療黴舒® 錠 250 毫克
Lamisil® Tablets 250 mg

NOVARTIS

衛署藥輸字第 019320 號

口服抗黴菌劑

成份與劑型：
Terbinafine hydrochloride 為 Lamisil 的主成分。
250 毫克錠劑（中有劃線）：
每錠中含有 250 毫克的 Terbinafine hydrochloride。
賦形劑請參閱“賦形劑”。
Lamisil 為口服錠劑。

適應症：
－甲癬（Onychomycosis）
－髮癬（Tinea capitis）
－嚴重且廣泛且經局部治療無效的皮膚黴菌感染
注意：不同於局部外用之療黴舒，口服療黴舒對花斑癬並無效。

劑量 / 使用方法：
本藥須由醫師處方使用。
治療時間（長短）須依感染之型態，及嚴重度而定。

兒童：
在 2 歲以下的小孩，沒有足夠資料顯示可以使用（通常＜ 12 公斤）。

小孩體重＜ 20 公斤	62.5 毫克（125 毫克半錠）	一天一次
小孩體重 20-40 公斤	125 毫克（125 毫克一錠）	一天一次
小孩體重＞ 40 公斤	250 毫克（125 毫克二錠）	一天一次

成人：
一天一次 250 毫克
治療時間：
皮膚感染
- 足癬（趾間性，厚皮性） 2-6 星期
- 體癬、股癬 2-4 星期
- 皮膚念珠菌感染 2-4 星期
- 感染之徵兆與症狀可能不會於黴菌治癒數週後完全消除。

頭皮、毛髮的感染
- 髮癬：4 星期
- 髮癬，主要發生於小孩身上。

甲癬（灰指甲）
- 大部份的病人，須進行 6~12 星期的治療療程。

手指甲甲癬（灰指甲）
- 大部份需要治療 6 星期。

腳趾甲甲癬（灰指甲）
- 大部份需要治療 12 星期
- 有些病人，其指甲長得慢，則須更長的時間。最理想的臨床效果會在停藥後及細菌培養檢查為陰性後的幾個月才看得到，這是與健康指甲生長的時間有關。

肝功能障礙：
Lamisil 錠劑禁忌使用於慢性或急性肝疾病患者（參閱“禁忌”和“警語及注意事項”）。

腎功能障礙：
Lamisil 錠劑使用於腎功能損害患者的研究尚未充份，因此不建議使用於這類患者（參閱“警語及注意事項”及“藥物動力學”）。

老年人：
沒有證據顯示老年人 (65 歲以上) 的劑量需不同於年輕病人的劑量，但老年人要服用 Terbinafine 時，必須考慮到原先已有腎或肝功能障礙的情況（參閱“警語及注意事項”）。

小孩：
2 歲以下沒有口服療黴舒的臨床證據，因此不建議使用。

給藥方式：
此錠劑需與水一起口服使用。最好在每天同一時間空腹或飯後服用。

禁忌：
對 Terbinafine 或療黴舒錠劑中之任何賦形劑過敏者。

慢性或急性肝疾病患者。

警語及注意事項：
肝功能
Lamisil 禁忌使用於慢性或急性肝病之患者。在服用 Lamisil 之前，應先進行肝功能檢查。不論先前患者是否曾患有肝病均可能發生肝毒性，因此，建議定期監測肝功能檢查（在治療後 4 至 6 週），若肝功能檢測值上升，則應立即停止服用 Lamisil。
以 Lamisil 錠劑治療的病患，曾有非常嚴重的肝臟衰竭之罕見病例報告（有些患者因此喪命，或需要進行肝臟移植）。在大部分的肝臟衰竭病例中，患者本身有嚴重的全身性潛伏病症（參閱“禁忌”和“藥物不良反應”）。必須警告服用 Lamisil 錠劑之病人，如果持續發生不明原因之噁心、食慾不振、疲勞、嘔吐、右上腹部疼痛，或黃疸、深色尿或淺色糞便之症狀必須立刻通知醫生。病人若發生上述症狀時，應立刻停藥，並進行肝功能檢查。
皮膚作用
服用 Lamisil 錠劑的病患曾有嚴重的皮膚反應（如 Stevens-Johnson 症候群、毒性表皮壞死、藥物出疹伴隨嗜酸性白血球增多症與全身性症狀）的極罕見病例報告。如果皮膚的出疹情形惡化，應立即中斷 Lamisil 的治療。由於 Terbinafine 的上市後經驗曾通報過會促進乾癬、皮膚紅斑性狼瘡與全身性紅斑性狼瘡，或是使之惡化，因此已經罹患乾癬或紅斑性狼瘡的病患應謹慎使用。
血液學作用
以 Lamisil 錠劑治療的病患曾有惡性血質（嗜中性白血球減少症、顆粒性白血球缺乏症、血小板減少症、全部血球減少症）的極罕見病例報告。病患因 Lamisil 治療而發生惡性血質的任何病因都必須評估，且要考慮可能要改變治療方式，包括停用 Lamisil 錠劑。
腎功能
腎功能障礙者（肌胺酸酐廓清率小於 50 毫升 / 每分鐘或血清肌胺酸酐大於 300 微莫耳 / 每公升）使用 Lamisil 錠劑的研究尚未充分，因此不建議使用（參閱“藥物動力學”）。
交互作用
體外與體內試驗顯示 terbinafine 會抑制 CYP2D6 代謝系統。因此，當病患同時服用經由 CYP2D6 代謝途徑之某些藥物，例如以下藥物類別中的某些成份，如：三環抗憂鬱劑 (TCAs)、交感神經 β 受體阻斷劑 (β-blockers)、選擇性 serotonine 再吸收抑制劑 (SSRIs)、抗心律不整藥（包括 1A、1B 及 1C 類）及乙型單胺氧化酶抑制劑，倘若此種藥物有狹窄範圍的治療濃度，須追蹤藥物血中濃度（參閱“交互作用”）。

