

Fidaxomicin Appears Promising for *C. difficile*

BY DOUG BRUNK

SAN FRANCISCO — Patients with *Clostridium difficile* infection who were treated with the novel macrocyclic antibiotic fidaxomicin had a 45% lower rate of recurrence compared with those who were treated with vancomycin. “It’s encouraging because fidaxomicin is an easier drug to take compared with the current therapies,” Dr. Yoav Golan

said in an interview during a poster session at the annual meeting of the Inter-science Conference on Antimicrobial Agents and Chemotherapy. “It’s only twice a day dosing versus 3 and 4 times a day for metronidazole and vancomycin. Also, it seems to have a much smaller impact on emergence of resistance among gut pathogens. This was shown previously.” The analysis involved 432 patients en-

rolled in a multicenter, randomized trial to compare the safety and efficacy of fidaxomicin, 200 mg every 12 hours, with vancomycin, 125 mg every 6 hours for 10 days, in patients with *C. difficile* infection. Fidaxomicin (Dificid) is a minimally absorbed, narrow spectrum antibiotic with limited impact on gut flora. It has been developed by Optimer Pharmaceuticals Inc., San Diego, Calif., which sponsored the trial. Dr. Golan disclosed that his re-

lationship with Optimer Pharmaceuticals is limited to functioning as an investigator in the fidaxomicin clinical trials. The drug has not been approved for use in the United States. Dr. Pamela Sears, executive director of biology and preclinical trials at Optimer Pharmaceuticals, anticipates that company will file for new drug approval with the FDA by early 2011. For the study, Dr. Golan and his associates analyzed the rate of recurrent *C. difficile* infection among 221 patients in the vancomycin group and 211 patients in the fidaxomicin group. This was defined as recurrence of diarrhea and pos-

