PharmaNote®

VOLUME 23, ISSUE 2 NOVEMBER 2007

ROTIGOTINE (NEUPRO®): THE FIRST TRANSDERMAL DOPAMINE AGONIST FOR PARKINSON'S DISEASE

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Approximately 1.5 million Americans currently have Parkinson's disease (PD) with about 60,000 new cases diagnosed every year. Parkinson's disease is uncommon in people younger than 40, and the incidence of the disease increases rapidly over 60 years, with a mean age at diagnosis of 70.5 years.[1] The increasing elderly population and the high prevalence of PD within this group create a large economic burden. The approximate annual service costs including formal healthcare and informal care from friends and family accounted for an estimated $25,000 yearly per individual with PD.[2]

Control of PD symptoms remains inadequate in many patients despite the availability of several classes of drugs. Current treatment options include levodopa preparations, dopamine agonists, MAO-B inhibitors, COMT inhibitors, NMDA antagonists, and anticholinergics. Although effective initially, as the disease progresses the effect of levodopa begins to wear off after approximately four hours leaving the patient experiencing motor fluctuations known as "on" and "off" periods. Dopamine agonists, however, provide the benefit of delaying levodopa-induced dyskinesia in early PD, and decreasing motor fluctuations in advanced PD.[3] The use of this class of drugs, however, has been limited by early morning "off" symptoms due to lack of continuous dopaminergic stimulation.[4]

Rotigotine (Neupro®) is a new, transdermal, non-ergolinic dopamine agonist manufactured by Schwarz Biosciences and was approved by the FDA in May 2007. Unlike any other treatment options for PD, the dosage form is transdermal – allowing once daily application and providing a benefit to patients who have difficulties swallowing and maintaining stable plasma levels. It is indicated for the treatment of the signs and symptoms of early-stage idiopathic PD.[5] This article will review the pharmacology, pharmacokinetics, clinical trials, dosing, toxicity, and cost of rotigotine.

Pharmacology and Pharmacokinetics

Rotigotine works similarly to other dopamine agonists by stimulating dopamine receptors in the brain. It is a non-ergolinic, $D_3/D_2/D_1$ dopamine agonist with its major effects thought to be due to its ability to stimulate D2 receptors in the caudate-putamen. (PI) It is eliminated in the urine as inactive conjugates. There is about a 3 hour lag time until rotigotine is detected in the plasma after initial use. There is, however, no characteristic peak concentration observed, but dose-proportionality over 2 mg/24 hours to 8 mg/24 hours. In the clinical trials the application sites varied amongst 6 different sites (abdomen, thigh, hip, flank, shoulder, and upper

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arm), and were rotated from day to day. The resulting bioavailability varied, with the biggest difference between the shoulder and thigh (64%) with the shoulder showing higher bioavailability. Because rotigotine is administered transdermally, it is not affected by food. Steady state concentrations were reached within 2 to 3 days. It is approximately 90% bound to plasma proteins. Rotigotine's metabolism is primarily mediated via conjugation and N-dealkylation with CYP isoensymes, sulfotransferases, and 2 UDP-glucoronosyltransferases catalyzing the metabolism. Due to the multiple pathways of metabolism, drug interactions are unlikely based upon one pathway. For example, if one CYP isoform is inhibited the other isoforms could catalyze the metabolism. There are no known drug interactions, but dopamine antagonists such as metoclopramide and antipsychotics could diminish the effects of rotigotine. The terminal half-life upon removal of the patch is 5 to 7 hours. The initial half-life is 3 hours with biphasic elimination. Rotigotine is excreted in the urine (71%) and feces (11%). No changes in dose are indicated based upon moderate hepatic or mild to severe renal dysfunction. The pharmacokinetics of rotigotine did not differ significantly based upon gender or ethnicity. Rotigotine had similar steady state concentrations for individuals 40 to 80 years old. However, steady state concentrations may be higher in the elderly (>80 years) due to skin changes with aging. It has not been studied in patients less than 18 years old.[5]

Clinical Trials

Three clinical trials were submitted to the FDA to demonstrate the effectiveness of rotigotine. All three studies were randomized, double-blind, placebo controlled involving patients with idiopathic early-stage PD not on any other PD medications.[6]

North American Study

Watts and colleagues evaluated the efficacy of rotigotine in a randomized, double-blind, multinational study using early-stage idiopathic PD patients. The primary outcome of the study was change in the combined Parts II and III of Unified Parkinson's Disease Rating Scale (UPDRS) from baseline to end of treatment at week 27. Patients were titrated up weekly from a starting dose of 2 mg/24 hours up to a maximum dose of 6 mg/24 hours. Of the 277 patients who participated in the study, 96 were randomly assigned placebo while 181 received rotigotine. A statistically significant difference was observed between the placebo and rotigotine with a mean difference from placebo of -5.3 on the UPDRS ($p<0.0001$). (**Figure 1**) The most common adverse event was application site skin reactions. Other adverse events experienced were similar to other dopamine agonists used to treat PD.[7]

Figure 1. Mean change in Unified Parkinson's Disease Rating Scale subtotal (parts II and III) by visit (full analysis set with last observation carried forward). Adapted from Watts RL, et al.[7]

