

Researchers Seek to Quantify Thermage Efficacy

BY TIMOTHY F. KIRN
Sacramento Bureau

PALM DESERT, CALIF. — The radio-frequency heating technique Thermage is probably the best studied of the technologies that tighten the skin, said Dr. Roy Geronemus at the annual meeting of the American Society for Dermatologic Surgery.

Even so, proving that the Thermage treatment works has been difficult be-

cause the effects are modest and it is hard to measure tightening objectively.

Before and after photos are simply too subjective to be of use in evaluating the effects of treatment, he said.

There have been successful attempts to be as objective as possible, mostly by demonstrating that the treatment can lift eyebrows relative to the eye pupil, said Dr. Geronemus, director of a laser practice in New York.

In a study that he conducted using Fitz-

patrick wrinkle scores to make the assessment objective, he and his associates found that 57% of patients at one site and 73% of patients at another had an improvement of 25% or more in their scores at 6 months.

The investigators also used a device that attempts to measure skin tension, and found that it recorded a significant improvement in the areas of skin treated, Dr. Geronemus said.

Techniques have also evolved since

Thermage was first introduced, and the better procedures have contributed to dispelling some of the skepticism, he noted. Practitioners now usually use multiple passes at a lower power level, instead of a single pass at a higher power level. The lower-power technique was used in his trial. Many physicians also recommend that a wider device tip be utilized (3 cm instead of 1.5 cm). The wider tip was not used in his trial.

Microscopic data appear to show that radiofrequency heating does result in the denaturing of collagen fibers, said Dr. Brian Zelickson, who practices in Min-

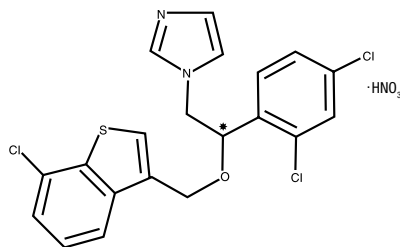


For Topical Dermatologic Use Only - Not for Oral, Ophthalmic or Intravaginal Use

DESCRIPTION:

ERTACZO® (sertaconazole nitrate) Cream, 2%, contains the imidazole antifungal, sertaconazole nitrate. Sertaconazole nitrate contains one asymmetric carbon atom and exists as a racemic mixture of equal amounts of R and S enantiomers.

Sertaconazole nitrate is designated chemically as (+)-1-[2,4-dichloro-β-(7-chlorobenzo-[b]thien-3-yl)methoxy]phenethylimidazole nitrate. It has a molecular weight of 500.8. The molecular formula is C₂₀H₁₅Cl₃N₂OS · HNO₃, and the structural formula is as follows:



Sertaconazole nitrate is a white or almost white powder. It is practically insoluble in water, soluble in methanol, sparingly soluble in alcohol and in methylene chloride. Each gram of ERTACZO® Cream, 2%, contains 17.5 mg of sertaconazole (as sertaconazole nitrate, 20 mg) in a white cream base of ethylene glycol and polyethylene glycol palmitostearate, glyceryl isostearate, light mineral oil, methylparaben, polyoxyethylened saturated glycerides and glycolized saturated glycerides, sorbic acid and purified water.

CLINICAL PHARMACOLOGY:

Pharmacokinetics: In a multiple dose pharmacokinetic study that included 5 male patients with interdigital tinea pedis (range of diseased area, 42 - 140 cm²; mean, 93 cm²), ERTACZO® Cream, 2%, was topically applied every 12 hours for a total of 13 doses to the diseased skin (0.5 grams sertaconazole nitrate per 100 cm²). Sertaconazole concentrations in plasma measured by serial blood sampling for 72 hours after the thirteenth dose were below the limit of quantitation (2.5 ng/mL) of the analytical method used.

Microbiology: Sertaconazole is an antifungal that belongs to the imidazole class of antifungals. While the exact mechanism of action of this class of antifungals is not known, it is believed that they act primarily by inhibiting the cytochrome P450-dependent synthesis of ergosterol. Ergosterol is a key component of the cell membrane of fungi, and lack of this component leads to fungal cell injury primarily by leakage of key constituents in the cytoplasm from the cell.

