



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Memorandum

DATE: April 7, 2004

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SUBJECT: ODS Postmarketing Safety Review (PID 040110)
Adverse Events: Lack of Efficacy, Cellulitis
Drugs: Topical Antifungal Agents (Butenafine, betamethasone + clotrimazole, ciclopirox, chloroxylenol + undecylenic acid, clotrimazole, econazole, ketoconazole, miconazole, naftifine, oxiconazole nitrate, sertaconazole, sulconazole, terbinafine, tolnaftate, undecylenic acid)

EXECUTIVE SUMMARY

This review summarizes all AERS reports of lack of efficacy and cellulitis associated with 15 topical antifungal agents¹. We have prepared this review at the request of DDDDP for the upcoming Nonprescription Drugs and Dermatologic and Ophthalmic Drugs Advisory Committee Meeting (May 6 -7, 2004). The meeting is being convened to discuss drug efficacy and labeling of topical antifungal agents marketed for the treatment of tinea pedis, and other dermatophyte infections. The request for a review of cellulitis reports was made because of the concern that topical antifungals may have been used in misdiagnosed bacterial infections or that poorly treated lesions from interdigital dermatophyte infections (tinea pedis) may provide a means of bacterial entrance, contributing to cellulitis development. In the interest of time and due to the volume of reports found, we are providing *crude counts* of the lack of efficacy reports and a brief analysis of the cellulitis reports. Drug use information is presented in a separate document authored by Laura Governale, Pharm.D., of the Office of Drug Safety.

¹ Oxiconazole nitrate, ciclopirox, miconazole, butenafine, ketoconazole, econazole, terbinafine, clotrimazole, naftifine, chloroxylenol + undecylenic acid, undecylenic acid, betamethasone + clotrimazole, sertaconazole, sulconazole, tolnaftate

We searched the AERS database on March 16, 2004 for all reports associated with 15 topical antifungal agents². We found 4,741 reports of all events since approval, of which 1,663 reported lack of efficacy. Most of the “lack of efficacy reports” were associated with five agents, including terbinafine (484), ketoconazole (312), clotrimazole (297), miconazole (287), and the combination of betamethasone + clotrimazole (138).

We found 13 cases reporting cellulitis associated with these drugs. Two antifungal agents, terbinafine (5) and miconazole (4), accounted for the majority of the cellulitis adverse event reports. In the majority of the 13 cases, cellulitis affected the lower extremities (thigh, leg, ankle, foot and toe). Seven of the 13 cases reported hospitalization as an outcome. There were no reports of death. One patient reported a history of diabetes. Although we found a small number of AERS reports, and cellulitis occurred after administration in some cases, the risk of cellulitis with the topical antifungal agents is unknown.

The presence or absence of lack of efficacy reports in AERS cannot be the sole source to determine if a product is ineffective or effective. Additionally, we did not review the individual lack of efficacy cases to analyze other information, such as the most likely suspect agent, the dose, duration or proper use of these drugs, or other confounding factors which may have contributed to the adverse event. Consequently, the *crude numbers* that we reported in this review should be interpreted with caution.

BACKGROUND INFORMATION

Topical imidazoles (miconazole, ketoconazole, econazole, clotrimazole, oxiconazole, sertaconazole and sulconazole), benzylamines (butenafine), and allylamines (terbinafine and naftifine) are considered generally effective therapies for tinea pedis (Athlete’s foot), tinea cruris (Jock Itch), and tinea corporis (infection of non-hairy areas). Undecylenic acid, ciclopirox, and tolnaftate are also considered generally effective treatments.

Topical antifungal agents to treat tinea infections are available by prescription (ketoconazole, econazole, oxiconazole, sertaconazole, sulconazole, naftifine, betamethasone + clotrimazole, and ciclopirox), and over-the-counter (OTC) (undecylenic acid, chloroxylenol + undecylenic acid, and tolnaftate). Additionally, some topical antifungal agents are available as both prescription and OTC products (miconazole, clotrimazole, terbinafine and butenafine). MedWatch adverse event reports are not required to be submitted by drug manufacturers for OTC monograph products. Consequently, adverse event reporting may be significantly underrepresented for those topical antifungal drug products available on an OTC basis.

