

CLINICAL REVIEW

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Applicant Novartis Pharmaceuticals Corp.

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Formulation Oral Granules
Dosing Regimen Once daily for 6 weeks
Indication Tinea capitis due to a dermatophyte
Intended Population Children

Clinical Review
Patricia C. Brown, MD
NDA 22-071
LAMISIL® (terbinafine hydrochloride) Oral Granules

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Clinical Review
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LAMISIL® (terbinafine hydrochloride) Oral Granules

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends that Lamisil® (terbinafine hydrochloride) Oral Granules be approved for oral administration for the treatment of tinea capitis in subjects 4 years and older.

1.2 Recommendation on Post-Marketing Actions

1.2.1 Risk Management Activity

The standard risk management measures of prescription status, professional labeling, and spontaneous adverse event reporting are adequate risk management activities for this drug at this time.

1.2.2 Required Phase 4 Commitments

No Phase 4 commitments are necessary at this time.

1.2.3 Other Phase 4 Requests

No other Phase 4 requests are necessary.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Lamisil® Oral Granules are intended to be taken by mouth once a day for 6 weeks for the treatment of tinea capitis. Dosing is based on weight and is as follows:

<25 kg 125 mg/day
25-35 kg 187.5 mg/day
>35 kg 250 mg/day

The sponsor has submitted a 505(b)(1) application.

To support the indication, the sponsor has performed two pivotal, multi-center (US and foreign), Phase 3 trials to evaluate safety and efficacy. These trials, SFO327C 2301 and SFO327C 2302, hereinafter referred to as C2301 and C2302 had two arms, Lamisil® oral granules and an active comparator, griseofulvin. A total of 1549 subjects were randomized in these studies, 1040 to the

terbinafine oral granules and 509 to griseofulvin. Since two subjects were randomized to griseofulvin but received terbinafine in error, those subjects receiving terbinafine were 1042 and those receiving griseofulvin were 507. The Phase 2 program included 5 dose-finding trials only one of which, C2101 enrolling 16 subjects, was conducted with the final-to-be-marketed formulation. The remaining four trials, W352, L2306, T201, and T202 enrolled a total of 388 subjects. The safety database includes a total of 1058 subjects exposed to Lamisil oral granules in the two pivotal Phase 3 trials and the Phase 2 study CSFO327C 2101, hereinafter referred to as C2101. Other studies in the clinical development program include two single dose bioavailability studies, L2104 and C2303, and four drug interaction studies; SF W152, SF W153, SF W154, and SF W156.

1.3.2 Efficacy

The applicant has submitted data from two (Study 2301 and Study 2302) randomized, well controlled clinical trials to demonstrate the efficacy and safety of Lamisil® Oral Granules taken once daily for six weeks for the treatment of tinea capitis due to dermatophyte infection in subjects ages 4 to 12. Dosing was based on body weight to achieve 5-8mg/kg . Griseofulvin at the maximum labeled strength (10-20 mg/kg) was used as a comparator.

A total of 1042 subjects were exposed to the terbinafine oral granules and 507 to griseofulvin. The studies were multicenter, US and international, with 768 (49.6%) subjects in the pooled ITT population (all subjects randomized and receiving at least one dose of treatment) being from the US and 781 (50.4%) subjects from non-US sites. In the mITT (all ITT subjects who also had a positive culture at baseline) population 48% of the subjects in study C2301 were from the US and in study C2302 45% of subjects were from the US.

The duration of each of these trials was 10 weeks, with treatment occurring for 6 weeks. The primary efficacy endpoint was complete cure defined as negative KOH, negative culture, and no signs of disease at week 10.

In reference to primary endpoint results, for study C2301, terbinafine achieved superiority over griseofulvin (46.2% versus 34% with a p value of .0013) in the mITT population. In study C2302, superiority was not achieved and treatment effects were nearly the same (44% versus 43.5% with a p value of .9539). Results in the ITT population were consistent with those for the mITT population.

Employing stratification (for primary endpoint) by genus and species of fungal organism, for *T. tonsurans*, terbinafine showed a superior treatment effect as compared with griseofulvin in both studies 2301 and 2302, $\delta = 21.7$ and 11.2 for the two studies respectively. In study 2301 the treatment effect is almost twice that seen in study 2302. For *M. canis*, however, both studies 2301 and 2302 showed negative treatment effects favoring griseofulvin, $\delta = -11.3$ and -20.5 , respectively. These findings are of significance in view of the fact that in the U.S., *T. tonsurans*

is the predominant cause of tinea capitis, incidence estimated to be 90-95%.^{1,2} *M. canis* is the second most prevalent cause of tinea capitis, incidence estimated to be 1-5%.^{1,2}

