cells. Male rats administered doses of metronidazole up to 600 mg/kg/day for five consecutive days, were mated to untreated females. Fetal deaths, the primary measure of dominant lethality, were not increased in those females mated to treated males.

Tumorigenicity Studies
Two separate tumorigenic studies were carried out in two different strains of mice with metronidazole. Metronidazole was administered in the diet at daily doses of 75, 150 and 600 mg/kg in both experiments. A study with the strain of Swiss mice was terminated after 78 weeks, while the other experiment with CF_1 mice was terminated at 92 weeks. There was no evidence that the administration of metronidazole at any dosage level produced an adverse effect upon the physical appearance, behavior, body weight and food consumption. However, the survival in mice in the treated groups was better than that in the controls.

Statistical analysis of necropsy data, gross and microscopic, using life-table and other techniques revealed a significant increase in the rate of benign lung tumors in the groups of mice treated with 600 mg/kg. With the lower dosage, there was also a trend for increased rate, however, the changes were not significant. It should, though, be noted that this type of tumor was also seen in up to 30% of mice in the untreated groups.

In the rat, dose levels of 75, 150 and 300 mg/kg/day were administered orally in the diet for 80 consecutive weeks; a dosage of 600 mg/kg was administered for 13 weeks only. No consistant deleterious effects were observed with doses of 75 and 150 mg/kg for 28-80 weeks on physical, behavioral, clinical laboratory or post-mortem examinations. At the dosage of 300 mg/kg, testicular dystrophy was regularly encountered at 13 weeks of longer and was not reversed by a 28 week recovery (no drug) period; prostatic atrophy was also seen at 26 weeks. The 600 mg/kg dosage group showed a high incidence of testicular dystrophy and prostatic atrophy with a pronounced reduction in the rate of body weight gain. There was a significant increase in the number of benign mammary tumors only in the females of the 300 mg/kg group.

Two independent tumorigenicity studies conducted in the hamster gave negative results.

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(metronidazole)

This leaflet is published and designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NORITATE®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
NORITATE (metronidazole, topical cream) is used to treat rosacea.
Rosacea is a chronic skin disease that affects the middle third of the face with persistent redness over the areas of the face and nose that normally blush: mainly the forehead, the chin and the lower half of the nose. The tiny blood vessels in these areas enlarge (dilate) and become more visible through the skin, appearing like tiny red lines.

What it does:
NORITATE is effective in reducing the inflammatory lesions of rosacea by reducing inflammation, sores, redness and/or killing bacteria.

When it should not be used:
Do not use NORITATE if you have a known allergy to metronidazole or any of the ingredients NORITATE contains (see **What the nonmedicinal ingredients are**)

What the medicinal ingredients are:
The active ingredient in NORITATE is metronidazole.

What the nonmedicinal ingredients are:
The nonmedicinal ingredients of NORITATE are: Glycerin, glyceryl monostearate, methyl paraben, propyl paraben, stearic acid, triethanolamine, and purified water.

What dosage forms it comes in:
NORITATE (metronidazole topical cream1%) is supplied in aluminum tubes of 45 g.

WARNINGS AND PRECAUTIONS

NORITATE is for use only on the skin. Avoid getting this medication in your eyes. If this does happen, rinse thoroughly with large amounts of cool water.

Do not use NORITATE for longer than recommended by your doctor.

Avoid unnecessary or prolonged exposure to sunlight. Metronidazole may make your skin sensitive to sunlight.

This medicine has not been studied in children and its use is not recommended in this population.

BEFORE you use NORITATE talk to your doctor or pharmacist if:

- You have any allergies to metronidazole or the nonmedicinal ingredients in NORITATE.
- You have a history of blood disease or your blood is not normal in some way.
- You are pregnant or nursing.

Call your doctor if you have severe stinging or burning when you apply NORITATE. Your doctor may advise that you use the medication less frequently, discontinue the medication temporarily or discontinue the medication.

INTERACTIONS WITH THIS MEDICATION

Inform your doctor or pharmacist about all of your medicines, including over-the-counter drugs that may interact with NORITATE such as:

- Drugs containing alcohol and alcoholic beverages
- oral anticoagulants (blood thinners) such as warfarin and coumarin

PROPER USE OF THIS MEDICATION

Usual Adult dose:
Use this medication exactly as it was prescribed for you. Do not use the medication in larger amounts, or use it for longer than recommended by your doctor.

Wash and gently dry your skin before applying NORITATE.

Squeeze out approximately ½ cm of NORITATE (metronidazole) cream and apply to the entire affected areas twice daily, morning and evening. Rub in lightly. Wash hands after use.

You may apply cosmetics after using NORITATE once the cream has dried.

Use this medication for the entire length of time prescribed by your doctor. Results should be evident within the first month of treatment with continuing improvement through 8 weeks of treatment.

This medicine is for external use only. Do not use NORITATE topical to treat any other skin infection your doctor has not prescribed it for. Do not use this medicine in or near the eyes. If this medicine does get into your

eyes, wash them out immediately, but carefully, with large amounts of cool tap water. If your eyes still burn or are painful, check with your doctor.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Topically applied metronidazole can be absorbed in sufficient amount to produce systemic effects. Massive ingestion may produce vomiting and slight disorientation.

Missed Dose:
If you miss a dose of NORITATE, apply it as soon as possible. However, if it is almost time for your next dose, go back to your regular dosing schedule. Do not use extra medicine to make up the missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Some side effects related to metronidazole were skin irritation such as dryness, burning sensation, stinging, inflammation or redness of the skin, rash, itching, contact dermatitis. Other side effects were nausea, stomach upset, cramps and constipation.

Temporary vision disorders were also reported such as: blurred vision, and changes in color vision.

Watering or tearing eyes may also occur if NORITATE (metronidazole) is applied too closely to the eyes.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
irritation, dryness, burning sensation, stinging, inflammation or redness of the skin, rash, itching, contact dermatitis	√		
nausea, stomach upset, cramps.	√		
blurred vision, and changes in color vision.		√	

This is not a complete list of side effects. For any unexpected effects while taking NORITATE, contact your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS
You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at: www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect .

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

Keep NORITATE in a safe place where children cannot reach it.

Store at room temperature between 15 – 30°C.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

http://webprod.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp

or by contacting the sponsor at:

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