This review is organized by separate presentation of the lack of efficacy reports, followed by the cellulitis reports. The data are presented for the active ingredients and not for individual products, since we are unable to separate adverse event data for agents with multiple topical formulations. An example of a drug with multiple topical formulations is miconazole, the active ingredient found in Lotrimin AF Spray Powder, Spray Liquid, Spray Deodorant Powder, Shaker Powder, Jock Itch Spray Powder, Desenex Shake Powder, as well as Monistat-Derm.

² Oxiconazole nitrate, ciclopirox, miconazole, butenafine, ketoconazole, econazole, terbinafine, clotrimazole, naftifine, chloroxylenol + undecylenic acid, undecylenic acid, betamethasone + clotrimazole, sertaconazole, sulconazole, tolnaftate

In the interest of time, we did not conduct a “hands-on” review of the lack of efficacy reports, but exported the demographic data to an interactive database for analysis, and as such, the data may contain duplicate reports. Additionally, we cannot say if there is a causal relationship between the adverse events of lack of efficacy, or cellulitis and the administration of the topical antifungal agent.

LITERATURE

A MEDLINE search of the English-language literature published from 1966 to 2004 did not produce any publications describing cellulitis associated with topical antifungal agents. We did not search MEDLINE for lack of efficacy reports.

SELECTION

On March 16, 2004, we searched the AERS database for each topical antifungal agent. We used the following search strategy:

- All adverse event reports
- Lack of efficacy reports
 - Drug Effect Decreased – PT
 - Drug Ineffective – PT
 - Drug Ineffective for Unapproved Indication – PT
 - Therapeutic Product Ineffective – PT
 - Therapeutic Response Decreased – PT
 - Therapeutic Response Delayed – PT
- Cellulitis reports
 - Cellulitis – PT
 - Cellulitis Enterococcal – PT
 - Cellulitis Gangrenous – PT
 - Cellulitis Pasteurella – PT
 - Cellulitis Staphylococcal – PT
 - Cellulitis Streptococcal – PT
 - Anorectal Cellulitis – PT

We searched the database for the following list of antifungal agents. For those with multiple routes of administration³ we limited our search to those reports indicating topical use.

- betamethasone dipropionate + clotrimazole⁴
- butenafine⁵
- chloroxylenol + undecylenic acid⁶
- ciclopirox⁷
- clotrimazole⁸

³ Clotrimazole (oral, topical, vaginal), miconazole (topical, vaginal, injectable - not currently available), terbinafine (oral, topical), ketoconazole (oral, topical)

⁴ Lotrisone

⁵ Mentax, Lotrimin Ultra

⁶ Gordochem

⁷ Loprox Cream/Gel/Suspension

- econazole⁹
- ketoconazole¹⁰
- miconazole nitrate¹¹
- naftifine¹²
- oxiconazole nitrate¹³
- sertaconazole¹⁴
- sulconazole¹⁵
- terbinafine¹⁶
- tolnaftate¹⁷
- undecylenic acid¹⁸

The AERS search for all adverse event reports associated with 15 topical antifungal agents¹⁹ retrieved 4,741 reports. Included in the 4,741 reports were 1,663 reports of lack of efficacy and 13 reports of cellulitis. Not all agents queried reported lack of efficacy, or cellulitis.

AERS SEARCH FINDINGS

Part I: Lack of Efficacy Reports

We separately searched the AERS database for lack of efficacy reports for 15 antifungal agents. We found 1,663 reports of lack of efficacy, representing 35% of all reports for the 15 antifungal agents included in this review. Analysis of the data demonstrates that lack of efficacy has been reported for almost all of the selected antifungal agents, except for butenafine, chloroxylenol + undecylenic acid, and sertaconazole. Additionally, five antifungals accounted for 90% of the lack of efficacy reports. These agents included terbinafine (484), with the largest number of lack of efficacy reports, followed by ketoconazole (312), clotrimazole (297), miconazole (287), and the combination of betamethasone + clotrimazole (138).