with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1, 2.5, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m² basis, similar to the maximum recommended human dose of 10 mg amlodipine/day*. For the rat, the highest dose level was, on a mg/m² basis, about twice the maximum recommended human dose*. Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome levels. There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times*) the maximum recommended human dose of 10 mg/day on a mg/m² basis). **Studies with atorvastatin:** In a 2-year carcinogenicity study with atorvastatin calcium in rats at dose levels equivalent to 10, 30, and 100 mg atorvastatin/kg/day, 2 rare tumors were found in muscle in high-dose females; in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose. A 2-year carcinogenicity study in mice given atorvastatin calcium at dose levels equivalent to 100, 200, and 400 mg atorvastatin/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose. *In vitro*, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test. There were no effects on fertility when rats were given atorvastatin calcium at doses equivalent to up to 175 mg atorvastatin/kg/day (15 times the human exposure). There was aplasia and aspermia in the epididymides of 2 of 10 rats treated with atorvastatin calcium at a dose equivalent to 100 mg atorvastatin/kg/day for 3 months (16 times the human AUC at the 80 mg dose). Testis weights were significantly lower at 30 and 100 mg/kg/day and epididymal weight was lower at 100 mg/kg/day. Male rats given the equivalent of 100 mg atorvastatin/kg/day for 11 weeks prior to mating had decreased sperm motility, sperm head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of atorvastatin calcium equivalent to 10, 40, or 120 mg atorvastatin/kg/day for two years. *Based on patient weight of 50 kg. **Pregnancy: Pregnancy Category X (see CONTRAINDICATIONS):** Safety in pregnant women has not been established with CADUET. CADUET should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking CADUET, it should be discontinued and the patient advised again as to the potential hazards to the fetus. **Studies with amlodipine:** No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day (respectively 8 times* and 23 times*) the maximum recommended human dose of 10 mg/day on a mg/m² basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine maleate at 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. *Based on patient weight of 50 kg. **Studies with atorvastatin:** Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses of atorvastatin calcium equivalent to up to 300 mg atorvastatin/kg/day or in rabbits at doses of atorvastatin calcium equivalent to up to 100 mg atorvastatin/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m²). In a study in rats given atorvastatin calcium at doses equivalent to 20, 100, or 225 mg atorvastatin/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity for pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 for pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses of atorvastatin correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day. Rare reports of congenital anomalies have been received following intrauterine exposure to HM-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. **Labor and Delivery:** No studies have been conducted in pregnant women on the effect of CADUET, amlodipine or atorvastatin on the mother or the fetus during labor or delivery, or on the duration of labor or delivery. Amlodipine has been shown to prolong the duration of labor in rats. **Nursing Mothers:** It is not known whether the amlodipine component of CADUET is excreted in human milk. Nursing rat pups taking atorvastatin had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking CADUET should not breast-feed (see CONTRAINDICATIONS). **Pediatric Use:** There have been no studies conducted to determine the safety or effectiveness of CADUET in pediatric populations. **Studies with amlodipine:** The effect of amlodipine on blood pressure in patients less than 6 years of age is not known. **Studies with atorvastatin:** Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in controlled clinical trials of 6 months duration in adolescent boys and postmenarcheal girls. Patients treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls. See **CLINICAL PHARMACOLOGY, Clinical Studies** section; **ADVERSE REACTIONS, Pediatric Patients**; and **DOSAGE AND ADMINISTRATION, Pediatric Patients (10-17 years of age) with Heterozygous Familial Hypercholesterolemia**. Adolescent females should be counseled on appropriate contraceptive methods while on atorvastatin therapy (see **CONTRAINDICATIONS** and **PRECAUTIONS, Pregnancy**). **Atorvastatin has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.** Clinical efficacy with doses of atorvastatin up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients. See **CLINICAL PHARMACOLOGY, Clinical Studies, Atorvastatin Effects in Homozygous Familial Hypercholesterolemia**. **Geriatric Use:** There have been no studies conducted to determine the safety or effectiveness of CADUET in geriatric populations. *In studies with amlodipine:* Clinical studies of amlodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection of the amlodipine component of CADUET for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40-60%, and a lower initial dose may be required (see **DOSAGE AND ADMINISTRATION**). *In studies with atorvastatin:* The safety and efficacy of atorvastatin (10-80 mg) in the geriatric population (>65 years of age) was evaluated in the ACCESS study. In this 54-week open-label trial, 1,958 patients initiated therapy with atorvastatin calcium 10 mg. Of these, 835 were elderly (>65 years) and 1,123 were non-elderly. The mean change in LDL-C from baseline after 6 weeks of treatment with atorvastatin calcium 10 mg was -38.2% in the elderly patients versus -34.6% in the non-elderly group. The rates of discontinuation in patients on atorvastatin due to adverse events were similar between the two age groups. There were no differences in clinically relevant laboratory abnormalities between the age groups. *In studies with Atorvastatin: Use in Patients with Recent Stroke or TIA:* In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study where LIPITOR 80 mg vs placebo was administered in 4,731 subjects without CHD who had a stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the LIPITOR 80 mg group compared to placebo. Subjects with hemorrhagic stroke on study entry appeared to be at increased risk for hemorrhagic stroke.

ADVERSE REACTIONS: CADUET: CADUET (amlodipine besylate/atorvastatin calcium) has been evaluated for safety in 1092 patients in double-blind placebo controlled studies treated for co-morbid hypertension and dyslipidemia. In general, treatment with CADUET was well tolerated. For the most part, adverse experiences have been mild or moderate in severity. In clinical trials with CADUET, no adverse experiences peculiar to this combination have been observed. Adverse experiences are similar in terms of nature, severity, and frequency to those reported previously with amlodipine and atorvastatin. The following information is based on the clinical experience with amlodipine and atorvastatin. **The Amlodipine Component of CADUET:** Amlodipine has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with amlodipine was well tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of amlodipine due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose related manner are as follows:

Adverse Event	2.5 mg N=275	amlodipine 5.0 mg N=296	10.0 mg N=268	Placebo N=520
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	2.6	4.6	0.0
Palpitations	0.7	1.4	2.5	0.6

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following:

Placebo-Controlled Studies	amlodipine (%) (N=1730)	Placebo (%) (N=1250)
Headache	7.3	7.8
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal Pain	1.6	0.3
Somnolence	1.4	0.6

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as shown in the following table:

Adverse Event	M= (%) (N=1218)	F= (%) (N=512)	Placebo 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 <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. **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. **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, 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. In the CAMELOT and PREVENT studies (see **CLINICAL PHARMACOLOGY Clinical Studies, Clinical Studies with Amlodipine**) the adverse event profile was similar to that reported previously (see above), with the most common adverse event being peripheral edema. 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)	atorvastatin	20 mg N=36	40 mg N=79	80 mg N=94
Body System/Adverse Event	Placebo N=270	10 mg N=863		
BODY AS A WHOLE				
Infection	10.0	10.3	2.8	7.4
Headache	7.0	5.4	16.7	6.4
Accidental Injury	3.7	4.2	0.0	3.2
Flu Syndrome	1.9	2.2	0.0	2.5
Abdominal Pain	0.7	2.8	0.0	3.8
Back Pain	3.0	2.8	0.0	3.8
Allergic Reaction	2.6	0.9	2.8	1.3
Asthenia	1.9	2.2	0.0	3.8
DIGESTIVE SYSTEM				
Constipation	1.8	2.1	0.0	2.5
Diarrhea	1.5	2.7	0.0	3.8
Dyspepsia	4.1	2.3	2.8	1.3
Flatulence	3.3	2.1	2.8	1.3
RESPIRATORY SYSTEM				
Sinusitis	2.6	2.8	0.0	2.5
Pharyngitis	1.5	2.5	0.0	1.3
SKIN AND APPENDAGES				
Rash	0.7	3.9	2.8	3.8
MUSCULOSKELETAL SYSTEM				
Arthralgia	1.5	2.0	0.0	5.1
Myalgia	1.1	3.2	5.6	1.3

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT): In ASCOT (see **CLINICAL PHARMACOLOGY, Clinical Studies, Clinical Studies with Atorvastatin**) 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. **Collaborative Atorvastatin Diabetes Study (CARDS):** In CARDS (see **CLINICAL PHARMACOLOGY, Clinical Studies, Clinical Studies with Atorvastatin**) involving 2838 subjects with type 2 diabetes treated with LIPITOR 10 mg daily (n=1428) or placebo (n=1410), there was no difference in the overall frequency of adverse events or serious adverse events between the treatment groups during a median follow-up of 3.9 years. No cases of rhabdomyolysis were reported. **Treating to New Targets Study (TNT):** In TNT (see **CLINICAL PHARMACOLOGY, Clinical Studies**) involving 10,001 subjects with clinically evident CHD treated with LIPITOR 10 mg daily (n=5006) or LIPITOR 80 mg daily (n=4995), there were more serious adverse events and discontinuations due to adverse events in the high-dose atorvastatin group (92, 1.8%; 497, 9.9%, respectively) as compared to the low-dose group (69, 1.4%; 404, 8.1%, respectively) during a median follow-up of 4.9 years. Persistent transaminase elevations (≥3 x ULN twice within 4-10 days) occurred in 62 (1.3%) individuals with atorvastatin 80 mg and in nine (0.2%) individuals with atorvastatin 10 mg. Elevations of CK (≥ 10 x ULN) were low overall, but were higher in the high-dose atorvastatin treatment group (13, 0.3%) compared to the low-dose atorvastatin group (6, 0.1%). **Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL):** In IDEAL (see **CLINICAL PHARMACOLOGY, Clinical Studies**) involving 8,888 subjects treated with LIPITOR 80 mg/day (n=4439) or simvastatin 20-40 mg daily (n=4449), there was no difference in the overall frequency of adverse events or serious adverse events between the treatment groups during a median follow-up of 4.8 years. 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, hyposthesia, 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, hematuria, albuminuria, urinary frequency, cystitis, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, 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:** Ectchymosis, 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), rhabdomyolysis, fatigue, tendon rupture, and hepatic failure. **Pediatric Patients (Ages 10-17 years):** In a 26-week controlled study in boys and postmenarcheal girls (n=100), the safety and tolerability profile of atorvastatin 10 to 20 mg daily was generally similar to that of placebo (see **CLINICAL PHARMACOLOGY, Clinical Studies** section and **PRECAUTIONS, Pediatric Use**). **Please see full prescribing information for additional information about CADUET.**

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