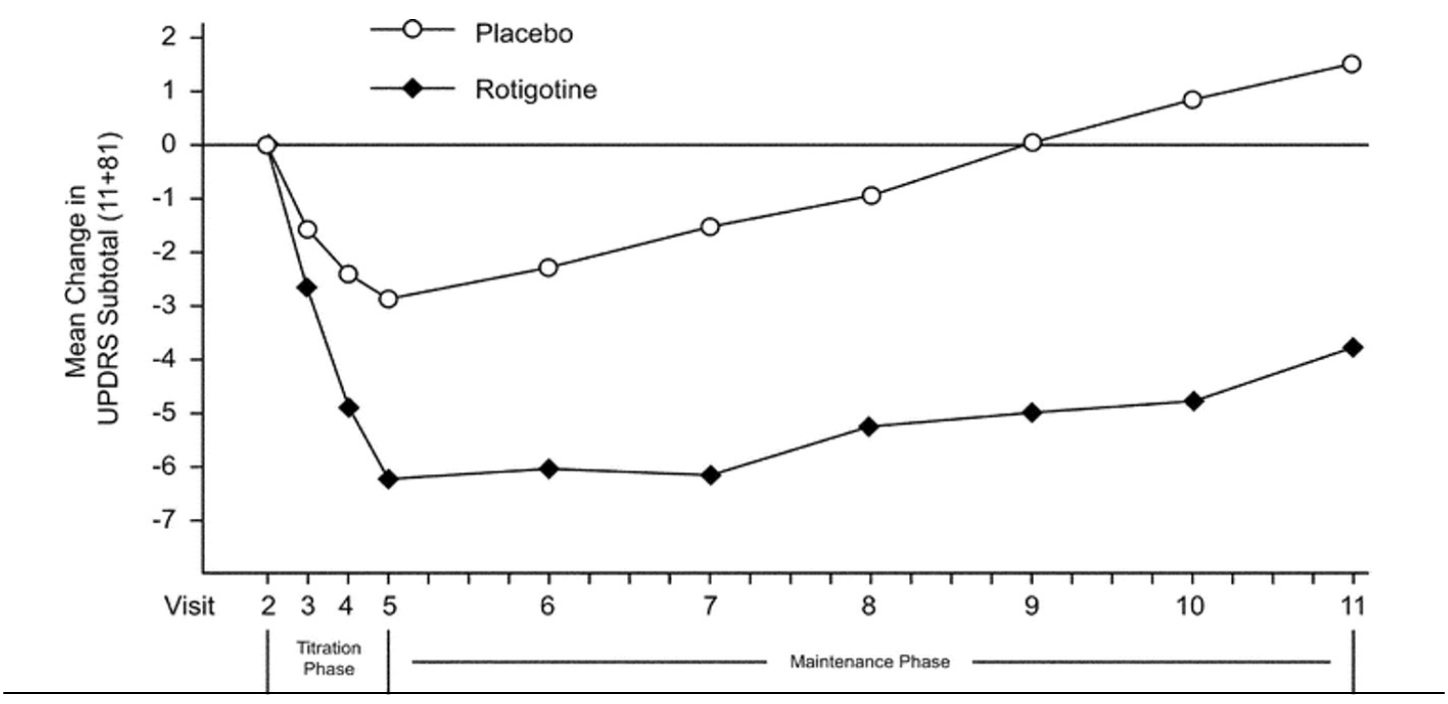


Table 1. Mean change in UPDRS from baseline at end of treatment for intent-to-treat population

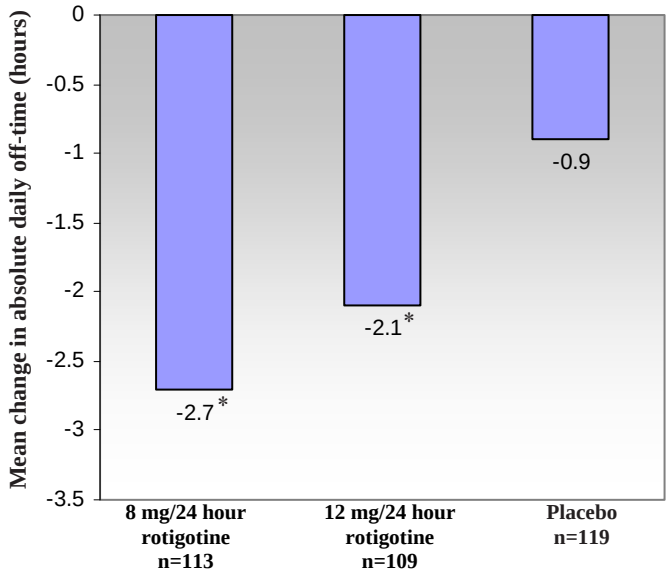
Rotigotine nominal dose	Difference from placebo
2 mg/24 hours	-2.1
4 mg/24 hours	-3.1*
6 mg/24 hours	-4.9*
8 mg/24 hours	-5.0*