Table 1 provides a breakdown and the rank order of the antifungal agents reporting lack of efficacy. To assist the reader we included the earliest year of approval of the topical antifungal agent, as well as the number of all adverse event reports for the agent found in the AERS database.

Table 1: Lack of Efficacy by Drug Product (crude AERS counts)

Drug Product	Earliest Year Approved ²⁰	All Adverse Event Reports	# of Lack of Efficacy Reports
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⁸ Cruex Cream, Lotrimin AF Cream, Desenex Cream, Lotrimin AF Lotion, Lotrimin AF Topical Solution, generic products

⁹ Spectazole, generic products

¹⁰ Nizoral Cream, generic products

¹¹ Lotrimin AF Spray, Spray Liquid, Spray Deodorant Powder, Shaker Powder and Jock Itch Spray Powder, Desenex Shake Powder, Micatin Spray Liquid, Monistat-Derm, others

¹² Naftin Cream, Gel

¹³ Oxistat Cream

¹⁴ Ertaczo Cream

¹⁵ Exelderm Cream

¹⁶ Lamisil AT Cream/Spray, DesenexMax Cream

¹⁷ Tinactin, generic products

¹⁸ Desenex Powder, Caldesene, Cruex, Cruex Aerosol, Blis-To-sol, Cruex cream, Gordochochom (undecylenic acid + chloroxynol)

¹⁹ Oxiconazole nitrate, ciclopirox, miconazole, butenafine, ketoconazole, econazole, terbinafine, clotrimazole, naftifine, chloroxylenol + undecylenic acid, undecylenic acid, betamethasone + clotrimazole, sertaconazole, sulconazole, tolnaftate

²⁰ Year of approval obtained from Electronic Orange Book, and/or FDA's DSS database for drug products

Drug Product	Earliest Year Approved²⁰	All Adverse Event Reports	# of Lack of Efficacy Reports
Terbinafine, topical	1992	1,204	484
Ketoconazole, topical	1987	1,251	312
Clotrimazole, topical	1975	505	297
Miconazole, topical	1973	542	287
Betamethasone + clotrimazole	1984	591	138
Undecylenic Acid	1974	98	65
Ciclopirox	1988	208	32
Econazole	1982	153	17
Naftifine	1990	75	14
Oxiconazole	1988	46	11
Sulconazole	1989	21	3
Tolnaftate	1965	42	3
Butenafine	1996	5	0
Sertaconazole	2003	0	0
Undecylenic Acid + Chloroxylenol	-----	0	0

Part II: Cellulitis

We found 13 cases in the AERS database of cellulitis as an adverse event associated with the use of topical antifungal agents. These 13 cases represented 0.27% of all AERS anti fungal adverse event reports. Although small, nearly 70% of the cellulitis reports were submitted for topical terbinafine (5) and topical miconazole (4).

There were 11 US, and two foreign cases, of which eight were female, and five were male. The patients ranged in age from 25 to 82 years, with a median age of 43 (n=10). The topical antifungal agents were used primarily to treat tinea pedis (8). One case each reported the following indications: tinea cruris, dermatophytosis, lupus flare, and vitiligo. The remaining case did not report the indication for use. The time of onset of symptoms ranged from less than 24 hours to 150 days, with a median time of onset of one day (n = 9). Seven of the 13 cases reported hospitalization, although it is unclear in two of the hospitalization cases the temporal relationship between the development of cellulitis and the use of the antifungal agent. There were no reports of death. Cellulitis affected the lower extremities (thigh, leg, ankle, foot and toe) in ten cases, and three cases did not describe the affected sites. One patient reported a history of diabetes. The appendix contains a narrative table for all 13 cases of cellulitis associated with the use of topical antifungal agents.

Table 2 provides characteristics of the cellulitis reports, and table 3 provides a breakdown and the rank order of the antifungal agents reporting cellulitis. To assist the reader we included the earliest year of approval of the topical antifungal agent, as well as the number of all adverse event reports for the agent found in the AERS database.