交互作用：
所觀察到、需列入考量的交互作用
交互作用對於使用 Lamisil 的影響 Terbinafine 的血漿清除率會因為其他引起代謝之藥物而增加，或是會受到抑制細胞色素 P450 之藥物的抑制。如果必須同時服用上述之藥物，Lamisil 劑量需要相對地進行調整。
以下藥品會增加 terbinafine 的藥效或血漿濃度
Cimetidine 會減少 33% 的 terbinafine 清除率。
由於 fluconazole 對 CYP2C9 及 CYP3A4 這兩種酵素都有抑制作用，因而會使 terbinafine 的血中最高藥物濃度 (Cmax) 及曲線下面積 (AUC) 分別增加 52% 和 69%。當 terbinafine 同時併用其他能抑制 CYP2C9 和 CYP3A4 的藥物（如 ketoconazole 及 amiodarone）時，可能會發生類似的曝藥量增加現象。
以下藥品會減少 terbinafine 的藥效或血漿濃度
Rifampicin 增加 100% 的 terbinafine 清除率。
交互作用對其他藥品造成的影響
Terbinafine 會增加以下藥品的藥效或血漿濃度
咖啡因
Terbinafine 會減少靜脈注射咖啡因 19% 之清除率。
主要由 CYP2D6 代謝的化合物
經由體外及體內試驗顯示 terbinafine 會抑制藉由 CYP2D6 媒介的代謝反應。這個研究發現當與主要經由此酵素代謝的藥物併用，例如以下藥物類別中的某些成份：三環抗憂鬱劑 (TCAs)、交感神經 β 受體阻斷劑、選擇性 serotonine 再吸收抑制劑 (SSRIs)、抗心律不整藥（包括 1A、1B 及 1C 類）及乙型單胺氧化酶抑制劑，倘若此等藥物在血液中之治療濃度範圍較窄時，須謹慎留意（參閱“注意事項”）。
Terbinafine 會減少 desipramine 82% 之清除率。
在一項針對 dextromethorphan（止咳劑及 CYP2D6 探針性試藥）快速代謝型健康受試者的試驗中，terbinafine 平均可增加尿液中 dextromethorphan/dextrorphan 代謝比率達 16-97 倍。因此，terbinafine 可能會將 CYP2D6 快速代謝者（基因型 (genotype)）轉換成緩慢代謝表現型 (phenotype) 的狀態。
其他與 Lamisil 併用時沒有交互作用、或作用可忽略不計的藥物資訊
根據體外及健康受試者試驗結果，Terbinafine 幾乎不會抑制或誘導經由細胞色素 P450 代謝的藥品（如 terfenadine、triazolam、tolbutamide 或口服避孕藥）。除了那些由 CYP2D6 代謝藥物（參見如下）。
Terbinafine 不會影響 antipyrine 或 digoxin 的清除率。
Terbinafine 不會影響 fluconazole 的藥物動力學，且 terbinafine 與潛在共同藥物 cotrimoxazole (trimethoprim 和 sulfamethoxazole)、zidovudine 或 theophylline 之間，過去並未在臨床上發現相關的交互作用。
有些病人口服療黴舒與口服避孕藥一起服用，而有月經不規律現象的報告，雖然此不正常現象亦存在於只服用口服避孕藥者。

Terbinafine 會減少以下藥品的藥效或血漿濃度
Terbinafine 會增加 ciclosporin 15% 之清除率。
藥物與飲食間的交互作用
Terbinafine 的生體可用率會稍微受到食物影響（AUC 的增加量低於 20%），但其影響並未大到需要進行劑量調整。

具有懷孕能力的女性、懷孕、授乳及生育力
具有懷孕能力的女性
有些病人口服療黴舒與口服避孕藥一起使用，而有月經不規律現象的報告，雖然此不正常現象亦存在於只服用口服避孕藥者。
針對具有懷孕能力的女性，目前的數據並未提供特殊建議。
懷孕
胎兒毒性的動物實驗中，顯示無不良作用。因為懷孕者使用療黴舒的臨床經驗很少，因此建議懷孕婦女不要使用，除非使用療黴舒可能的好處大於可能的危險性。
授乳
Terbinafine 可能出現在乳汁中，口服使用療黴舒者不可授乳。
生育力
沒有來自人類用藥經驗的相關資訊。老鼠的生育試驗顯示生育或繁殖表現上沒有不良現象。

藥物不良反應：
表 1 為臨床試驗和上市後經驗中發生的藥物不良反應，依 MedDRA 的系統器官分類列出。於每個系統器官類別，依資料庫中不良反應發生的頻率排序，首先列出的是最常發生的不良反應。每個頻率分組的不良反應，依嚴重度遞減來列出。此外，每個不良反應發生頻率依下列的定義來分類（CIOMS III）：很常見（≧ 1/10），常見（≧ 1/100，＜ 1/10），不常見（≧ 1/1,000，＜ 1/100），罕見（≧ 1/10,000，＜ 1/1,000），非常罕見（≧ 1/10,000）。

表 1　臨床試驗和上市後經驗中發生的藥物不良反應

血液和淋巴系統的問題	
不常見	貧血
非常罕見	嗜中性白血球減少症，顆粒性白血球缺乏症，血小板減少症，全部血球減少症
免疫系統的問題	
非常罕見	過敏性反應（包括血管水腫），皮膚及全身性紅斑性狼瘡
精神方面的問題	
常見	沮喪
不常見	焦慮
神經系統及精神疾病之問題	
很常見	頭痛
常見	味覺干擾 * 包括味覺喪失 *，頭暈
不常見	感覺異常，感覺遲鈍
眼睛視力方面的問題	
常見	視覺損傷
耳朵和內耳方面的問題	
不常見	耳鳴
胃腸道的問題	
很常見	胃腸道症狀（腹脹、食慾下降、消化不良、噁心、輕微的腹痛、腹瀉）
肝膽的問題	
罕見	肝衰竭，肝炎，黃疸，膽汁淤積，肝酶增加（參閱“警語及注意事項”）
皮膚及皮下組織的問題	
很常見	出疹、蕁麻疹
不常見	光敏感反應
非常罕見	Stevens-Johnson 症候群、毒性表皮壞死、急性全身性膿疱疹、多形性紅斑、毒性皮膚疹、剝脫性皮炎、水泡性皮炎 癬狀皮疹或牛皮癬惡化 落髮
肌肉骨骼、結締組織的問題	

很常見	肌肉骨骼的反應（關節疼痛、肌肉痛）
一般異常和投藥部位狀況	
不常見	發燒
常見	疲倦
調查研究	
不常見	體重下降 **

* 味覺干擾，包括味覺喪失，通常在藥物中止後幾個星期內就會恢復。曾有個案發生長時間的味覺干擾。
** 由於味覺干擾造成體重下降。

自發性通報及文獻個案中的藥物不良反應（發生頻率未知）

以下藥物不良反應係來自 Lamisil 上市後經驗（依據自發性通報病例與文獻個案）。由於這些自願性通報不良反應的族群大小未定，進而無法確實估計發生頻率，因此歸類為頻率未知。各項藥物不良反應係依 MedDRA 系統器官分類逐項列出。於每個系統器官類別的不良反應，依嚴重度遞減來列出。

表 2　自發性通報及文獻個案中的藥物不良反應（發生頻率未知）

免疫系統異常：過敏反應、類血清病反應（serum sickness-like reaction）
神經系統異常：嗅覺喪失症（包括永久的嗅覺喪失）、嗅覺減退
眼睛異常：視覺模糊、視力降低
耳部及迷路異常：聽力減退、聽覺受損
血管異常：血管炎
皮膚及皮下組織異常：藥物出疹伴隨嗜酸性白血球增多症與全身性症狀
胃腸道異常：胰臟炎
肌肉骨骼及結締組織異常：橫紋肌溶解症
一般異常及使用部位異常：類流感
檢查值異常：血中肌酸磷酸激酶增加