UPDRS = Unified Parkinson's Disease Rating Scale
*p < 0.05

Dose-Response Study

An international, randomized, double-blind trial was conducted by the Parkinson Study Group on 242 early-stage PD patients to compare dosing of rotigotine. The primary outcome of the study was a mean change in the sum of scores in the UPDRS. Of a total of 242 patients, 47 were randomized to receive placebo and 49, 47, 48, and 51 received one of several fixed doses of respectively 2 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, or 8 mg/24 hours for up to 11 weeks. Mean changes in Parts II and III of UPDRS are shown in **Table 1**. The mean changes of the 4 mg/24 hours, 6 mg/24 hours, and 8 mg/24 hours doses were statistically significant. The minimum effective dose was established to be 4 to 6 mg/24 hours. Nine serious adverse events occurred during the study including one patient suddenly falling asleep while driving.[8]

Figure 2. Mean changes from baseline to the end of week 24 in absolute daily "off " time in the PREFER trial.[9]



*p < 0.001 vs placebo

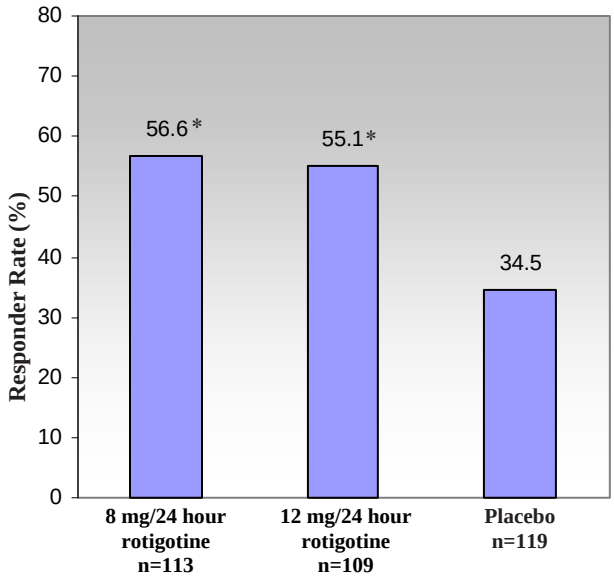
Foreign Multinational Study

A multinational, double-blind, randomized trial was conducted with 561 early stage PD patients. Patients were randomly assigned to placebo, rotigotine, or comparator for 39 weeks. All rotigotine patients received a weekly dose escalation of patch by 2 mg/24 until a maximal dose of 8 mg/24 hours or until a maximum effective and tolerable dose was met. The comparator group dose was also escalated to maximum efficacy. Rotigotine patients experienced a mean change of -6.83 from baseline to end of treatment compared to placebo with a mean change of -2.33. The mean difference from placebo for the 8 mg/24 hour dose was -4.5 which was statistically significant.[5]

Pooled Trials Studying Rotigotine in Advanced PD

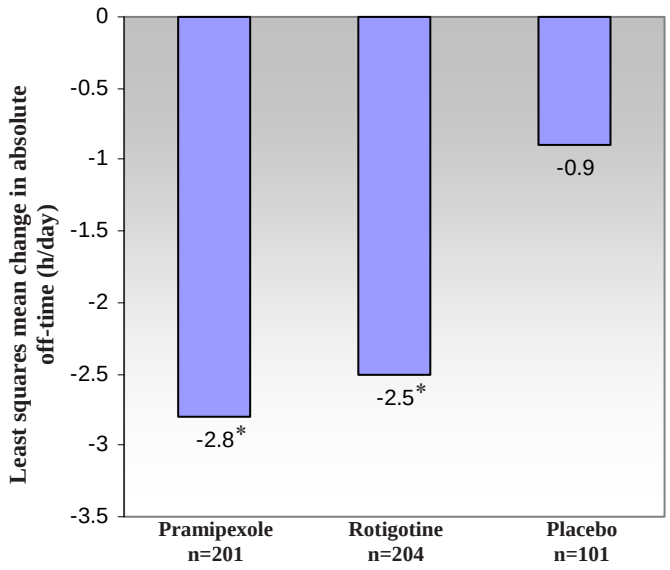
The PREFER and CLEOPATRA-PD trials were done to study the safety and efficacy of rotigotine in advanced PD.[9-10] Advanced PD was defined as motor fluctuations of the wearing-off type with an average of at least 2.5 h per day in patients with PD for more than 3 years and currently taking stable doses of levodopa and other antiparkinsonian medications for at least 4 weeks. Dual primary efficacy parameters were mean change in total daily hours "off" time and percent responders defined as patients with 30% or more reduction in absolute off time from baseline to end of maintenance in both studies. In the PREFER trial, there were significant

Figure 3. Responder rates[a] in the PREFER trial.[9]



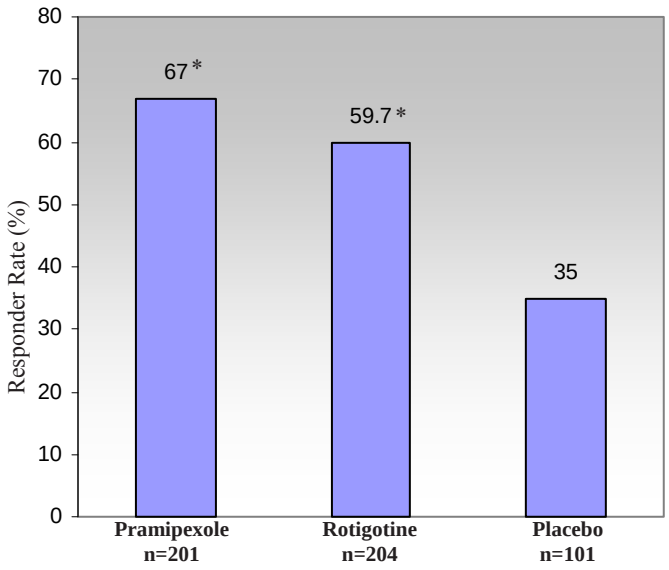
[a]Patients with ≥30% reduction in absolute off time; *p < 0.001 vs placebo

