

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:** 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  $\leq 0.1\%$  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, 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  $\geq 2\%$  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	atorvastatin				
	Placebo N=270	10 mg N=863	20 mg N=36	40 mg N=79	80 mg N=94
<b>BODY AS A WHOLE</b>					
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
<b>DIGESTIVE SYSTEM</b>					
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
<b>RESPIRATORY SYSTEM</b>					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
<b>SKIN AND APPENDAGES</b>					
Rash	0.7	3.9	2.8	3.8	1.1
<b>MUSCULOSKELETAL SYSTEM</b>					
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, 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<sup>2</sup> 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 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.

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

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Distributed by:



**Pfizer Labs**

Division of Pfizer Inc., NY, NY 10017

Rev. 1 October 2004

LN233581

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# Set the Appendectomy Bar Low for Pregnant Patients

BY BETSY BATES

Los Angeles Bureau

PASADENA, CALIF. — The diagnosis of appendicitis can be exquisitely difficult in a nonpregnant patient. Pregnancy only makes the task more daunting.

But early diagnosis and prompt surgery can mean the difference between life and death for the mother and the fetus, said Dr. J. Gerald Quirk, chairman of obstetrics, gynecology, and reproductive medicine at the State University of New York at Stony Brook.

“The risks of temporizing appendicitis in pregnant women are quite grave,” he said at a meeting of the Obstetrical and Gynecological Assembly of Southern California.

About 1 in 1,000 pregnancies are complicated by appendicitis, and appendectomy confirms the disease in two-thirds to three-fourths of patients.

Perforation is not an uncommon result of delay, with dire consequences. Fetal death results from unperforated appendicitis in 3%-5% of cases; a perforated appendix is associated with a 20%-30% fetal mortality rate. Maternal mortality, seen in about 0.1% of cases of unperforated appendicitis, rises to 4% with perforation.

The threshold for surgery should therefore be low, and increasingly so as the pregnancy progresses, since perforation is twice

as common in the third trimester as it is in the first or second. “What you’re doing is just increasing the risks ... by waiting.”

And still, in part out of reluctance to operate unnecessarily, “We are loathe to make the diagnosis, and a lot of surgeons are loathe to act on the diagnosis,” he said.

In fact, when special accommodations are made for physiologic changes associated with pregnancy, uncomplicated surgery and anesthesiology are not thought to be linked to adverse perinatal outcomes, said Dr. Quirk. “In most cases, I think one can be assured that what’s best for Mom is best for the fetus.”

It is not surgery that poses the greatest risk, but, in the words of Dr. E.A. Babler in 1908, “[the mortality of appendicitis is] the mortality of delay.”

Uncertainty drives that delay, since many classic signs and symptoms may not be present or may be confusing in the pregnant patient, and the differential diagnosis of appendicitis is long and complex. (See box.)

The location of the appendix varies during different stages of pregnancy. “What we do know is that it moves around,” he said. Direct abdominal tenderness is a fairly reliable sign of appendicitis during pregnancy, but rebound tenderness is much less reliable, because the enlarged uterus shields the abdominal wall. Rectal tenderness is frequently absent, said Dr. Quirk.

Anorexia, present in nearly all nonpregnant patients with appendicitis, occurred in only one- to two-thirds of pregnant patients in a 1975 study from Parkland Hospital in Dallas, he noted. In early pregnancy, anorexia may be associated with morning sickness, further complicating its usefulness as a contributor to a diagnosis of appendicitis. Dr. Quirk said a urinalysis showing many white cells but no bacteria may reinforce the diagnosis of appendicitis in a pregnant woman, because periureteritis can develop over the right ureter. Ultrasound or spiral CT imaging can help but is not always reliable. In any case, do a surgical consult immediately and promptly decide to operate or not. Perioperative antibiotics should be administered. General anesthesia is usually well tolerated in pregnancy; laparoscopy and laparotomy appear equally safe. The incision generally is made over the point of maximal tenderness or at the midline if the diagnosis is seriously in doubt or if diffuse peritonitis might be present.

The table should be tilted 30 degrees to the left, and uterine manipulation should be minimized. Some institutions advocate external fetal monitoring. Post surgery, Dr. Quirk recommends monitoring the uterus for contractions. The mother should ambulate early and be kept well hydrated. During rest, the patient should maintain the tilt position. ■

## Differential Dx of Appendicitis

### Nonobstetric Conditions

Urinary calculi  
Cholelithiasis  
Cholecystitis  
Bowel obstruction  
Gastroenteritis  
Mesenteric adenitis  
Colonic carcinoma  
Rectus hematoma  
Acute intermittent porphyria  
Perforated duodenal ulcer  
Pneumonia  
Meckel’s diverticulum

### Obstetric Conditions

Preterm labor  
Abruptio placentae  
Chorioamnionitis  
Adnexal torsion  
Ectopic pregnancy  
Pelvic inflammatory disease  
Round ligament pain  
Uteroovarian vein rupture  
Carneous degeneration of myomas  
Uterine rupture (placenta percreta; rudimentary horn)

Source: Dr. Quirk