藥物過量：

有少數藥物過量的個案報告，曾用到 5 公克。在人體表現的副作用反應，主要是頭痛、噁心、上腹痛及頭昏。藥物過量的建議治療方式為持續排出藥物，主要方法可給予活性碳來除去藥物或必要時採取解除症狀的支持性治療。

臨床藥理學：

作用機轉

Terbinafine 是屬於 Allylamine 類藥物，於皮膚、頭髮及指甲具廣效抗黴菌作用，其中包含皮癬菌（Dermatophytes）如 Trichophyton（e.g. T. rubrum、T. mentagrophytes、T. verrucosum、T. tonsurans、T. violaceum），小芽胞癬菌屬（Microsporum）（e.g. M. canis）、Epidermophyton floccosum，與念珠菌類之酵母菌（e.g. C. albicans）及皮屑芽胞菌屬（Malassezia）。對於皮癬菌（Dermatophytes）、菌絲黴菌（Moulds）與某些同質二形性黴菌（Dimorphic Fungi），terbinafine 在低濃度即有殺黴菌作用（Fungicidal）。對於酵母菌類（Yeasts）的作用，則依不同的菌種而有殺黴菌或抑黴菌作用（Fungistatic）。

Terbinafine 可干擾黴菌麥角硬脂醇（Ergosterol）早期之生合成，導致麥角硬脂醇之不足及細胞內積聚很多的 Squalene，然後造成黴菌細胞的死亡。Terbinafine 是抑制了黴菌細胞膜上的 Squalene epoxidase，而此酵素（Squalene epoxidase）的作用與細胞色素 P450 系統（Cytochrome P450 System）並無相關。

藥效學

口服 Terbinafine 後，其集中於皮膚、頭髮、指甲上的藥品濃度和殺黴菌的作用有關。

藥物動力學

吸收

口服 terbinafine 後的吸收程度良好（>70%）。單一口服劑量 250 毫克的 terbinafine 可以在服用後 1.5 小時達到 1.3 微克 / 毫升（microgram/mL）的平均最高血中濃度。在穩定狀態中（在約 28 天達到穩定狀態濃度的 70%），terbinafine 的高峰濃度相較於單一劑量平均高出了 25%，且血漿 AUC 增加了 2.3 倍。

分佈

Terbinafine 與血漿蛋白結合很強，可達 99%，能藉著快速擴散作用，穿透真皮層而集中在親脂性的角質層中。Terbinafine 也可經由皮脂分泌，因此在毛囊、頭髮與皮脂多的皮膚中，可達到相當高的濃度，臨床也證實在治療的最初幾個星期，Terbinafine 已可達到指甲內。

生物轉化 / 代謝

Terbinafine 可快速且廣泛地被至少 7 種 CYP 酵素所代謝，主要代謝酵素為 CYP2C9, CYP1A2, CYP3A4, CYP2C8 和 CYP2C19。生體轉化後的代謝物，不具有抗黴菌作用。

排除

代謝物主要由尿液排泄。從血漿 AUC 的增加，可以計算藥效半衰期約為 30 小時。多劑量給藥後將延長採血，結果顯示三相式的藥物排除，終半衰期為 16.5 天左右。

生體可用率

Lamisil 錠劑經過首次代謝後，terbinafine 的絕對生體可用率約為 50%。

特殊族群

並未發現在穩定狀態的 terbinafine 血漿濃度與年齡的變化有臨床上之相關性。

在對腎功能障礙患者（肌胺酸酐廓清率小於 50 毫升 / 每分鐘）或已有肝功能疾病的患者做單一劑量的藥物動力學研究中顯示，Lamisil 的廓清率有可能降低約 50%。

臨床試驗：

甲癬

針對甲癬的治療，在美國 / 加拿大有三項以安慰劑對照、感染手指甲及 / 或腳趾甲的臨床試驗 (SFD301、SF5、SF1508)，參與病患在治療上的反應說明了 Lamisil 錠劑的療效。

第一項腳趾甲試驗在第 48 週 (治療 12 週、療程完成後追蹤 36 週) 進行評估，結果顯示有 70% 的病患治癒黴菌，其定義係指氫氧化鉀與培養同時出現陰性。59% 的病患顯示治療效果 (黴菌治癒且牽連 0% 的指甲、或新長出的無黴菌指甲 >5mm)；38% 的病患證實治癒黴菌、臨床上也已痊癒 (牽連 0% 的指甲)。

第二項皮癬性甲癬的腳趾甲試驗也同時培養非皮癬菌，證實具有類似的抗皮癬菌療效。目前尚未建立皮癬性甲癬存在時的非皮癬菌病理培養機轉。目前無從得知這類相關性的臨床意義。

手指甲的試驗在第 24 週 (治療 6 週、療程完成後追蹤 18 週) 評估，結果顯示 79% 的病患已治癒黴菌，75% 的病患具備有效治療，59% 的病患不但治癒黴菌、臨床上也已痊癒。

第一項腳趾甲試驗的甲癬成功治療時間平均約 10 個月，手指甲試驗為 4 個月。在第一項腳趾甲試驗中，在病患達成臨床治癒後至少 6 個月、完成 Lamisil 療程後至少 1 年進行評估，臨床復發率約 15%。

髮癬

在 SF 8001、SFE 304、SF 8002 等三項比較性療效試驗中，共有 117 位可評估病患接受口服的 Lamisil (每天 62.5 – 250 mg)，其中 97% 是兒童。每日晚餐後給予單一劑量，持續 4 週 (Lamisil) 或 8 週 (griseofulvin)。療效於 8 週後以及追蹤檢查 (試驗 SF 8001 與 SFE 304 為第 12 週、試驗 SF 8002 為第 24 週) 時評估，以黴菌檢測陰性與症狀學減輕予以證實。在三項試驗中，服用 Lamisil 的病患有 85%、88% 和 72% 在追蹤時達到黴菌檢測結果陰性 – griseofulvin 的對應數字為 73%、89% 和 69%。在接受 Lamisil 治療的病患中，有 82%、78% 和 69% 達到衍生變數「有效治療」(黴菌陰性加上無症狀與徵象、或只有輕微程度)，相較之下服用 griseofulvin 的病患為 66%、74% 和 59%；試驗 SF 8001 的結果具統計上顯著差異，且對 Lamisil 有利。

有兩項第二期藥效與治療時間關係的研究 (treatment duration study)、共 342 名髮癬病患 (多為兒童) 的試驗已經完成。美國與加拿大針對感染 Trichophyton 髮癬的兒童進行一項為期 12 週、隨機分配、雙盲、平行分組的試驗 (SFO327C T201)。試驗目標為判定 Lamisil 治療 (錠劑) 的理想週期 (1、2 或 4 週) 與安全性，劑量依體重調整、每天一次。

