

Adverse Event	amlodipine		Placebo	
	M=% (N=1218)	F=% (N=512)	M=% (N=914)	F=% (N=336)
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

The following events occurred in $\leq 1\%$ but $>0.1\%$ of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship: **Cardiovascular:** arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis. **Central and Peripheral Nervous System:** hypoaesthesia, neuropathy peripheral, paresthesia, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, agitation, gingival hyperplasia. **General:** allergic reaction, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease. **Musculoskeletal System:** arthralgia, arthrosis, muscle cramps, myalgia. **Psychiatric:** sexual dysfunction (male and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization. **Respiratory System:** dyspnea, epistaxis. **Skin and Appendages:** angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular. **Special Senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus. **Urinary System:** micturition frequency, micturition disorder, nocturia. **Autonomic Nervous System:** dry mouth, sweating increased. **Metabolic and Nutritional:** hyperglycemia, thirst. **Hemopoietic:** leukopenia, purpura, thrombocytopenia. The following events occurred in $\leq 0.1\%$ of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertension, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia. Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina. Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine. The following postmarketing event has been reported infrequently with amlodipine treatment where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine. Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles. **The Atorvastatin Component of CADUET:** Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, $<2\%$ of patients were discontinued due to adverse experiences attributable to atorvastatin calcium. The most frequent adverse events thought to be related to atorvastatin calcium were constipation, flatulence, dyspepsia, and abdominal pain. Clinical Adverse Experiences: Adverse experiences reported in $\geq 2\%$ of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in Table 3.

Table 3. Adverse Events in Placebo-Controlled Studies (% of Patients)

Body System/ Adverse Event	Placebo N=270	atorvastatin			
		10 mg N=863	20 mg N=36	40 mg N=79	80 mg N=94
BODY AS A WHOLE					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
DIGESTIVE SYSTEM					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
RESPIRATORY SYSTEM					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
SKIN AND APPENDAGES					
Rash	0.7	3.9	2.8	3.8	1.1
MUSCULOSKELETAL SYSTEM					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT): In ASCOT involving 10,305 participants treated with atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up. The following adverse events were reported, regardless of causality assessment, in patients treated with atorvastatin in clinical trials. The events in italics occurred in $\geq 2\%$ of patients and the events in plain type occurred in $<2\%$ of patients. **Body as a Whole:** Chest pain, face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema. **Digestive System:** Nausea, gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice. **Respiratory System:** Bronchitis, rhinitis, pneumonia, dyspnea, asthma, epistaxis. **Nervous System:** Insomnia, dizziness, paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertension. **Musculoskeletal System:** Arthritis, leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis. **Skin and Appendages:** Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer. **Urogenital System:** Urinary tract infection, urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage. **Special Senses:** Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion. **Cardiovascular System:** Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension. **Metabolic and Nutritional Disorders:** Peripheral edema, hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia. **Hemic and Lymphatic System:** Echinomiasis, anemia, lymphadenopathy, thrombocytopenia, petechia. **Postintroduction Reports with Atorvastatin:** Adverse events associated with atorvastatin therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), and rhabdomyolysis. **Pediatric Patients (ages 10-17 years):** In a 26-week controlled study in boys and postmenarcheal girls (n=140), the safety and tolerability profile of atorvastatin 10 to 20 mg daily was generally similar to that of placebo (see **PRECAUTIONS, Pediatric Use**).

OVERDOSAGE: There is no information on overdosage with CADUET in humans. **Information on Amlodipine:** Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg in dogs (11 or more times the maximum recommended clinical dose on a mg/m² basis) caused a marked peripheral vasodilation and hypotension. Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted. If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit. **Information on Atorvastatin:** There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

*Based on patient weight of 50 kg.

**These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

Rx only
Manufactured by:
Pfizer Ireland Pharmaceuticals
Dublin, Ireland

© 2004 Pfizer Ireland Pharmaceuticals

Distributed by:



Pfizer Labs

Division of Pfizer Inc., NY, NY 10017

Rev. 1 October 2004

Opportunistic Fungi Often Elude Diagnosis

BY ERIK L. GOLDMAN
Contributing Writer

SAN DIEGO — The rise in incidence of unusual fungi, especially in immunocompromised individuals, is complicating the diagnosis of cutaneous mycoses, said Dr. Ted Rosen at the American Academy of Dermatology's Academy 2006 conference.