Activity In Vivo: Sertaconazole nitrate has been shown to be active against isolates of the following microorganisms in clinical infections as described in the INDICATIONS AND USAGE section:

Trichophyton rubrum
Trichophyton mentagrophytes
Epidermophyton floccosum

CLINICAL STUDIES:

In two randomized, double-blind, clinical trials, patients 12 years and older with interdigital tinea pedis applied either ERTACZO® Cream, 2%, or vehicle, twice daily for four weeks. Patients with moccasin-type (plantar) tinea pedis and/or onychomycosis were excluded from the study. Two weeks after completion of therapy (six weeks after beginning therapy), patients were evaluated for signs and symptoms related to interdigital tinea pedis.

Treatment outcomes are summarized in the table below.

	Treatment Outcomes as Percent (%) of Total Subjects			
	Study 1		Study 2	
	Sertaconazole	Vehicle	Sertaconazole	Vehicle
Complete Cure* (Primary Efficacy Variable)	13/99 (13.1%)	3/92 (3.3%)	28/103 (27.2%)	5/103 (4.9%)
Effective Treatment**	32/99 (32.3%)	11/92 (12.0%)	52/103 (50.5%)	16/103 (15.5%)
Mycological Cure***	49/99 (49.5%)	18/92 (19.6%)	71/103 (68.9%)	20/103 (19.4%)

* **Complete Cure** - Patients who had complete clearing of signs and symptoms and Mycological Cure.
** **Effective Treatment** - Patients who had minimal residual signs and symptoms of interdigital tinea pedis and Mycological Cure.
*** **Mycological Cure** - Patients who had both negative microscopic KOH preparation and a negative fungal culture.

In clinical trials, complete cure in sertaconazole treated patients was achieved in 32 of 160 (20%) patients with *Trichophyton rubrum*, in 7 of 28 (25%) patients with *Trichophyton mentagrophytes* and in 2 of 13 (15%) patients with *Epidermophyton floccosum*.

INDICATIONS AND USAGE:

ERTACZO® (sertaconazole nitrate) Cream, 2%, is indicated for the topical treatment of interdigital tinea pedis in immunocompetent patients 12 years of age and older, caused by: *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum* (see CLINICAL STUDIES Section).

CONTRAINDICATIONS:

ERTACZO® Cream, 2%, is contraindicated in patients who have a known or suspected sensitivity to sertaconazole nitrate or any of its components or to other imidazoles.

WARNINGS:

ERTACZO® Cream, 2%, is not indicated for ophthalmic, oral or intravaginal use.

PRECAUTIONS:

General: ERTACZO® Cream, 2%, is for use on the skin only. If irritation or sensitivity develops with the use of ERTACZO® Cream, 2%, treatment should be discontinued and appropriate therapy instituted.

Diagnosis of the disease should be confirmed either by direct microscopic examination of infected superficial epidermal tissue in a solution of potassium hydroxide or by culture on an appropriate medium.

Physicians should exercise caution when prescribing ERTACZO® Cream, 2%, to patients known to be sensitive to imidazole antifungals, since cross-reactivity may occur.

Information for Patients: The patient should be instructed to:

1. Use ERTACZO® Cream, 2%, as directed by the physician. The hands should be washed after applying the medication to the affected area(s). Avoid contact with the eyes, nose, mouth and other mucous membranes. ERTACZO® Cream, 2%, is for external use only.
2. Dry the affected area(s) thoroughly before application, if you wish to use ERTACZO® Cream, 2%, after bathing.
3. Use the medication for the full treatment time recommended by the physician, even though symptoms may have improved. Notify the physician if there is no improvement after the end of the prescribed treatment period, or sooner, if the condition worsens.
4. Inform the physician if the area of application shows signs of increased irritation, redness, itching, burning, blistering, swelling or oozing.
5. Avoid the use of occlusive dressings unless otherwise directed by the physician.
6. Do not use this medication for any disorder other than that for which it was prescribed.

Drug/Laboratory Test Interactions: Potential interactions between ERTACZO® Cream, 2%, and other drugs or laboratory tests have not been systematically evaluated.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies to evaluate the carcinogenic potential of sertaconazole nitrate have not been conducted. No clastogenic potential was observed in a mouse micronucleus test. Sertaconazole nitrate was considered negative for sister chromatid exchange (SCE) in the *in vivo* mouse bone marrow SCE assay. There was no evidence that sertaconazole nitrate induced unscheduled DNA synthesis in rat primary hepatocyte cultures. Sertaconazole nitrate exhibited no toxicity or adverse effects on reproductive performance or fertility of male or female rats given up to 60 mg/kg/day orally by gastric intubation (16 times the maximum recommended human dose based on a body surface area comparison).