第二項試驗為歐洲針對感染小芽胞癬菌髮癬 (>4 歲) 的病患進行一項為期 16 週、隨機分配、有效對照、平行分組的多中心試驗。Lamisil 的治療週期組 (6、8、10 和 12 週) 為雙盲，而 griseofulvin 活性對照組為開放標示 (SFO327C T202)。試驗目標係針對感染小芽胞癬菌的髮癬病患，找出安全的 Lamisil (錠劑) 最適治療週期。Lamisil 在兩項試驗中是以體重作為給藥劑量的基礎，方式如下：<20kg：62.5 mg，20-40 kg：125 mg，>40 kg：250mg，每天一次。Lamisil 在兩項試驗中均耐受良好。分析療效數據之後，顯示 2 週和 4 週的治療週期對於 Trichophyton 菌屬感染造成的髮癬均能提供良好療效。在小芽胞癬菌的試驗中，不同治療週期組之間的完全治癒率並無明顯差異，完全治癒率最高 (62%) 的是 6 週的療程，耐受性與順應性良好。這些結果都顯示出相較於 griseofulvin 的標準療程，Lamisil 能夠將 Trichophyton 菌屬感染的髮癬從 6-8 週的治療週期降低至僅需 2-4 週。

在針對髮癬執行的第二期臨床試驗中，588 名招募兒童通報的通常是輕微而相對少見的不良反應，而且通常與治療沒有特定的關係。有 11 人通報出血清丙胺酸轉胺酶 (SGPT) 濃度上升，1 人喪失味覺。其他事件包括輕度的胃腸道症狀或皮膚症狀、以及實驗室檢查顯示有併發感染的現象。

針對皮膚黴菌感染 (體癬、股癬、足癬) 和念珠菌屬 (例如白色念珠菌) 造成的皮膚酵母菌感染，由於感染的部位、嚴重性或範圍之故，一般咸認適用口服療程

在 5OR (4 週試驗)、6-7OR (4 週試驗) 和 11-21OR (6 週試驗) 等三項對照、雙盲、隨機分配的多中心試驗中，評估 Lamisil 錠劑對於治療體癬和股癬的療效和安全性。

有兩項雙盲、以安慰劑為對照的試驗 (5OR、6-7OR) 係針對診斷體癬 / 股癬的病患，評估 Lamisil 125 mg、每天兩次 (b.i.d) 的療效。試驗包括隨機分配至 Lamisil 的病患共 46 人、安慰劑 49 人。各組之間的人口統計和免疫記憶數據並無顯著差異。療效於 4 週後以及追蹤檢查時進行評估，以黴菌檢測陰性與臨床症狀學減輕予以證實。這兩項試驗證實了口服 Lamisil 在療程結束和追蹤時的療效，相較之下接受安慰劑治療的病患幾乎不具有療效。

第三項試驗 (11-21OR) 是一項為期 6 週、雙盲、隨機分配的多中心試驗，比較 Lamisil 125mg b.i.d. 和 griseofulvin 250mg b.i.d 的療效和安全性。每組納入 126 名病患進行療效分析。本試驗顯示接受 Lamisil 治療的試驗組具有高度的黴菌治癒率、徵象與症狀皆有所減少，Lamisil 125mg b.i.d. 在療程結束與追蹤時的整體療效也明顯更佳 (93-94%)，相較之下對照組的整體療效為 86-87%。

簡而言之，在上文治療體癬 / 股癬的主要療效試驗中，服用 4-6 週的 Lamisil 125mg b.i.d. 經統計證實具有比安慰劑和上市藥物 griseofulvin 更優越的療效。

在一項雙盲、以安慰劑為對照的 4 週試驗 SF 00438 中，針對皮膚念珠菌病的病患比較 Lamisil 125 b.i.d 與安慰劑。每個治療組隨機分配 22 名病患，並分別評估其中 19 人。在治療結束時，有 29% 的治療組病患與 17% 的安慰劑病患證實已治癒黴菌，67% 的 Lamisil 治療病患在追蹤結束時黴菌結果為陰性。考慮到上文的反應率，Lamisil 療程的最短治療週期應該要有 2 週，同時大約一半的病患需治療 3-4 週才能達成治癒。

關於足癬的治療，有兩項雙盲對照試驗比較了 Lamisil 125mg b.i.d. 與安慰劑 (39-40OR) 及 griseofulvin 250mg b.i.d (20OR)。兩項試驗均招募慢性復發性疾病的病患。在試驗 39-40OR 中，有 65% 的 Lamisil 病患在追蹤時通報黴菌治癒，以安慰劑治療的病患卻沒有反應。試驗 20OR 顯示 Lamisil 具有高度的療效，6 週療程後有 88% 的病患於追蹤時已治癒，相較之下 griseofulvin 的病患為 45%。10 個月後再觀察這些病患，通報出 94% 的治癒率，相較之下相同病患族群的 griseofulvin 療效為 30%。

表 3　主要療效試驗－體癬 / 股癬、足癬、念珠菌感染

試驗	類型	藥物	可評估病患人數	退出人數	黴菌結果陰性 %		臨床結果 %	
					療程結束	追蹤	療程結束	追蹤
5OR	4 週 DB- 安慰劑	Lamisil 125 b.i.d	13	4	64	89	54	62
		安慰劑	15	2	0	0	0	0
6-7OR	4 週 DB- 安慰劑	Lamisil 125 b.i.d	33	8	97	97	85	91
		安慰劑	34	6	29	36	12	12
11-21	6 週 125 b.i.d.	Lamisil 125 b.i.d	126	13	95	100	93	94
OR	DB-Griseofulvin	Griseofulvin 250 b.i.d	126	16	88	94	87	86
SF	2 週 DB- 安慰劑	Lamisil 125 b.i.d	19	3	29	67	11	47
00438		安慰劑	19	3	17	47	11	11
39-40	6 週 125 b.i.d.	Lamisil 125 b.i.d	23	3	68	77	59	65
OR	DB- 安慰劑	安慰劑	18	6	13	0	0	0
20OR	6 週 125 b.i.d.	Lamisil 125 b.i.d	16	2	94	100	75	88
	DB-Griseofulvin	Griseofulvin 250 b.i.d	12	6	27	55	27	45

非臨床安全性數據：

在老鼠和狗的長期試驗（為期 1 年）中，在高達每天 100 毫克 / 公斤的口服劑量下，兩個物種都沒有見到顯著的毒性。口服高劑量下，肝臟和腎臟，經顯示為可能的目標器官。

在一項為期二年的小白鼠口服致癌性的試驗中，在每天 130（雄性）及 156（雌性）毫克 / 公斤的劑量下，顯示沒有因治療所造成的腫瘤或其他的異常結果。在為期二年的大白鼠口服致癌性的試驗中，在每天 69 毫克 / 公斤的最高劑量下，觀察到雄性的肝腫瘤發生率會增加。此項變化，可能與細胞酵小體的增生有關，已經證明具物種特定性，因為在小白鼠、狗、或猴子的致癌性或其他的試驗中並沒有見到。

