| Adverse Event | amlodipine M=% (N=1218) | amlodipine F=% (N=512) | Placebo M=% (N=914) | Placebo 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 ≤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:** hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dyspepsia,** dysphagia, diarrhea, flatulence, pancreatitis, vomiting, 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 ≤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, hypertonia, 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 ≥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 | atorvastatin 20 mg N=36 | atorvastatin 40 mg N=79 | atorvastatin 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 ≥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, hypertonia. **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:** Ecchymosis, 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 postmenarchal 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/m$^2$ 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.

℞ **only**



Manufactured by:
**Pfizer Ireland Pharmaceuticals**
Dublin, Ireland

*Distributed by:*

**Pfizer Labs**
Division of Pfizer Inc., NY, NY 10017

**Rev. 1 October 2004**



# Study: Fibroid Symptoms Drive Women to Surgery

BY HEIDI SPLETE
*Senior Writer*

BETHESDA, MD. — Large fibroids appear to grow faster than smaller fibroids, but symptoms, rather than growth rate, spur women to surgery.

A preliminary analysis of data from 120 women in the Fibroid Growth Study suggests that large fibroids (greater than 50 cm$^3$) and medium fibroids (7-50 cm$^3$), showed a significantly greater increase in size over 1 year, compared with small fibroids (less than 7 cm$^3$).

"Most women have fibroids, but there is a subset of women that are symptomatic," Barbara J. Davis, Ph.D., said at an international conference on uterine leiomyoma research sponsored by the National Institutes of Health.

Data on the factors that cause fibroids to grow and become clinically symptomatic are limited. "Our hypothesis was that fibroids are heterogenous and that growing tumors will have different cellular and molecular characteristics than nongrowing tumors," said Dr. Davis, formerly chief of the Laboratory of Women's Health at the National Institute of Environmental Health Sciences and now a principal scientist at AstraZeneca.

She and her associates sought to compare leiomyoma growth over time as a function of the number and location of the tumors. To describe relationships between growth, clinical symptoms, and outcome, the investigators studied women at high risk for hysterectomy or myectomy.

The study results also indicated that intramural fibroids appeared to grow more slowly than did submucosal fibroids, fibroid growth might depend on the accumulation of fibrous tissue, and race had no effect on growth rate.

The study, funded by the National Institute of Environmental Health Sciences and the National Center on Minority Health and Health Disparities, included clinically symptomatic, premenopausal women with large uteri—the size of 12 weeks' gestation—who had tumors of at least 2 cm in diameter, confirmed by ultrasound at baseline.

Approximately 48% of the women were black and 41% were white.

The women had MRIs at baseline, 3 months, 6 months, and 1 year. They also underwent physicals, completed extensive medical history forms, donated blood and urine, and participated in monthly questionnaires via a 20-minute phone interview.

Women who opted for surgery donated their fibroid tissues to the study investigators and had a presurgical MRI to map the tumors for the surgeon so they could be identified by type and location.

A total of 31 women had either a hysterectomy or myomectomy during the course of the study. The average age of the surgery patients was slightly younger than the overall average (37.8 years vs. 39 years).

Overall, 1,076 fibroid volumes were calculated, including data from 52 women who completed all four MRIs—16 women who had surgery and 36 who did. The investigators used a computer program that allowed them to overlay MRI images of the fibroids at different times and determine their growth rates.

In this pulminary analysis, growth rate, defined by change in volume, was mostly a function of location and other factors.

"We were surprised that there were not significant differences in the rate of growth between women of different race or ethnicity," Dr. Davis said. The difference in the prevalence of fibroids between blacks and whites appears not to be caused by tumors growing faster in blacks.

"We did find that size was a factor in determining rates of growth," she noted. The investigators were surprised that both large and medium fibroids grew at a faster rate than small ones. "We thought that small tumors would be the fast-growing ones, and we thought we might find some that shrank, but we didn't," Dr. Davis said. In fact, all the fibroids studied grew to some extent.

Intramural fibroid growth was slower than that of subserosal fibroids. However, growth rates between intramural vs. submucosal and between submucosal vs. subserosal tumors were not significantly different. As for the impact of growth rates on clinical outcomes, there were no significant differences in growth rates between patients who had surgery and those who did not. "That was a surprise to us," Dr. Davis said. "We wondered why the women were going to surgery."

The answer is their symptoms. Symptom severity scores related to bleeding in surgery patients were almost double those of nonsurgery patients. Similarly, there was a significant difference in reported pain before and after surgery among surgery patients, compared with pain scores of nonsurgery patients.

Although the clinical symptomology differed between women who chose surgery and those who did not, the fibroid growth rates appeared similar in both groups. Dr. Davis noted that the investigators have yet to review the impact of number of tumors on outcome. The total number of fibroids per woman ranged from 1 to 11.

The most common reasons for choosing surgery were to reduce heavy bleeding (40%) and to attempt pregnancy (20%).

The investigators found a greater proportion of fibrous tissues, compared with smooth tissues, in the large tumors than in smaller tumors. The large tumors were the fastest growing, suggesting that connective tissue contributes to tumor growth rather than regression. The vascularity varied as well—the fibroids had fewer blood vessels compared with normal tissue, but the fibroid tissue bled more. Larger fibroids had a larger total area of vascularity, but the smaller fibroids had a larger cross-section of blood vessels.

Ultimately, these results and future analyses might help physicians develop a model that they can use to predict fibroid growth over time, Dr. Davis noted. ■