Pregnancy: Teratogenic Effects. Pregnancy Category C: Oral reproduction studies in rats and rabbits did not produce any evidence of maternal toxicity, embryotoxicity or teratogenicity of sertaconazole nitrate at an oral dose of 160 mg/kg/day (40 times (rats) and 80 times (rabbits) the maximum recommended human dose on a body surface area comparison). In an oral peri-postnatal study in rats, a reduction in live birth indices and an increase in the number of still-born pups was seen at 80 and 160 mg/kg/day.

There are no adequate and well-controlled studies that have been conducted on topically applied ERTACZO® Cream, 2%, in pregnant women. Because animal reproduction studies are not always predictive of human response, ERTACZO® Cream, 2%, should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known if sertaconazole is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when prescribing ERTACZO® Cream, 2%, to a nursing woman.

Pediatric Use: The efficacy and safety of ERTACZO® Cream, 2%, have not been established in pediatric patients below the age of 12 years.

Geriatric Use: Clinical studies of ERTACZO® Cream, 2%, did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE EVENTS:

In clinical trials, cutaneous adverse events occurred in 7 of 297 (2%) patients (2 of them severe) receiving ERTACZO® Cream, 2%, and in 7 of 291 (2%) patients (2 of them severe) receiving vehicle. These reported cutaneous adverse events included contact dermatitis, dry skin, burning skin, application site reaction and skin tenderness.

In a dermal sensitization study, 8 of 202 evaluable patients tested with ERTACZO® Cream, 2%, and 4 of 202 evaluable patients tested with vehicle, exhibited a slight erythematous reaction in the challenge phase. There was no evidence of cumulative irritation or contact sensitization in a repeated insult patch test involving 202 healthy volunteers. In non-US post-marketing surveillance for ERTACZO® Cream, 2%, the following cutaneous adverse events were reported: contact dermatitis, erythema, pruritus, vesiculation, desquamation, and hyperpigmentation.

OVERDOSAGE:

Overdosage with ERTACZO® Cream, 2%, has not been reported to date. ERTACZO® Cream, 2%, is intended for topical dermatologic use only. It is not for oral, ophthalmic, or intravaginal use.

DOSAGE AND ADMINISTRATION:

In the treatment of interdigital tinea pedis, ERTACZO® Cream, 2%, should be applied twice daily for 4 weeks. Sufficient ERTACZO® Cream, 2%, should be applied to cover both the affected areas between the toes and the immediately surrounding healthy skin of patients with interdigital tinea pedis. If a patient shows no clinical improvement 2 weeks after the treatment period, the diagnosis should be reviewed.

HOW SUPPLIED:

ERTACZO® Cream, 2%, is supplied in tubes in the following sizes:

30-gram tube NDC 0062-1650-03
60-gram tube NDC 0062-1650-02

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Rx only.

Patent No. 5,135,943

Distributed By: OrthoNeutrogena
DIVISION OF ORTHO-McNEIL PHARMACEUTICAL, INC.
Los Angeles, CA 90045

Revised November 2005

128354



Proving that Thermage works is difficult because the effects are modest and it is hard to measure tightening.

DR. GERONEMUS

neapolis and is with the department of dermatology at the University of Minnesota there.

Light microscopy does not show very much effect from the Thermage technology, said Dr. Zelickson, who is a microscopy expert. An electron-microscope view of treated skin, however, shows what he called "islands" of changes in the collagen fibers.

Dr. Zelickson has also reported that one can see additive effects of each pass of the Thermage device, with up to five passes.

"In our patients, we see some modest tightening," Dr. Zelickson said. "We can certainly see some tightening of the skin when you look at the before and after pictures."

What is the most convincing evidence that Thermage works, however, is that patients have the impression that the treatment improves their looks, said Dr. Geronemus.

"Most of the patients I have seen over the last 2 months are people who are coming in for second treatments because of the success they have achieved with their first treatment with Thermage," he said.

Still, even these two experts expressed some reservations about what can actually be accomplished with Thermage's ThermaCool system.

The procedure does not appear to be appropriate for all of his patients, said Dr. Zelickson.

In his experience, selecting the proper patient is crucial to obtaining a good result, but he did not elaborate on his criteria any further except to say that the right patient is one with obvious skin "laxity."

Dr. Geronemus noted that in his research there was some evidence that the benefits of Thermage treatment appeared to be wearing off after a period of about 6 months.

Dr. Zelickson has received research grants from Thermage Inc., and Dr. Geronemus is a company shareholder. ■