在猴子的高劑量試驗期間，於較高的劑量下（無毒性濃度 50 毫克 / 公斤）可觀察到網膜中不規則的折射。這些不規則性現象與眼球組織中出現的 terbinafine 代謝物有關，並在停藥之後消失。它們與組織學的變化無關。

在一項為期八週的幼鼠口服無毒性濃度（no-toxic-effect level, NTEL）試驗中，每日劑量接近 100 毫克 / 公斤，只發現肝臟重量稍微增加，而於每日給予成犬≧ 100 毫克 / 公斤時（AUC 值相當於兒童的 13 倍（雄性）及 6 倍（雌性）），觀察到中樞神經系統障礙的症狀包括各別動物發生痙攣的單一症狀。在成鼠或猴子靜脈注射 terbinafine 時也發現類似情形。

在標準的體外和體內的遺傳毒性的試驗組合中，沒有證據顯示有導致突變或細胞分裂的可能。

在大白鼠或兔子的試驗中沒有觀察到有任何在生育力或其他生殖方面的不良反應。

賦形劑：

magnesium stearate、silica colloidal anhydrous、hydroxypropylmethyl cellulose、microcrystalline cellulose、sodium carboxymethyl starch.

不可調配性：

未知

貯存：

須避光貯存於 30℃以下，請參閱外盒說明。

藥物超過有效期，不可再使用，其有效期限會印製在包裝上。

使用及處置指示：

Lamisil 須放在小孩拿不到及看不到的地方。

製造廠：Novartis Pharma Produktions GmbH
Öflinger Strasse 44, 79664 Wehr, Germany
藥　商：台灣諾華股份有限公司
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Information issued: 22-Dec-2015
TWI-070116

Lamisil® tablets 250mg

NOVARTIS

Oral antifungal agent

Description and Composition

Pharmaceutical form

Tablets (scored) for oral administration.

Active substance

Terbinafine hydrochloride.

250 mg tablets (scored): Each tablet contains 250 mg terbinafine as the hydrochloride.

Active moiety

Terbinafine

Excipients

250 mg: magnesium stearate; silica colloidal anhydrous; hydroxypropylmethyl cellulose; microcrystalline cellulose; sodium carboxymethyl starch.

Indications

- Onychomycosis.
- Tinea capitis.
- Fungal infections of the skin where oral therapy is generally considered appropriate owing to the site, severity or extent of the infection.

Note: In contrast to topical Lamisil, oral Lamisil is not effective in pityriasis versicolor.

Dosage and administration

The duration of treatment varies according to the indication and the severity of the infection.

Children

No data are available in children under two years of age (usually <12 kg).

Children weighing	<20 kg	62.5 mg	(half a 125 mg tablet) once daily
Children weighing	20 to 40 kg	125 mg	(one 125 mg tablet) once daily
Children weighing	>40 kg	250 mg	(two 125 mg tablets) once daily

Adults

250 mg once daily.

Skin infections

Recommended duration of treatment:

- Tinea pedis (interdigital, plantar/moccasin type): 2 to 6 weeks.
- Tinea corporis, cruris: 2 to 4 weeks.
- Cutaneous candidiasis: 2 to 4 weeks.

Complete resolution of the signs and symptoms of infection may not occur until several weeks after mycological cure.

Hair and scalp infections

Recommended duration of treatment:

- Tinea capitis: 4 weeks.

Tinea capitis occurs primarily in children.

Onychomycosis

For most patients the duration of successful treatment is 6 to 12 weeks.

Fingernail onychomycosis

Six weeks of therapy is sufficient for fingernail infections in most cases.

Toenail onychomycosis

Twelve weeks of therapy is sufficient for toenail infections in most cases.

Some patients with poor nail outgrowth may require longer treatment. The optimal clinical effect is seen some months after mycological cure and cessation of treatment. This is related to the period required for outgrowth of healthy nail.

Special populations

Hepatic impairment

Lamisil tablets are not recommended for patients with chronic or active liver disease (see section WARNINGS AND PRECAUTIONS).

Renal impairment

The use of Lamisil tablets has not been adequately studied in patients with renal impairment and is therefore not recommended in this population (see section WARNINGS AND PRECAUTIONS and section PHARMACOKINETICS (PK)).

Geriatric patients

There is no evidence to suggest that elderly patients (aged 65 years and above) require different dosages or experience different side effects than younger patients. When prescribing Lamisil tablets for patients in this age group, the possibility of pre-existing impairment of liver or kidney function should be considered (see section warnings and precautions).

Pediatric patients

No data are available in children under two years of age.

Method of administration

The scored tablets are taken orally with water. They should preferably be taken at the same time each day and can be taken on an empty stomach or after a meal.

Contraindications

Known hypersensitivity to terbinafine or to any of the excipients of Lamisil tablets.

Warnings and precautions

Liver function

Lamisil tablets are not recommended for patients with chronic or active hepatic disease. Before prescribing Lamisil tablets, liver function tests should be performed. Since hepatotoxicity may occur in patients with and without pre-existing liver disease. Therefore periodic monitoring (after 4-6 weeks of treatment) of liver function tests is recommended. Lamisil should be immediately discontinued in case of elevation of liver function tests. Very rare cases of serious liver failure (some with a fatal outcome, or requiring liver transplant) have been reported in patients treated with Lamisil tablets. In the majority of hepatic failure cases the patients had serious underlying systemic conditions and a causal association with the intake of Lamisil tablets was uncertain (see section ADVERSE DRUG REACTIONS). Patients prescribed Lamisil tablets should be warned to report immediately any symptoms of unexplained persistent nausea, decreased appetite, fatigue, vomiting, right upper abdominal pain, or jaundice, dark urine or pale feces. Patients with these symptoms should discontinue taking oral terbinafine and the patient's hepatic function should be immediately evaluated.

Dermatological effects

Serious skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms) have been very rarely reported in patients taking Lamisil tablets. If progressive skin rash occurs, treatment with Lamisil tablets should be discontinued.

Terbinafine should be used with caution in patients with pre-existing psoriasis or lupus erythematosus as precipitation and exacerbation of psoriasis and cutaneous and systemic lupus erythematosus have been reported in a post-marketing setting.

Haematological effects

Very rare cases of blood dyscrasias (neutropenia, agranulocytosis, thrombocytopenia, pancytopenia) have been reported in patients treated with Lamisil tablets. Etiology of any blood dyscrasias that occur in patients treated with Lamisil tablets should be evaluated and consideration should be given for a possible change in medication regimen, including discontinuation of treatment with Lamisil tablets.

Renal function

In patients with renal impairment (creatinine clearance less than 50 mL/min or serum creatinine of more than 300 micro mol/L) the use of Lamisil tablets has not been adequately studied, and therefore, is not recommended (see section PHARMACOKINETICS (PK)).

Interactions

In vitro and *in vivo* studies have shown that terbinafine inhibits the CYP2D6 metabolism. Therefore, patients receiving concomitant treatment with drugs predominantly metabolized by CYP2D6, e.g. certain members of the following drug classes, tricyclic antidepressants (TCAs), beta-blockers, selective serotonine reuptake inhibitors (SSRIs), antiarrhythmics (including class 1A, 1B and 1C) and monoamine oxidase inhibitors (MAO-Is) Type B, should be followed up, especially if the co-administered drug has a narrow therapeutic window (see section INTERACTIONS).