1.3.3 Safety

To evaluate safety, the sponsor conducted two pivotal Phase 3 trials, C2301 and C2301 and one Phase 1 pharmacokinetic study, C2101. These three studies were conducted with the final-to-be marketed formulation. These three studies also were similar in population and indication studied. Design was also generally similar except that C2101 employed no control while the Phase 3 trials employed an active control, griseofulvin. Information from other trials, W352, L2306, T201 and T202 is considered supportive for safety, as these did not use the oral granule formulation, and generally studied different populations with different dosing regimens. The three principal safety studies enrolled a total of 1058 subjects who were exposed to the terbinafine oral granule formulation, 1042 in the pivotal studies and 16 in the Phase 1 study. For the pivotal studies, median duration of exposure was 42 days. For the Phase 1 study, all 16 patients finished the study, duration of treatment was 42 days and no instances of study drug discontinuation were reported. The 4 month safety update report was reviewed and did not contain new safety information.

No deaths were reported in the pivotal trials or in the dose finding trials. A total of ten serious adverse events involving 6 subjects occurred in the two pivotal trials. In the terbinafine groups, these included events of viral hepatitis, pneumonia, traumatic head injury, fever, nausea, scalp itching, scalp pain, traumatic cataract and traumatic glaucoma. In the griseofulvin group an episode of bacterial arthritis was noted. For 8 of 10 of these events in the terbinafine group a relationship to study drug appears unlikely. For two of them, scalp itching and scalp pain, a relationship to study drug in the terbinafine group is equivocal.

In the pooled pivotal trials, 17/1042 (1.6%) subjects in the terbinafine group and 6/507 (1.2%) subjects in the griseofulvin group experienced discontinuations of study drug for adverse events. In the terbinafine group more subjects experienced study drug discontinuations due to gastrointestinal disorders .6%, infections and infestations .3%, and skin and subcutaneous disorders .6% than in the griseofulvin group; .2%, 0%, and .2% respectively. In the griseofulvin group more subjects experienced study drug discontinuations due to investigations (abnormal) .6% than in the terbinafine group .1%. Subjects having adverse events leading to dose adjustment/temporary interruptions of study drug were 30/1042 (2.9%) in the terbinafine group and 15/507 (3%) in the griseofulvin group.

Overall, roughly the same percentage of subjects 52% (541/1042 exposed to terbinafine as those exposed to griseofulvin 49% (249/507) experienced adverse events. Adverse event rates

¹ Foster KW, Ghannon MA. Epidemiologic surveillance of cutaneous fungal infection in the United States from 1999 to 2002. *J. American Academy of Dermatology* 2004;50:748-752.

² Kenna ME, Elewski BE. A U.S. epidemiologic survey of superficial fungal diseases. *J. American Academy of Dermatology* 1996;39:539-542.

between the two study drugs were very similar, differing by less than three percent, across system organ class and preferred term. The most common adverse event across treatment groups was nasopharyngitis occurring in 9.6% of subjects (100/1042) exposed to terbinafine and 10.5% of subjects (53/507) of those exposed to griseofulvin. The second most common adverse event was headache occurring in 7.1% of subjects (74/1042) exposed to terbinafine and 7.7% (39/507) of those exposed to griseofulvin. The third most common adverse event was pyrexia occurring in 7.0% (73/1042) of those exposed to terbinafine and in 7.7% (30/507) of those exposed to griseofulvin.

Of subjects exposed to terbinafine 9.2% (96/1042) were assessed as having treatment related adverse events. Of subjects exposed to griseofulvin 8.3% (42/507) were assessed as having treatment related adverse events. Vomiting occurred in 1.6% (17/1042) of subjects on terbinafine as compared with 1.6% (8/507) of those on griseofulvin. Upper abdominal pain occurred in 1.2% (13/1042) of subjects on terbinafine as compared with 1.0% (5/507) of those on griseofulvin. Diarrhea occurred in 1.1% (11/1042) of subjects on terbinafine as compared with 1.0% (5/507) of those on griseofulvin. Headache occurred in 1.0% (10/1042) of subjects on terbinafine as compared with 1.4% (7/507) of those on griseofulvin. Nausea occurred in 1.0% (10/1042) of subjects on terbinafine as compared with 1.2% (6/507) of those on griseofulvin. Abdominal pain occurred in 1.0% (10/1042) of subjects on terbinafine as compared with .2% (1/507) of those on griseofulvin.

The most common adverse events suspected to be related to study drug and not in current Lamisil labeling include; increased weight, decreased weight, increased appetite, dizziness, hypoesthesia, somnolence, and insomnia. These were not included in the label since the evidence that the drug caused the effect was not strong. An additional three subjects having sore scalp may have been experiencing the effects of terbinafine on fungal organisms. Other adverse events reported in the safety population included neutropenia and elevated transaminases.