Figure 4. Changes from baseline to end of maintenance period for the three treatment groups in the CLEOPATRA-PD trial.[10]



*p < 0.0001 vs placebo

Figure 5. Responder rates[a] for the three treatment groups in the CLEOPATRA-PD trial.[10]



[a]Patients with ≥30% reduction in absolute off time; *p < 0.0001 vs placebo

decreases in mean "off " time of 2.7 hours/day for the rotigotine 8 mg/24 hours group and 2.1 hours/day for the 12 mg/24 hours group compared to 0.9 for placebo.[9] (**Figure 2**) For rotigotine 8 and 12 mg/24 hours groups, responder rates were 56.6% and 55.1% compared to 34.5% for placebo. (**Figure 3**) Poewe and colleagues found in the CLEOPATRA-PD trial that mean absolute change in off time from baseline was -2.5 ± 0.2 h with rotigotine (maximum of 16 mg/24 h as a transdermal patch), -2.8 ± 0.2 h with pramipexole (maximum of 4.5 mg/day orally), and -0.9 ± 0.29 h with placebo ($p<0.0001$ for pramipexole and rotigotine vs placebo).[10] (**Figure 4**) Responder rates were 67% for pramipexole, 59.7% for rotigotine, and 35% for placebo ($p<0.0001$ for pramipexole and rotigotine vs placebo) (**Figure 5**). Noninferiority was met for mean change in off time, however, rotigotine was inferior to pramipexole for the responder rate endpoint (-7.3% difference). In both trials, adverse events were typical of dopaminergic agents of mild-to-moderate intensity with the addition of patch site reactions for rotigotine.

Dosing and Administration

Rotigotine is available in 2 mg, 4 mg, and 6 mg transdermal systems with the rotigotine content per system being 4.5 mg, 9 mg, and 13.5 mg respectively. The starting dose should be 2 mg/24 hours with weekly titration by 2 mg/24 hours if therapeutically needed and tolerated. Rotigotine doses ranging from 4 mg/24 hours to 6 mg/24 hours have been evaluated in clinical trials with higher doses demonstrating an increase in adverse reactions and no clinical benefit in early-stage PD patients.[8] Although higher doses have been studied in patients with advanced PD, no dosing recommendations are available at this time. When discontinuing rotigotine, the daily dose should be decreased by 2 mg/24 hour every other day until complete withdrawal to prevent neuroleptic malignant syndrome. Application of rotigotine should be done on clean, dry, intact, healthy skin on the abdomen, thigh, hip, flank, shoulder, or upper arm, rotating these sites daily. The same application site should not be used more than once every 14 days. No dose adjustment is warranted in patients with renal or hepatic insufficiencies.[5]

Toxicity and Safety

The safety of rotigotine has been evaluated in approximately 1200 patients with early-stage PD. Investigators found that 13% of patients experienced an adverse event related to the study drug. Application site reactions were reported most frequently, followed by gastrointestinal adverse events such as nausea and vomiting. Other adverse events reported included somnolence, dizziness, headache, and insomnia. Side effects that occurred in > 2% of patients in the studies are presented in **Table 2**. Clinical trials

Table 2. Treatment-related adverse events with a 2% or greater incidence

Body system/preferred term	Placebo N=289 (%)	Rotigotine N=649 (%)
Application site reactions	14	37
Autonomic nervous system		
Sweating increased	2	4
Mouth dry	1	3
Body as a Whole		
Fatigue	7	8
Accident NOS	4	5
Cardiovascular		
Extremity edema	6	7
Hypertension	2	3
Central and peripheral nervous system		
Dizziness	11	18
Headache	10	14
Vertigo	2	3
Gastrointestinal system		
Nausea	15	38
Vomiting	2	13
Constipation	4	5
Dyspepsia	1	4
Anorexia	1	3
Musculoskeletal system		
Back pain	5	6
Arthralgia	3	4
Psychiatric		
Somnolence	16	25
Insomnia	5	10
Dreaming abnormal	<1	3
Hallucination	1	2
Respiratory system - Sinusitis	2	3
Skin and appendage – erythematous rash	1	2
Urinary tract infection	1	3
Vision abnormal	1	3

N = number of patients; NOS = not otherwise specified

have also shown an increase in adverse events with higher doses. These adverse events are shown in **Table 3** for placebo and doses up to 8 mg/24 hours, even though the 8 mg/24 hours dose is not recommended therapy for early-stage PD. Laboratory changes included an average decrease in blood hemoglobin levels of about 2% or 0.3 g/dL and a concomitant decline in serum albumin. Also, patients on rotigotine had an increase of blood urea nitrogen levels of 3.7% or 0.21 mg/dL. Subjects had a greater likelihood of low blood glucose (< 50 mg/dL) at 7% compared to 4% with placebo. Warnings for rotigotine include sulfite sensitivity and falling asleep during daily activities. The latter includes excessive drowsiness with reports of patients falling asleep in motor vehicles leading to accidents. Rotigotine should be used with caution in patients using sedating medications or having sleep disorders.[5]

Cost

As of August 2007, the average retail price of Neupro® is $91 ($83 - $100) for a 30 day supply of the 2 mg/24 hour strength and $290 ($282 - $305) for a 30 day supply of either the 4 mg/24 hour or 6 mg/24 hour strength. Patches may be purchased in 7 or 30 day supplies.