Interactions

Observed interactions to be considered

Interactions affecting the use of Lamisil

The plasma clearance of terbinafine may be accelerated by drugs, which induce metabolism and may be inhibited by drugs, which inhibit cytochrome P450. Where co-administration of such agents is necessary, the dosage of Lamisil tablets may need to be adjusted accordingly.

The following medicinal products may increase the effect or plasma concentration of terbinafine

Cimetidine decreased the clearance of terbinafine by 33%.

Fluconazole increased the Cmax and AUC of terbinafine by 52% and 69% respectively, due to inhibition of both CYP2C9 and CYP3A4 enzymes. Similar increase in exposure may occur when other drugs which inhibit both CYP2C9 and CYP3A4 such as ketoconazole and amiodarone are concomitantly administered with terbinafine.

The following medicinal products may decrease the effect or plasma concentration of terbinafine

Rifampicin increased the clearance of terbinafine by 100%.

Interactions resulting in effects on other medicinal products

Terbinafine may increase the effect or plasma concentration of the following medicinal products

Compounds predominantly metabolized by CYP2D6

In vitro and in vivo studies have shown that terbinafine inhibits the CYP2D6-mediated metabolism. This finding may be of clinical relevance for compounds predominantly metabolized by CYP2D6, e.g. certain members of the following drug classes, tricyclic antidepressants (TCAs), beta-blockers, selective serotonine reuptake inhibitors (SSRIs), antiarrhythmics (including class 1A, 1B and 1C) and monoamine oxidase inhibitors (MAO-Is) Type B, especially if they also have a narrow therapeutic window (see section warnings and precautions).

Terbinafine decreased the clearance of desipramine by 82% (see section WARNINGS AND PRECAUTIONS).

In studies in healthy subjects characterized as extensive metabolizers of dextromethorphan (antitussive drug and CYP2D6 probe substrate), terbinafine increased the dextromethorphan/dextrorphan metabolic ratio in urine by 16- to 97-fold on average. Thus, terbinafine may convert extensive CYP2D6 metabolizers (genotype) to poor metabolizer phenotype status.

Caffeine

Terbinafine decreased the clearance of caffeine administered intravenously by 19%.

Information on other drugs concomitantly used with Lamisil resulting in no or negligible interactions

According to the results from studies undertaken in vitro and in healthy volunteers, terbinafine shows negligible potential for inhibiting or enhancing the clearance of most drugs that are metabolized via the cytochrome P450 system (e.g. terfenadine, triazolam, tolbutamide or oral contraceptives) with exception of those metabolized through CYP2D6 (see below).

Terbinafine does not interfere with the clearance of antipyrine or digoxin.

There was no effect of terbinafine on the pharmacokinetics of fluconazole. Further there was no clinically relevant interaction between terbinafine and the potential comedications cotrimoxazole (trimethoprim and sulfamethoxazole), zidovudine or theophylline.

Some cases of menstrual irregularities have been reported in patients taking Lamisil tablets concomitantly with oral contraceptives, although the incidence of these disorders remains within the background incidence of patients taking oral contraceptives alone.

Terbinafine may decrease the effect or plasma concentration of the following medicinal products

Terbinafine increased the clearance of ciclosporin by 15%.

Drug-food/drink interactions

The bioavailability of terbinafine is moderately affected by food (increase in the AUC of less than 20%), but not sufficiently to require dose adjustments.

Women of child-bearing potential, pregnancy, breast-feeding and fertility

Women of child-bearing potential

Some cases of menstrual irregularities have been reported in patients taking Lamisil tablets concomitantly with oral contraceptives, although the incidence of these disorders remains within the background incidence of patients taking oral contraceptives alone.

There are no data to support special recommendations for women of child-bearing potential.

Pregnancy

Foetal toxicity studies with terbinafine in animals suggest no adverse effects. Since documented clinical experience in pregnant women is very limited, Lamisil tablets should not be used during pregnancy unless the potential benefits outweigh any potential risks.

Breast-feeding

Terbinafine is excreted in breast milk; mothers receiving oral treatment with Lamisil should therefore not breast-feed.

Fertility

There is no relevant information from human experience. Fertility studies in rats indicated no adverse findings in fertility or reproductive performance.

Adverse drug reactions

Adverse drug reactions from clinical trials or post-marketing experience (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000)

Table 1 Adverse drug reactions from clinical trials and post-marketing experience

Blood and lymphatic system disorders	
Uncommon	Anemia
Very rare	Neutropenia, agranulocytosis, thrombocytopenia, pancytopenia.
Immune system disorders	
Very rare	Anaphylactoid reactions (including angioedema), cutaneous and systemic lupus erythematosus.
Psychiatric disorders	
Common:	Depression
Uncommon:	Anxiety
Nervous system disorders	
Very common	Headache
Common:	Dysgeusia* including ageusia*, dizziness.
Uncommon	Paresthesia and hypoesthesia
Eye disorders	
Common:	Visual impairment
Ear disorders	
Uncommon;	Tinnitus
Gastrointestinal disorders	
Very common	Gastrointestinal symptoms (abdominal distension, decreased appetite, dyspepsia, nausea, mild abdominal pain, diarrhea).
Hepatobiliary disorders	
Rare	Hepatic failure, hepatitis, jaundice, cholestasis, hepatic enzyme increased (see section WARNINGS AND PRECAUTIONS)
Skin and subcutaneous tissue disorders	
Very common	rash, urticaria.
Uncommon:	Photosensitivity reaction
Very rare	Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis), erythema multiforme, toxic skin eruption, dermatitis exfoliative, dermatitis bullous.
	Psoriasiform eruptions or exacerbation of psoriasis.
	Alopecia
Musculoskeletal and connective tissue disorders	
Very common	Musculoskeletal reactions (arthralgia, myalgia).
General disorders	
Uncommon:	Pyrexia
Common:	Fatigue.
Investigations	
Uncommon:	Weight decreased**

* Hypogeusia, including ageusia, which usually recover within several weeks after discontinuation of the drug. Isolated cases of prolonged hypogeusia have been reported.

** Weight decreased secondary to dysgeusia.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Lamisil via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Immune system disorders
Anaphylactic reaction, serum sickness-like reaction.
Nervous system disorders
Anosmia including permanent anosmia, hyposmia.
Eye disorders
Vision blurred, visual acuity reduced.
Ear and labyrinth disorders
Hypoacusis, impaired hearing
Vascular disorders
Vasculitis.
Gastrointestinal disorders
Pancreatitis.
Skin and subcutaneous tissue disorders
Drug rash with eosinophilia and systemic symptoms.
Musculoskeletal and connective tissue disorders
Rhabdomyolysis.
General disorders and administration site conditions

Influenza-like illness.