1.3.4 Dosing Regimen and Administration

The dosing regimen for Lamisil® Oral Granules is once a day for six weeks based on body weight as follows:

<25 kg	125 mg/day
25-35 kg	187.5 mg/day
>35 kg	250 mg/day

This is the dose that was studied in one Phase 2 trial, C2101, and in the pivotal Phase 3 trials, C2301 and C2302. In study C2101 the parent/guardian was instructed to put the terbinafine study medication into 1 teaspoon of pudding, administer to subject, and then follow with water. Subjects were instructed not to chew the medication but to swallow it whole. For trials C2301 and C2302, because the active comparator griseofulvin needed to be taken with food, all subjects

were instructed to take study medication with a meal. Instructions were to empty bottles containing terbinafine oral granules on to a tablespoon of pudding and the entire tablespoon was to be swallowed. The instructions specified that acidic foods (e.g. orange juice and grapefruit juice) must be avoided when taking study medication. This latter advice was necessary because the terbinafine is sensitive to acids and acidic food with pH such as orange juice or other fruit juices.

1.3.5 Drug-Drug Interactions

Studies for drug-drug interactions were not performed with the oral granule formulation.

Four randomized, open-label, single-dose studies were performed to assess the interaction of the already approved product, Lamisil® tablets, with fluconazole (SF W152), Cotrimoxazole DS (SF W153), zidovudine (SF W154) and theophylline (SF W156).

The proposed labeling for Lamisil® Oral Granules will follow that for the already approved product Lamisil® Tablets with the addition of the following statements:

The influence of terbinafine on the pharmacokinetics of fluconazole, trimethoprim, sulfamethoxazole, zidovudine or theophylline was not considered to be clinically significant.

Co-administration of a single dose of fluconazole (100mg) with a single dose of terbinafine resulted in a 52% and 69% increase in terbinafine C_{max} and AUC, respectively. Fluconazole is an inhibitor of CYP 2C9 and CYP 3A enzymes. Based on these findings, it is likely that other CYP 2C9 inhibitors (e.g. amiodarone) and CYP 3A inhibitors (e.g. ketoconazole) may also lead to a substantial increase in the systemic exposure (C_{max} and AUC) of terbinafine.

1.3.6 Special Populations

Pediatrics:

The indication for Lamisil® Oral Granules is tinea capitis which affects children primarily between ages 3 and 7.¹ Lamisil® Oral Granules is a new dosage form; therefore a pediatric assessment is required by the Pediatric Research Equity Act (PREA). In accord with the Best Pharmaceuticals for Children Act, the FDA issued a Pediatric Written Request (PWR) for terbinafine on December 28, 2001. This was amended July 14, 2003, October 17, 2003, March 16, 2006, and May 15, 2006.

Lamisil® Oral Granules were studied in two Phase 3 trials enrolling 1042 subjects, ages 4 to 12, having tinea capitis, and who were treated with Lamisil® oral granules (1021 at a known dose). Subjects received oral granules at the labeled dose for 6 weeks (mean exposure was 39.8 days, median was 42 days). The most common adverse reactions were nasopharyngitis, headache,

¹ Elewski BE. Tinea capitis: A current perspective. Continuing Medical Education. Journal Of American Academy of Dermatology 2000;42:1-20.

pyrexia, vomiting, upper respiratory tract infection, abdominal pain (including upper), and diarrhea.

Lamisil® Oral Granules were tested for safety and efficacy within the pediatric population across subgroups including age, race, and gender. Notable differences within and between these subgroups were not seen for efficacy or safety.

Pregnancy:

For the pivotal studies, females of childbearing potential (all post-menarche females) must have had a negative serum pregnancy test at entry and were required to use a medically acceptable contraception method during the study and for one month after termination of treatment. This is appropriate since there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and because treatment of tinea capitis can be postponed until after pregnancy is completed, it is recommended that LAMISIL® (terbinafine hydrochloride) Oral Granules not be initiated during pregnancy. The pregnancy category assigned is B.

Nursing Mothers:

Recommended labeling generally follows that for the already approved product, Lamisil® Tablets and is as follows: After oral administration, terbinafine is present in breast milk of nursing mothers. The ratio of terbinafine in milk to plasma is 7:1. Treatment with LAMISIL® Oral Granules is not recommended in nursing mothers.

Geriatric Use:

Recommended labeling generally follows that for the already approved product, Lamisil® Tablets and is as follows: LAMISIL® (terbinafine hydrochloride) Oral Granules has not been studied in geriatric patients.