Table 2: Characteristics of Cellulitis Reports

Age Range: 25 to 82 years, median = 43 years, n = 10
 Gender: Female (8), male (5)
 Location: US (11), Foreign (2)
 Indications: Tinea Pedis (8), Tinea Cruris (1), Lupus Flare (1), Vitiligo (1),
 Dermatophytosis (1), NR²¹ (1)
 Onset: Range < 24 hours to 150 days, median = 1 day, n = 9
 Risk Factors: Diabetes (1)
 Outcome: Hospitalization (7), LT (1), Other (5)
 Event Year: 1986 (1), 1993 (1), 1998 (1), 1999 (1), 2000 (2), 2001 (3), 2002 (2), 2003 (1)
 NR (1)
 Site Affected: Ankle/Foot/Toe (7), Leg (2), Thigh (1), NR (3)

Table 3: Cellulitis Reports by Drug Product (crude AERS counts)

Drug Product	Earliest Year Approved	All Adverse Event Reports	# of Cellulitis Reports
Terbinafine	1992	1,204	5
Miconazole	1973	542	4
Betamethasone + clotrimazole	1984	591	1
Ketoconazole	1987	1,251	1
Tolnaftate	1965	42	1
Undecylenic Acid	1993	98	1

Discussion and Conclusion

Topical antifungal agents are available as both prescription and non-prescription OTC products to treat the dermatophyte infections of tinea pedis, tinea cruris and tinea corporis. The Office of Drug Safety was asked to query the AERS database for reports of lack of efficacy, and cellulitis associated with these products.

We selected 15 topical antifungal agents with an indication for dermatophyte infections for the search. Overall, of 4,741 adverse event reports associated with topical antifungal use, we found 1,663 reports of lack of efficacy, and 13 reports of cellulitis. Five agents accounted for the majority of the lack of efficacy reports. These five agents included terbinafine (484), ketoconazole (312), clotrimazole (297), miconazole (287) and the combination of betamethasone + clotrimazole (138). We did not find lack of efficacy reported for three agents (butenafine, sertaconazole, and chloroxylenol + undecylenic acid). Please note that sertaconazole, approved December 2003, had no reports in the AERS database at the time of this review.

Poorly treated lesions from interdigital dermatophyte infections (tinea pedis) may provide a means of bacterial entrance, contributing to an environment that supports the development of cellulitis. Therefore, cellulitis may not be a direct adverse event of antifungal agents. In the 13 cases of cellulitis reported with topical antifungal use, we found that two agents, terbinafine (5) and miconazole (4) were associated with the majority of the cellulitis adverse event reports. Seven of

²¹ NR = Not Reported

the 13 cases reported hospitalization as an outcome. There were no reports of death. Cellulitis affected the lower extremities (thigh, leg, ankle, foot and toe) in the majority of cases. One patient reported a history of diabetes. Although we found a small number of AERS reports, and cellulitis occurred after administration in some cases, the risk of cellulitis with the topical antifungal agents is unknown. The appendix contains a narrative table for all 13 cases of cellulitis associated with the use of topical antifungal agents.

The presence or absence of lack of efficacy reports in AERS cannot be the sole source to determine if a product is ineffective or effective. Additionally, we did not review the individual lack of efficacy cases to analyze other information, such as the most likely suspect agent, the dose, duration or proper use of these drugs, or other confounding factors which may have contributed to the adverse event. Consequently, the *crude numbers* that we reported in this review should be interpreted with caution.