Investigations

Blood creatine phosphokinase increased.

Overdosage

A few cases of overdosage (up to 5 g) have been reported, giving rise to headache, nausea, epigastric pain and dizziness.

The recommended treatment of overdosage consists of eliminating the drug, primarily by the administration of activated charcoal, and giving symptomatic supportive therapy, if needed.

Clinical pharmacology

Mechanism of action (MOA)

Terbinafine is an allylamine which has a broad spectrum of activity against fungal pathogens of the skin, hair and nails including dermatophytes such as Trichophyton (e.g. T. rubrum, T. mentagrophytes, T. verrucosum, T. tonsurans, T. violaceum), Microsporum (e.g. M.canis), Epidermophyton floccosum, and yeasts of the genera Candida (e.g. C. albicans) and Pityrosporum. At low concentrations terbinafine is fungicidal against dermatophytes, moulds and certain dimorphic fungi. Its activity against yeasts is fungicidal or fungistatic, depending on the species.

Terbinafine interferes specifically with fungal sterol biosynthesis at an early step. This leads to a deficiency in ergosterol and to an intracellular accumulation of squalene, resulting in fungal cell death. Terbinafine acts by inhibition of squalene epoxidase in the fungal cell membrane. The enzyme squalene epoxidase is not linked to the cytochrome P450 system.

Pharmacodynamics (PD)

When given orally, the drug concentrates in skin, hair and nails at levels associated with fungicidal activity.

Pharmacokinetics (PK)

Absorption

Following oral administration, terbinafine is well absorbed (>70%). A single oral dose of 250 mg terbinafine resulted in a mean peak plasma concentration of 1.3 microgram/mL within 1.5 hours of administration. At steady-state (70% steady state is achieved in approximately 28 days), in comparison to a single dose, peak concentration of terbinafine was on average 25% higher and plasma AUC increased by a factor of 2.3.

Distribution

Terbinafine binds strongly to plasma proteins (99%). It rapidly diffuses through the dermis and accumulates in the lipophilic stratum corneum. Terbinafine is also secreted in sebum, thus achieving high concentrations in hair follicles, hair and sebum-rich skin. There is also evidence that terbinafine is distributed into the nail plate within the first few weeks after commencing therapy.

Biotransformation/Metabolism

Terbinafine is metabolized rapidly and extensively by at least seven CYP isoenzymes with major contributions from CYP2C9, CYP1A2, CYP3A4, CYP2C8 and CYP2C19. Biotransformation results in metabolites with no antifungal activity.

Elimination

The metabolites are excreted predominantly in the urine. From the increase in plasma AUC at steady state an effective half-life of ~30 hours was calculated. Multiple dose administration followed by extended blood sampling revealed a triphasic elimination with a terminal half-life of approximately 16.5 days.

Bioavailability

The absolute bioavailability of terbinafine from Lamisil tablets as a result of first-pass metabolism is approximately 50%.

Special populations

No clinically relevant age-dependent changes in steady-state plasma concentrations of terbinafine have been observed.

Single dose pharmacokinetic studies in patients with renal impairment (creatinine clearance <50 mL/min) or with pre-existing liver disease have shown that the clearance of Lamisil tablets may be reduced by about 50%.

Clinical studies

Onychomycosis

The efficacy of Lamisil Tablets in the treatment of onychomycosis is illustrated by the response of patients with toenail and/or fingernail infections who participated in three US/Canadian placebo-controlled clinical trials (SFD301, SF5 and SF1508).

Results of the first toenail study, as assessed at week 48 (12 weeks of treatment with 36 weeks follow-up after completion of therapy), demonstrated mycological cure, defined as simultaneous occurrence of negative KOH plus negative culture, in 70% of patients. Fifty-nine percent (59%) of patients experienced effective treatment (mycological cure plus 0% nail involvement or >5mm of new unaffected nail growth); 38% of patients demonstrated mycological cure plus clinical cure (0% nail involvement).

In a second toenail study of dermatophytic onychomycosis, in which non-dermatophytes were also cultured, similar efficacy against the dermatophytes was demonstrated. The pathogenic role of the non-dermatophytes cultured in the presence of dermatophytic onychomycosis has not been established. The clinical significance of this association is unknown.

Results of the fingernail study, as assessed at week 24 (6 weeks of treatment with 18 weeks follow-up after completion of therapy), demonstrated mycological cure in 79% of patients, effective treatment in 75% of the patients, and mycological cure plus clinical cure in 59% of the patients.

The mean time to treatment success for onychomycosis was approximately 10 months for the first toenail study and 4 months for the fingernail study. In the first toenail study, for patients evaluated at least six months after achieving clinical cure and at least one year after completing Lamisil therapy, the clinical relapse rate was approximately 15%.

Tinea capitis

In the three comparative efficacy studies SF 8001, SFE 304, SF 8002 oral Lamisil (62.5 – 250 mg daily) was given to a total of 117 evaluable patients, of whom over 97% were children. Single daily doses were given after the evening meal for 4 weeks (Lamisil) or 8 weeks (griseofulvin). Efficacy, demonstrated by negative mycology tests and a reduction in symptomatology, was evaluated at 8 weeks and at the follow-up examination (Week 12 for Studies SF 8001 and SFE 304, Week 24 for Study SF 8002). Negative mycology test results at follow-up were achieved by 85%, 88% and 72% of patients given Lamisil in the three studies – the corresponding figures for griseofulvin were 73%, 89% and 69%. The derived variable “effective treatment” (negative mycology plus no, or only mild, symptoms and signs) was achieved in 82%, 78% and 69% of Lamisil-treated patients, compared with 66%, 74% and 59% in patients given griseofulvin; the difference was statistically significant in favor of Lamisil in Study SF 8001.

Two phase II treatment duration finding studies totaling 342 patients (mostly children) with T. capitis have been completed.

A 12-week randomized, double-blind, parallel group study was conducted in the United States and in Canada in children with Tinea capitis infection due to Trichophyton species (SFO327C T201). The objective of the study was to determine the optimal duration (1, 2 or 4 weeks) and safety of treatment with Lamisil (tablets), given at weight adjusted doses once daily.

A second 16-week randomized, active-controlled, parallel-group, multicenter study was conducted in Europe in patients with Tinea capitis (>4 years) due to Microsporum species. The Lamisil treatment duration arms (6, 8, 10, and 12 weeks) were double blinded, while the Griseofulvin active comparator arm was open-label (SFO327C T202). The objective of the study was to identify a safe and most appropriate treatment duration with Lamisil (tablets) in patients with Tinea capitis caused by Microsporum species. Dose administration of Lamisil was based on body weight in both studies as follows: <20 kg: 62.5 mg, 20-40 kg: 125 mg, >40 kg: 250 mg, given once daily. In both studies, Lamisil was very well tolerated. Analysis of the efficacy data showed that both 2 and 4-week treatment duration provided good efficacy in T. capitis caused by Trichophyton species. In the Microsporum study, there was no significant difference in complete cure rates between the different treatment duration groups and 6-week treatment showed high complete cure rate (62%) with good tolerability and compliance. These results show that Lamisil reduced treatment duration from 6-8 weeks to only 2-4 weeks in T capitis caused by Trichophyton species compared to standard therapy with griseofulvin.