Summary

Rotigotine is a new transdermal, non-ergolinic dopamine agonist that stimulates D2 receptors. It is indicated for early-stage PD without concomitant treatment with antiparkinsonian drugs. Rotigotine offers a valuable therapeutic alternative for early-stage treatment differing from other dopamine agonists by providing constant blood levels over a 24 hour period. This could possibly lower the

Table 3. Incidence (%) of rotigotine dose-related treatment-emergent adverse events

Adverse Event	Daily rotigotine dose				
	Placebo N = 64	2 mg/24 h N = 67	4 mg/24 h N = 63	6 mg/24 h N = 65	8 mg/24 h N = 70
Application site reaction	19	24	21	34	46
Nausea	11	34	38	48	41
Vomiting	3	10	16	20	11
Weight decrease	0	0	0	2	3
Myalgia	0	0	2	2	3
Somnolence	3	13	16	19	21
Insomnia	8	6	13	14	14
Dreaming abnormal	0	2	5	3	7
Hallucination	2	0	2	3	3
Rash erythematous	2	2	6	3	3

on-off symptoms experienced in advanced PD by delaying the time until levodopa treatment is needed. There are no known drug interactions of rotigotine due to multiple pathways of metabolism. The adverse event profile includes similar side effects to other dopamine agonists including nausea, dizziness, vertigo, insomnia and somnolence. Adverse events specific to rotigotine include application site reactions.

References

1. National Parkinson Foundation. http://www.parkinson.org (Accessed August 2, 2007).
2. McCrone P, Allcock LM, Burn DJ. Predicting the cost of Parkinson's disease. Mov Disord 2007; 22: 804-12.
3. Kenney C, Jankovic J. Rotigotine transdermal patch in the treatment of Parkinson's disease and restless legs syndrome. Expert Opin Pharmacother 2007; 8: 1329-35.
4. Metman LV, Gillespie M, Farmer C, et al. Continuous transdermal dopaminergic stimulation in advanced Parkinson's disease. Clin Neuropharmacol 2001; 24: 163-9.
5. Neupro® (rotigotine) [Package Insert]. Mequon, WI; Scwarz Pharma, LLC; 2007.
6. FDA news May 9, 2007. FDA approves Neupro patch for treatment of early Parkinson's disease. www.fda.gov/bbs/topics/NEWS/2007/NEW01631.html (Accessed August 10, 2007).
7. Watts RL, Jankovic J, Waters C, et al. Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease. Neurology. 2007; 68: 272-6.
8. The Parkinson Study Group. A controlled trial of rotigotine monotherapy in early Parkinson's disease. Arch Neurol 2003; 60: 1721-8.
9. LeWitt PA, Lyons KE, Pahwa R; SP 650 Study Group. Advanced Parkinson disease treated with rotigotine transdermal system: PREFER Study. Neurology 2007; 68: 1262-7.
10. Poewe WH, Rascol O, Quinn N, et al.; SP 515 Investigators. Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial. Lancet Neurol 2007; 6: 475-6.
11. Naidu Y, Chaudhuri KR. Transdermal rotigotine: a new non-ergot dopamine agonist for the treatment of Parkinson's disease. Expert Opin Drug Deliv 2007; 4: 111-8.

PHARMACOTHERAPY OF ONYCHOMYCOSIS: A FOCUS ON TERBINAFINE

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Onychomycosis, also known as *tinea unguium*, is responsible for up to 50% of nail disorders and affects as much as 8% of the general population.[1,2] A fungal infection of the fingernails and toenails, onychomycosis is characterized by nail thickening and discoloration. While it is often regarded as simply a cosmetic problem, it can cause pain, irritation and disfigurement. Additionally, it can lead to complications in immunocompromised individuals, including systemic infection, if left untreated.[3]

Dermatophytes, yeasts and molds are all potential causative agents of onychomycosis.[4] Dermatophytes are responsible for the majority of infections, particularly *Trichophyton rubrum* and *Trichophyton mentagrophytes*.[1] Diagnosis of onychomycosis involves evaluation of clinical presentation, direct microscopy and fungal culture. Direct microscopy utilizes a 20% potassium hydroxide preparation (KOH) in dimethyl sulfoxide (DMSO) to rule out presence of fungi, while fungal culture is used to determine the specific pathogen involved.[3]

Terbinafine tablets (Lamisil®) are indicated for treatment of onychomycosis and became available as a generic formulation on July 2, 2007. This article will review the pharmacokinetics, efficacy and safety of terbinafine, as well as its role in the treatment of fungal nail infections.