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Concur,

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NDA: 17-619, 20-888, 20-889, 18-813, 17-613, 20-890, 20-749, 21-124, 20-524, 21-307, 18-827, 21-385, 18-748, 19-824, 20-519, 19-356, 19-599, 19-828, 20-209, 19-648, 18-751, 18-738

Electronic only cc:
HFD-400/Seligman
HFD-430/Avigan/Chen/Lee/Nguyen
HFD-540/Luke/Kozma-Fornaro/Owens
HFD-560/Ganley

Appendix: Cellulitis Cases Associated with Topical Antifungal Agents

	Product	Indication	Image #	Year	Location	Outcome	Concomitant Drugs	Narrative
1	Lamisil Topical	Tinea Pedis	975769	1993	US	Other	None	25 year old female developed an “allergic reaction with resultant cellulitis ” five days after starting Lamisil topical twice daily for interdigital tinea pedis.
2	Lamisil AT Athlete’s Foot Cream	Tinea Cruris	3443934-7	1999	US	Other	None	46 year old male used Lamisil AT for jock itch daily for one week. On the eight day of treatment the patient noticed a rash that spread 6 to 8 inches on his inner thighs. Lamisil AT was changed to oral antibiotic and topical clotrimazole. The patient’s physician felt the patient had developed either cellulitis or topical dermatitis while using the Lamisil AT cream. Prior to use of the Lamisil AT cream the patient had used tolnaftate without improvement. The patient’s condition cleared.
3	Lamisil Topical	“Lupus Flare”	3843612-6	2001	US	Hospitalization	Enbrel, Lamotrigrine, Lorazepam, Warfarin, Furosemide, Hydroxychloroquine, propranolol, calcium supplement	41 year old female with a history of lupus, hypertension and stroke was hospitalized for a severe skin reaction during the concomitant use of Enbrel and topical terbinafine. The patient used topical terbinafine for lupus flares. Approximately 10 days after terbinafine was started the patient developed toxic dermal necrolysis (TEN). Enbrel and topical terbinafine were discontinued, and the patient was hospitalized for treatment. Enbrel was not restarted. Approximately 4 to 5 months later the patient was re-hospitalized for “ cellulitis ” of her left ankle. The report is not clear if terbinafine was restarted prior to the 2 nd hospitalization, and diagnosis of cellulitis. The patient was treated with IV clindamycin. The physician believed the TEN was terbinafine induced, and related to exacerbation of lupus erythematous, and unrelated to Enbrel use. The patient was treated, and recovered.
4	Lamisil AT Athlete’s Foot Cream	Tinea Pedis	3526041-4	2000	US	Other	Prenatal Vitamin	A pregnant woman of unknown age used Lamisil AT to treat athlete’s foot characterized by itchiness, redness, cracked and scaly skin in between the last three digits of her right foot. The next morning after the first application, the woman experienced severe redness, pain and swelling at the application site. The physician diagnosed cellulitis . The patient was treated with amoxicillin, acetaminophen with codeine, and discontinuation of Lamisil AT. The patient’s condition improved.
5	Lamisil AT Spray Pump	Tinea Pedis	4004525-2	2002	Foreign	Other	Not Reported	A 40 year old woman used Lamisil AT Spray Pump once daily to treat tinea pedis. The length of use was unknown. Immediately after applying the spray the patient experienced a stinging sensation in both the feet and the hand used to apply to product. The stinging continued even after washing, and progressed to swollen and blistered hand and feet, with eventual bursting and weeping. The patient’s physician diagnosed cellulitis in the left leg, and prescribed antibiotics and an antihistamine.
6	Miconazole 2% (Desenex Spray Liquid)	Tinea Pedis	3991603-7	2002	US	Hospitalization	None	A 39 year old male was hospitalized for right toe cellulitis one day after using Desenex Spray Liquid for self-diagnosed athlete’s foot. The patient was treated with intravenous antibiotics, and surgical debridement. The physician initially thought the patient had suffered a chemical burn, but later diagnosed cellulitis , possibly due to picking between the toes with a wooden stick.
7	Miconazole Cream	Tinea Pedis	4256515-2	2003	Foreign	Hospitalization	Not Reported	An 82 year old woman used miconazole cream for athlete’s foot for six days. The patient developed aggravation of the erythema, fever, edema and heat on the left foot. The symptoms continued to worsen spreading along the vein to the back of the left knee. The patient was diagnosed with cellulitis . Miconazole cream was discontinued. The patient outcome was unknown. The hospitalization was due to a worsening of the patient’s Parkinson’s disease.
8	Miconazole (Desenex AF Spray Powder, Desenex AF Powder)	Tinea Pedis	3676965-2	2000	US	Hospitalization	Ibuprofen, Augmentin, Allegra, albuterol	A woman of unknown age developed acute leg swelling and infection. The patient was hospitalized for acute left leg cellulitis . The patient used the foot powder one day prior to her foot swelling. The patient has a history of talc powder allergy, which is found in the Desenex AF foot powder.
9	Miconazole (Lotrimin AF Spray Liquid, Lotrimin AF	Tinea Pedis	3858196-6	2001	US	Other	Not Reported	A 38 year old male used Lotrimin AF Spray liquid, and Lotrimin AF Spray Powder to treat athlete’s foot. Within 24 hours of application the patient experienced erythema, swelling, pain and exudative dermatitis. Cellulitis was also noted. The patient was treated with steroids, oral antibiotics and local compressions. The patient’s condition improved.