In phase II clinical studies conducted in Tinea capitis, adverse events reported from the 588 children enrolled were, in general, mild, relatively infrequent and often had an uncertain relationship to treatment. There were 11 reports of elevated SGPT levels and one of taste loss. Other events included mild gastrointestinal or skin symptoms, and laboratory findings indicative of intercurrent infections.

Fungal infections of the skin (tinea corporis, tinea cruris,tinea pedis) and yeast infections of the skin caused by the genus Candida (e.g. Candida albicans) where oral therapy is generally considered appropriate owing to the site, severity or extent of the infection

Three controlled, double blind, randomised, multicenter studies 5OR (4 week study), 6-7OR (4 week study) and 11-21OR (6 week study), evaluated efficacy and safety of Lamisil tablets in the treatment of Tinea corporis and cruris.

Two double blind, placebo controlled studies (5OR, 6-7OR) evaluated the efficacy of Lamisil 125mg b.i.d.in patients diagnosed with Tinea corporis/cruris. The studies included a total of 43 patients randomised to Lamisil and 45 on placebo. There was no significant difference in terms of demographic and anamnestic data within groups. Efficacy, demonstrated by negative mycology tests and a reduction in clinical symptomatology, was evaluated at 4 weeks and at the follow-up examination. In both studies, minimal efficacy was demonstrated in patients treated with placebo compared to the efficacy of orally administered Lamisil at the end of therapy and at follow up.

The third study (11-21OR), a 6 weeks, double blind, randomised, multicenter study compared efficacy and safety of Lamisil 125mg b.i.d. to griseofulvin 250mg b.i.d. One hundred twenty six (126) patients in each group were included in the efficacy analysis. This study showed high rate of mycological cure, reduction in signs and symptoms in the Lamisil treated study arm and significantly better (93-94%) overall efficacy at the end of therapy and at follow up of Lamisil 125mg b.i.d. compared to 86-87% overall efficacy of comparator.

In summary, Lamisil 125mg b.i.d. administered for the period of 4-6 weeks demonstrated statistically superior efficacy compared to placebo and marketed drug griseofulvin in the treatment of Tinea corporis/cruris in the above major efficacy studies.

In a double blind, placebo controlled 4 weeks study SF 00438, Lamisil 125 b.i.d was compared to placebo in patients with cutaneous candidiasis. Twenty one patients were randomised to each treatment arm, of which 19 were evaluated respectively. Of those, 29% of patients in the treatment arm and 17% of patients on placebo demonstrated mycological cure at the end of treatment and 67% of Lamisil treated patients had negative mycological results at the end of follow up. Given the above response rates, 2 weeks therapy of Lamisil should be the minimum duration of treatment period and approximately half of the patients would require 3-4 weeks of treatment to achieve cure.

Two double blind, controlled studies compared Lamisil 125mg b.i.d. to placebo (39-40OR) and to griseofulvin 250mg b.i.d. (20OR) in the treatment of Tinea pedis. Both studies recruited patients with chronic, recurrent disease. In the study 39-40OR, 65% of patients on Lamisil reported mycological cure at follow up whereas none of the placebo treated patients responded. In the study 20OR, Lamisil was shown to be highly effective with 88% of cure at follow up after 6 weeks therapy compared to 45% of patients on griseofulvin. These patients when observed after 10 months reported 94% cure rate, compared to 30% efficacy of griseofulvin in the same patient population.

Table 3 Major efficacy studies – Tinea corporis/cruris, Tinea pedis, Candida infections

Study	Type	Drug	No. of evaluable patients	Dropouts	Mycological results % negative		Clinical results %	
					End Rx	F/up	End Rx	F/up
5OR	4wk DB-placebo	Lamisil 125 b.i.d	13	4	73	89	54	62
		Placebo	15	2	0	0	0	0
6-7OR	4wk DB-placebo	Lamisil 125 b.i.d	33	7	97	97	89	91
		Placebo	33	3	29	37	12	12
11-21OR	6wk 125 b.i.d. DB-Griseofulvin	Lamisil 125 b.i.d	126	13	97	100	93	94
		Griseofulvin 250 b.i.d	126	16	90	94	87	86
SF 00438	2wk DB-placebo	Lamisil 125 b.i.d	19	3	29	67	11	47
		Placebo	19	3	17	47	11	11
39-40OR	6wk 125 b.i.d. DB-placebo	Lamisil 125 b.i.d	23	0	68	77	59	65
		Placebo	19	0	14	0	0	0
20OR	6wk 125 b.i.d. DB-Griseofulvin	Lamisil 125 b.i.d	16	2	94	100	75	88
		Griseofulvin 250 b.i.d	22	6	27	55	27	45

Non-clinical safety data

In long-term studies (up to 1 year) in rats and dogs no marked toxic effects were seen in either species up to oral doses of about 100 mg/kg a day. At high oral doses, the liver and possibly also the kidneys were identified as potential target organs.

In a two-year oral carcinogenicity study in mice, no neoplastic or other abnormal findings attributable to treatment were made up to doses of 130 (males) and 156 (females) mg/kg a day. In a two-year oral carcinogenicity study in rats, an increased incidence of liver tumors was observed in males at the highest dose level of 69 mg/kg a day. The changes, which may be associated with peroxisome proliferation have been shown to be species-specific since they were not seen in the carcinogenicity study in mice or in other studies in mice, dogs or monkeys.

During high-dose studies in monkeys, refractile irregularities were observed in the retina at the higher doses (non-toxic effect level 50 mg/kg). These irregularities were associated with the presence of a terbinafine metabolite in ocular tissue and disappeared after drug discontinuation. They were not associated with histological changes.

An 8-week oral study in juvenile rats provided a no-toxic-effect level (NTEL) of close to 100 mg/kg/day, with the only finding being slightly increased liver weights, while in maturing dogs at ≥100 mg/kg/day (AUC values about 13x (m) and 6x (f) those in children), signs of central nervous system (CNS) disturbance including single episodes of convulsions in individual animals were observed. Similar findings have been observed at high systemic exposure upon intravenous administration of terbinafine to adult rats or monkeys.

A standard battery of *in vitro* and *in vivo* genotoxicity tests revealed no evidence of mutagenic or clastogenic potential.

No adverse effects on fertility or other reproduction parameters were observed in studies in rats or rabbits.

Incompatibilities

None known.

Storage

See folding box.

Lamisil tablets should not be used after the date marked “EXP” on the pack.

Lamisil tablets must be kept out of the reach and sight of children.

Instructions for use and handling

Manufacturer:

See folding box.

International Package Leaflet

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Novartis Pharma AG, Basel, Switzerland

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