Pharmacology and Pharmacokinetics

Terbinafine is a synthetic allylamine that has fungicidal activity against dermatophytes, including *T. rubrum* and *T. mentagrophytes* and fungistatic activity against some non-dermatophyte yeasts and molds.[5] Terbinafine's antifungal activity is due to its inhibition of the enzyme squalene monooxygenase, a major enzyme in fungal sterol biosynthesis.[6] Inhibition of this enzyme prevents conversion of squalene to 2,3-oxidosqualene, creating a deficiency in ergosterol and leading to weakened cell membranes in sensitive fungi.[7]

Pharmacokinetic properties of terbinafine af-

Table 1. Overview of the pharmacokinetic properties of oral terbinafine in healthy adult volunteers after administration of a single 250mg dose.[7]

Parameter	Range
C_{max} (mg/L)[a]	0.8 – 1.5
t_{max} (h)[b]	1.3 – 2
AUC (mg * h/L)[c]	3.55 – 4.74
Bioavailability (%)	40 – 50%
Vd_{ss} (L)[d]	947.5
Serum protein binding (%)	94
$t_{1/2abs}$ (h)[e]	0.8 – 1.2
$t_{1/2\beta}$ (h)[f]	16-26
$t_{1/2\gamma}$ (h)[g]	90
CL (L/h)[h]	76
Excretion	80% urine; 20% feces

[a]C_{max} = maximum serum concentration; [b]t_{max} = time to C_{max}; [c]AUC = area under the plasma concentration-time curve; [d]Vd_{ss} = volume of distribution at steady state; [e]$t_{1/2abs}$ = absorption half-life; [f]$t_{1/2\beta}$ = initial elimination half-life; [g]$t_{1/2\gamma}$ = terminal elimination half-life; [h]CL = plasma clearance

ter a single 250mg dose are summarized in **Table 1**. Terbinafine's mean peak plasma concentration (C_{max}) is reached within approximately 2 hours following oral administration. Concomitant food intake increases the area under the plasma concentration-time curve (AUC) by approximately 20%, resulting in small delays in time to C_{max} (t_{max}) and slight C_{max} elevations. Terbinafine is highly protein bound (94-99%), but also widely distributed in nail beds, hair, stratum corneum and breast milk. Bioavailability is approximately 40-50%, due to extensive hepatic first-pass metabolism. No identified metabolites of terbinafine have antifungal activity. Between 70-80% of terbinafine is eliminated in the urine as metabolites, while approximately 20-30% is eliminated in feces.[7] At steady state, peak concentration increases by 25% and AUC increases 2.5-fold. Additionally, the elimination half-life of terbinafine increases to 36 hours, and the terminal half-life ranges from 200 to 400 hours. This long terminal half-life may represent the slow elimination of the drug from skin and adipose tissue.[8] Terbinafine is a potent inhibitor of the hepatic enzyme CYP2D6, and as a result, may potentiate the effects of other medications metabolized by this enzyme.[6]

Clinical Trials

Two randomized, double-blind, placebo-controlled trials were conducted comparing terbinafine and placebo.[9-10] Data from these trials, as well as several other trials evaluating the efficacy of terbinafine versus active treatment options, are summarized in **Table 2**. In Drake et al., 358 patients in the United States and Canada were randomized to one of three groups: oral terbinafine 250 mg/day for 12 weeks, followed by placebo for 12 weeks (n=142), oral terbinafine 250 mg/day for 24 weeks (n=145), or placebo for 24 weeks (n=71).[9] This treatment phase was followed by 24 weeks of blinded follow-up, with patients not receiving any treatment. A cohort of patients with negative mycologic findings (negative culture and microscopy) and at least 5 mm of unaffected new nail growth by week 48 were selected for an additional 48 weeks of follow-up. The purpose of this cohort was to examine long-term efficacy and relapse rates of patients taking terbinafine. At week 48, there was a significant difference in negative mycology between the terbinafine and placebo group (70% of the 12-week terbinafine group and 87% of the 24-week terbinafine group versus 9% of the placebo group; $p<0.001$). Clinical success, defined as the percentage of patients with at least 90% clear nail at week 48, was significantly higher in the terbinafine groups versus the placebo group (60% of the 12-week terbinafine group and 75% of the 24-week terbinafine group versus less than 10% of the placebo group; $p <0.001$). A total of 167 terbinafine treated patients were included in the cohort selected for 48 weeks of additional follow-up. Of those patients, 95% of the terbinafine 12-week group and 88% of the terbinafine 24-week group still had negative mycologic findings at the end of the extended observation period. Based on these results, terbinafine was considered to be effective for treatment of onychomycosis.

In Goodfield et al., 99 patients in the United Kingdom were randomized to receive oral terbinafine 250 mg daily for 12 weeks (n=70) or placebo (n=29) to treat toenail onychomycosis.[10] Additionally, 18 patients were randomized to receive oral terbinafine 250 mg daily for 6 weeks (n=13) or placebo (n=5) to treat fingernail onychomycosis. Mycologi-