"Fungal illnesses can mimic lots of different things, especially in immunocompromised patients. For example, *Cryptococcus* infection can look like Kaposi's sarcoma, bacterial cellulitis, molluscum, or even herpes," said Dr. Rosen of the department of dermatology, Baylor College of Medicine, Houston. "In HIV-positive patients, all morphologic bets are off."

As a result, many patients with strange fungal infections go undiagnosed or misdiagnosed for long periods. If one is in doubt about any cutaneous symptoms, taking a biopsy and getting fungal cultures is worthwhile, he said.

Dr. Rosen mentioned a case in which a 41-year-old HIV-positive white man presented with brown-purple papules and plaques, some of which were ulcerated. The referring physicians thought it was Kaposi's sarcoma (KS) with a secondary bacterial infection. Like many HIV-positive patients, the man had a complicated history peppered with opportunistic infections, including *Pneumocystis carinii* pneumonia, herpes zoster, and cytomegalovirus. He'd also had oral KS, so it was reasonable for the referring physician to think about cutaneous KS.

"I saw the lesions and understood right away why they thought it was KS. But the diffuse, brownish ulceration was strange, so I took a biopsy of all the brownish areas, and they came back showing *Cryptococcus neoformans*," Dr. Rosen said. The patient's blood and bone marrow were also positive for *Cryptococcus*.

Unfortunately, the patient committed suicide before Dr. Rosen was able to treat the fungal infection with amphotericin B. He recommends 1 mg/kg for 2 weeks of the standard form of amphotericin B, rather than the lipid-based form. In some cases, it makes sense to add flucytosine, 100 mg/kg per day, and then fluconazole, 400 mg per day for 10 weeks. Some HIV-positive patients should remain on fluconazole maintenance, at a dose in the 200- to 400-mg range, for life.

Dr. Rosen said between 5% and 10% of all HIV-positive individuals get *Cryptococcus*, and nearly 90% of all *Cryptococcus* cases are in HIV-positive people, though it can also affect organ transplant patients and pregnant women.

Fungal infections need not be life threatening to cause major problems for patients. Dr. Rosen described another case involving a 24-year-old, otherwise healthy woman who'd had a chronic eczema-like rash on

her cheeks for 13 years. She had been applying steroid creams for years, to no avail.

Biopsy showed pseudoepitheliomatous hyperplasia, granulomata, and small, short budding yeast forms. The culture grew out a thick fungal plaque that turned out to be *Phoma* complex, an aggregate of soil fungi that normally affect celery, beets, tomatoes, potatoes, and peppers.

"We reread the original biopsy specimen from 13 years ago, and we were able to grow out the *Phoma*. For 13 years, this patient was smearing steroids on a plant pathogen." The patient had spent a lot of time as a child on a pig farm, which is where she likely picked up the plant fungus.

"I asked for in vitro testing, to see what [the fungi were] sensitive to. You really need help from a good microbiologist in cases like this." They proved sensitive to ketoconazole and itraconazole, but not to fluconazole or griseofulvin. Dr. Rosen went with ketoconazole, 200 mg, twice daily, which resulted in a clinical and histologic cure within 18 months.

With worldwide travel and immigration come new and unusual fungal infections that mimic other common skin diseases. A case in point is a 47-year-old male construction worker who Dr. Rosen saw for a scaly, horseshoe-shaped plaque-like lesion on his forearm. The presenting lesion was actually a recurrence of the original lesion, which had been excised by a physician who thought it was a skin cancer.

The surface of the lesion was coated with a blackish powdery substance. Dr. Rosen cultured it and grew out *Fonsecaea pedrosoi*, a soil fungus that is rare in the United States and usually seen in Central American agricultural workers. It is also common in Madagascar and parts of South America. The lesions can be dead ringers for skin cancers.

For relatively mild cases of *Fonsecaea* infection, itraconazole is a good choice, said Dr. Rosen. Roughly 60% of U.S. isolates are sensitive to this drug at a dose in the 200- to 400-mg range. For more severe cases, posaconazole is the most promising choice. Cryotherapy or thermotherapy can also help, in conjunction with drug treatment. But large lesions can be hard to clear and often take a year or more of continuous treatment before showing a complete resolution, he warned.

Whenever one sees something that looks a bit unusual, especially in patients who are immunocompromised or taking any medication that might impair the immune system, one should think "fungi," said Dr. Rosen.

Novel "biologics" and anti-TNF drugs can leave patients susceptible to opportunistic fungi such as *Sporothrix*. Clinical conditions such as alcoholism, diabetes, and some forms of cancer can also leave patients vulnerable to odd fungi, he said. ■