	Product	Indication	Image #	Year	Location	Outcome	Concomitant Drugs	Narrative
	Spray Powder)							
10	Betamethasone + Clotrimazole (Lotrisone)	Not Reported	3987977-3	2001	US	Hospitalization	Dilantin, Glucophage, Oxycontin, Buspar, Tricor, lorazepam, nystatin, Effexor, Hyzaar, Humulin N, Humulin R, Premphase, Famvir, Zyrtec, Humalog, Temazepam, Diflucan, Lotrisone, Wellbutrin, Trileptal, tobradex, Sonata, Actiq, Denavir, Patanol, Bactroban, Percocet, Cephalexin, Lida-Mantle, Clobetasol, Fluoxetine, Cobalamin, Rhinocort, Aygestin, Augmentin,	A 45 year old woman with a complicated medical history, including, but not limited to diabetes mellitus, taking multiple medications experienced drug addiction, drug withdrawal, mental anguish and pain while taking Oxycontin. The drug addiction and withdrawal were the adverse events stimulating the AE report by the patient's attorney. Prior to the onset of opiate addiction the patient was hospitalized for diabetic right foot and cellulitis . It is unclear in the report the time of Lotrisone use relative to the development of the diabetic right foot and cellulitis . While hospitalized the patient received intravenous antibiotics and Oxycontin. The report indicated that the foot ulcer healed. The rest of the report described adverse events attributed to Oxycontin use.
11	Ketoconazole	Vitiligo	3965993-5	NR	US	LT, Other	Simvastatin, erythromycin, ketoconazole topical, ketoconazole oral, hydrocortisone	A physician (the patient) developed aggravation of vitiligo, memory loss, hypothyroidism, myxedema, headache; severe keratoderma with secondary cellulitis , pruritus, and lividity, massive discoloration purpuric in appearance with components of petechiae after concomitantly using simvastatin, erythromycin, oral and topical ketoconazole. The patient attribute adverse events to simvastatin, and reported that when the simvastatin was stopped the keratoderma went away. The report is unclear of the location of the cellulitis, and the area of application of the ketoconazole cream.
12	Tolnaftate (Tinactin)	Dermatophytosis	447008	1986	US	Hospitalization	NR	A 70 year old male diagnosed with cellulitis secondary to dermatophytosis of the toe. Patient was using tolnaftate. Patient was hospitalized for one week, and treated with oxacillin and cephalothin. The patient's condition improved.
13	Undecylenate 25% (Desenex AF Spray Powder)	Tinea Pedis	3411826-5	1998	US	Hospitalization	Ziac	A 62 year old female was diagnosed with cellulitis , and hospitalized after using undecylenic acid 25% (Desenex AF Spray Powder) for athlete's foot. The patient's symptoms included severe pain, erythema, blister at application site and abscess. An x-ray of the foot revealed mild soft tissue swelling consistent with edema and cellulitis. The patient had a history of hypertension, gall bladder condition nos, peritoneal tube insertion.