Table 2. Results from clinical trials with terbinafine

Author	N	Design	Study drug/ dose	Comparator	Results	Conclusions
Drake, et al.[9]	358	RDB	TERB 250mg/ day x 12 wks (OR) x 24 wks	PLA x 24 wks	At week 48: MYC = 70% TERB 12-wk gp and 87% TERB 24-wk gp vs 9% PLA gp Overall response rate of both treatment gps was comparable: 71% for TERB 12-wk gp vs 77% for TERB 24-wk gp	Oral TERB effective for treatment of ONY
Goodfield, et al.[10]	99	RDB	TERB 250 mg/ day x 12 wks for toenails (OR) x 6 wks for fingernails	PLA x 12 wks (OR) x 6 wks	At 48 wks – ITT: MYC = 73% TERB gps vs 6% PLA gps (p<0.007) CLIN = 69% and 71% for TERB groups (toenail and fingernail) vs 0% for PLA	Oral TERB effective for treatment of ONY
De Backer, et al.[11]	372	RDB	TERB 250mg/ day x 12 wks	ITRA 200mg/ day x 12 wks	At week 48: MYC = 73% TERB gp vs 45.8% ITRA group (p<0.0001) MYC with cleared/min clinical sxs = 64.2% TERB gp vs 37.5% ITRA gp (p<0.0001) MYC with cleared clinical sxs = 37.7% TERB gp vs 23.2% ITRA gp (p=0.004)	Compared with ITRA, TERB produced higher rates of MYC and CLIN at F/U
Brautigam[12]	195	RDB	TERB 250mg/ day x 12 wks	ITRA 200mg/ day x 12 wks	At week 52: MYC = 81.4% TERB gp vs 63.1% ITRA gp (2p<0.01) Unaffected area of target nail = 9.44mm TERB gp vs 7.85mm ITRA gp (2p<0.05)	Compared with ITRA, TERB produced higher rates of MYC and unaffected nail growth at F/U
Gupta, et al.[13]	70	RSB	TERB 250mg/ day x 12 wks	ITRA "pulse" 200mg twice daily (1 wk on, 3 wks off) x 12 wks	At week 48: MYC = 79.3% TERB gp vs 88.2% ITRA gp (p not significant) MYC with less than 10% nail plate involvement = 51.7% TERB gp vs 52.9% ITRA gp (p not significant)	Both continuous TERB and pulse ITRA are effective for the management of toenail ONY in diabetic patients
Havu, et al.[14]	137	RDB	TERB 250mg/ day x 12 wks	FLUC 150mg once wkly x 12 wks (OR) x 24 wks	At week 60: MYC = 89% TERB gp vs 51% FLUC 12-wk gp and 49% FLUC 24-wk gp (p<0.001) Complete CLIN of target nail = 67% TERB gp vs 21% FLUC 12-wk gp and 32% FLUC 24-wk gp (p<0.0001)	TERB 250mg/ day for 12 wks significantly more effective for treatment of ONY than FLUC 150mg once wkly for 12 or 24 wks

RDB = randomized, double-blind trial design; RSB = randomized, single-blind trial design; TERB = terbinafine; PLA = placebo; ITRA = itraconazole; FLUC = fluconazole; ONY = onychomycosis; MYC = mycologic cure; CLIN = clinical cure; ITT = intention-to-treat analysis; gp = group; wk = week; F/U = follow-up

Table 3. Most frequently reported adverse events observed in three placebo-controlled trials.[8]

Adverse Event	Terbinafine (%) n=465	Placebo (%) n=137
Headache	12.9	9.5
Gastrointestinal:		
Diarrhea	5.6	2.9
Dyspepsia	4.3	2.9
Abdominal pain	2.4	1.5
Nausea	2.6	2.9
Flatulence	2.2	2.2
Dermatologic:		
Rash	5.6	2.2
Pruritus	2.8	1.5
Urticaria	1.1	0.0
Liver enzyme abnormalities*	3.3	1.4
Taste disturbance	2.8	0.7
Visual disturbance	1.1	1.5

* Liver enzyme abnormalities ≥ 2x the upper limit of the normal range

cal cure was defined as negative findings on microscopy and culture, with trial endpoints of 12 weeks (end of treatment period) and 48 weeks (end of follow-up period). Clinical cure was defined as full, unaffected, normal nail growth. At the end of the treatment period, the mycological cure rates for patients with toenail and fingernail infections were 29% and 71% respectively for the terbinafine groups versus 12% and 31% for the placebo groups. On an intention to treat basis, the mycological cure rates for toenail infection at the end of the follow-up period significantly favored treatment with terbinafine over placebo (73% vs 6%, $p<0.007$). Clinical cure rates at the end of follow-up were 69% for patients with toenail infection and 71% for patients with fingernail infection treated with terbinafine. No patients receiving placebo achieved clinical cure.

Toxicity and Safety

The prescribing information for terbinafine specifically warns that rare cases of liver failure have occurred with its use, in patients with and without pre-existing liver disease, some leading to death or liver transplant.[8] As a result, assessing liver function is recommended prior to prescribing terbinafine. In addition, the prescribing information recommends treatment discontinuation if progressive skin rash occurs, as there have been isolated reports of serious skin reactions (including Stevens-Johnson Syndrome and toxic epidermal necrolysis) with its use. For patients with known or suspected immunodeficiency and taking terbinafine for longer than 6 weeks, the manufacturer recommends monitoring complete blood counts, as transient decreases in absolute lymphocyte counts have been observed in clinical trials.[8]

Several studies have evaluated the safety of terbinafine.[8,9,11,15] The most common adverse reactions experienced in clinical trials were headache, diarrhea and rash (**Table 3**). Generally, adverse reactions were found to be transient and mild-to-moderate in severity.

Dosing and Administration

Terbinafine tablets may be taken with food if desired. Standard dosing of terbinafine is 250 mg daily for 6 weeks for treatment of fingernail onychomycosis and 250 mg daily for 12 weeks for treatment of onychomycosis.[6] Two identical trials (n=2005) were conducted to compare efficacy, safety and tolerability of the standard dosing regimen with an intermittent dosing regimen. Intermittent dosing consisted of 3 cycles of 350 mg daily for 2 weeks followed by 2 weeks of no treatment. Response rates for mycological and clinical cure were significantly lower for the intermittent dosing regimen in both Trial 1 (-5.8%; 95% CI -11.8, 0.07) and Trial 2 (-5.9%; 95% CI -12, 0.1). Continuous therapy with terbinafine 250 mg was determined to be more efficacious than intermittent dosing.[16]

Cost

Prices for a 30 day supply of terbinafine 250 mg vary widely between pharmacies. The median retail cost from 7 different pharmacies is $231.55

(range $4 to $444). Thus, a 12-week course of terbinafine 250 mg is expected to cost $12 - $1332.

Median retail cost from 7 different pharmacies for Lamisil® 250 mg is $435 (range $418.62 to $502.97). Thus, a 12-week course of Lamisil® 250 mg is expected to cost $1674 - $2012.

Summary

Terbinafine is a synthetic allylamine approved for the treatment of onychomycosis that recently became available as a generic formulation. It demonstrates fungicidal activity against dermatophytes and fungistatic activity against some non-dermatophyte yeasts and molds. Pharmacokinetic data suggests significant distribution into nail beds and a long half-life at steady state concentrations, which contributes to its efficacy. Clinical trials indicate terbinafine is safe and effective treatment option for onychomycosis. Generally, adverse reactions were found to be transient and mild-to-moderate in severity, with headache, diarrhea and rash being the most common adverse reactions experienced.

References

1. Ghannoum MA, Hajjeh RA, Scher R, et al. A large-scale North American study of fungal isolates from nails: the frequency of onychomycosis, fungal distribution, and antifungal susceptibility patterns. J Am Acad Dermatol 2000; 43: 641-8.
2. Finch J, Warshaw E. Toenail onychomycosis: current and future treatment options. Dermatol Ther 2007; 20: 31-46.
3. Elewski BE. Onychomycosis: pathogenesis, diagnosis, and management. Clin Microbiol Rev 1998; 11: 415-29.
4. Müggе C, Haustein UF, Nenoff P. Causative agents of onychomycosis--a retrospective study. J Dtsch Dermatol Ges 2006; 4: 218-28.
5. Debruyne D, Coquerel A. Pharmacokinetics of antifungal agents in onychomycoses. Clin Pharmacokinet 2001; 40: 441-72.
6. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2007. URL: http://www.clinicalpharmacology.com. Updated October, 2007.
7. Darkes MJ, Scott LJ, Goa KL. Terbinafine: a review of its use in onychomycosis in adults. Am J Clin Dermatol 2003; 4: 39-65.
8. Terbinafine Prescribing Information. Watson Pharmaceuticals, Inc. Retrieved 10 October 2007. http://pi.watson.com/data_stream.asp?product_group=1602&p=pi&language=E
9. Drake LA, Shear NH, Arlette JP, et al. Oral terbinafine in the treatment of toenail onychomycosis: North American multicenter trial. J Am Acad Dermatol 1997; 37: 740-5.
10. Goodfield MJ, Andrew L, Evans EG. Short term treatment of dermatophyte onychomycosis with terbinafine. BMJ 1992; 304: 1151-4.
11. De Backer M, De Vroey C, Lesaffre E, et al. Twelve weeks of continuous oral therapy for toenail onychomycosis caused by dermatophytes: a double-blind comparative trial of terbinafine 250 mg/day versus itraconazole 200 mg/day. J Am Acad Dermatol 1998; 38: S57-63.
12. Bräutigam M. Terbinafine versus itraconazole: a controlled clinical comparison in onychomycosis of the toenails. J Am Acad Dermatol 1998; 38: S53-6.
13. Gupta AK, Gover MD, Lynde CW. Pulse itraconazole vs. continuous terbinafine for the treatment of dermatophyte toenail onychomycosis in patients with diabetes mellitus. J Eur Acad Dermatol Venereol 2006; 20: 1188-93.
14. Havu V, Heikkilä H, Kuokkanen K, et al. A double-blind, randomized study to compare the efficacy and safety of terbinafine (Lamisil) with fluconazole (Diflucan) in the treatment of onychomycosis. Br J Dermatol 2000; 142: 97-102.
15. Chang CH, Young-Xu Y, Kurth T, et al. The safety of oral antifungal treatments for superficial dermatophytosis and onychomycosis: a meta-analysis. Am J Med 2007; 120: 791-8.
16. Sigurgeirsson B. Intermittent versus continuous terbinafine in the treatment of toenail onychomycosis: a randomized, double-blind comparison. J Dermatolog Treat 2006; 17: 38-44.

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The Department of Pharmacy Services, UF Family Practice Medical Group, Departments of Community Health and Family Medicine and Pharmacy Practice University of Florida