

## UPCOMING MEETINGS

American College of Gastroenterology  
 American Society for Reproductive Medicine  
 North American Primary Care Research Group  
 North American Association for the Study of Obesity  
 American College of Chest Physicians  
**We Are There For You**

## POLICY &amp; PRACTICE

## Lawmakers OK Rx Rule Delay

Coming down to the wire on a new federal mandate requiring the use of tamper-resistant prescription pads for all Medicaid prescriptions beginning Oct. 1, lawmakers in the House and the Senate passed legislation in late September that would delay the mandate's start until March 31, 2008. At press time, President Bush was expected to sign the legislation, although it was not clear whether he would sign it by Oct. 1, National Community Pharmacists Association spokesman John Norton told this newspaper. The delay was bundled

with extensions on several programs due to expire Sept. 30, including an abstinence education initiative that the Bush administration supports, Mr. Norton said. The original mandate, passed as part of war funding legislation earlier this year, requires all Medicaid prescriptions to be written on "tamper resistant" paper to be eligible for federal reimbursement. Even though many states have similar requirements, pharmacists' organizations have maintained that most physicians do not currently use these types of pads, nor are supplies readily available.

## LOVAZA™ (omega-3-acid ethyl esters) Capsules

### Brief Summary of Prescribing Information

#### CLINICAL STUDIES

##### High Triglycerides: Add-on to HMG-CoA reductase inhibitor therapy

The effects of Lovaza 4 g per day as add-on therapy to treatment with simvastatin were evaluated in a randomized, placebo-controlled, double-blind, parallel-group study of 254 adult patients (122 on Lovaza and 132 on placebo) with persistent high triglycerides (200 - 499 mg/dL) despite simvastatin therapy (Table 1). Patients were treated with open-label simvastatin 40 mg per day for 8 weeks prior to randomization to control their LDL-C to no greater than 10% above NCEP ATP III goal and remained on this dose throughout the study. Following the 8 weeks of open-label treatment with simvastatin, patients were randomized to either Lovaza 4 g per day or placebo for an additional 8 weeks with simvastatin co-therapy. The median baseline triglyceride and LDL-C levels in these patients were 268 mg/dL and 89 mg/dL, respectively. Median baseline non-HDL-C and HDL-C levels were 138 mg/dL and 45 mg/dL, respectively.

The changes in the major lipoprotein lipid parameters for the Lovaza plus simvastatin and the placebo plus simvastatin groups are shown in Table 1.

Table 1: Response to the Addition of LOVAZA 4 g per day to On-going Simvastatin 40 mg per day Therapy in Patients with High Triglycerides (200 to 499 mg/dL)

Parameter	LOVAZA + Simvastatin N=122			Placebo + Simvastatin N=132			Difference	P-Value
	BL	EOT	Median % Change	BL	EOT	Median % Change		
Non-HDL-C	137	123	-9.0	141	134	-2.2	-6.8	<0.0001
TG	268	182	-29.5	271	260	-6.3	-23.2	<0.0001
TC	184	172	-4.8	184	178	-1.7	-3.1	<0.05
VLDL-C	52	37	-27.5	52	49	-7.2	-20.3	<0.05
Apo-B	86	80	-4.2	87	85	-1.9	-2.3	<0.05
HDL-C	46	48	+3.4	43	44	-1.2	+4.6	<0.05
LDL-C	91	88	+0.7	88	85	-2.8	+3.5	=0.05

BL = Baseline (mg/dL); EOT = End of Treatment (mg/dL); Median % Change = Median Percent Change from Baseline; Difference = LOVAZA Median % Change - Placebo Median % Change

Lovaza 4 g per day significantly reduced non-HDL-C, TG, TC, VLDL-C, and Apo-B levels and increased HDL-C and LDL-C from baseline relative to placebo.

##### Very High Triglycerides: Monotherapy

The effects of Lovaza 4 g per day were assessed in two randomized, placebo-controlled, double-blind, parallel-group studies of 84 adult patients (42 on Lovaza, 42 on placebo) with very high triglyceride levels (Table 2). Patients whose baseline triglyceride levels were between 500 and 2000 mg/dL were enrolled in these two studies of 6 and 16 weeks duration. The median triglyceride and LDL-C levels in these patients were 792 mg/dL and 100 mg/dL, respectively. Median HDL-C level was 23.0 mg/dL.

The changes in the major lipoprotein lipid parameters for the Lovaza and placebo groups are shown in Table 2.

Table 2: Median Baseline and Percent Change From Baseline in Lipid Parameters in Patients with Very High TG Levels (≥500 mg/dL)

Parameter	LOVAZA N=42		Placebo N=42		Difference
	BL	% Change	BL	% Change	
TG	816	-44.9	788	+6.7	-51.6
Non-HDL-C	271	-13.8	292	-3.6	-10.2
TC	296	-9.7	314	-1.7	-8.0
VLDL-C	175	-41.7	175	-0.9	-40.8
HDL-C	22	+9.1	24	0.0	+9.1
LDL-C	89	+44.5	108	-4.8	+49.3

BL = Baseline (mg/dL); % Chg = Median Percent Change from Baseline; Difference = Lovaza Median % change - Placebo Median % Change

Lovaza 4 g per day reduced median TG, VLDL-C, and non-HDL-C levels and increased median HDL-C from baseline relative to placebo. Lovaza treatment to reduce very high TG levels may result in elevations in LDL-C and non-HDL-C in some individuals. Patients should be monitored to ensure that the LDL-C level does not increase excessively.

The effect of Lovaza on the risk of pancreatitis in patients with very high TG levels has not been evaluated.

The effect of Lovaza on cardiovascular mortality and morbidity in patients with elevated TG levels has not been determined.

#### INDICATIONS AND USAGE

##### Very High Triglycerides

Lovaza is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (≥500 mg/dL) triglyceride levels.

##### Usage Considerations:

In individuals with hypertriglyceridemia (HTG), excess body weight and excess alcohol intake may be important contributing factors and should be addressed before initiating any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, (such as hypothyroidism or diabetes mellitus) should be looked for and adequately treated. Estrogen therapy, thiazide diuretics, and beta blockers are sometimes associated with massive rises in plasma TG levels. In such cases, discontinuation of the specific etiologic agent, if medically indicated, may obviate the need for specific drug therapy for HTG.

The use of lipid-regulating agents should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use lipid-regulating agents, the patient should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet (See PRECAUTIONS).

#### CONTRAINDICATIONS

Lovaza is contraindicated in patients who exhibit hypersensitivity to any component of this medication.

#### PRECAUTIONS

##### General:

**Initial Therapy:** Laboratory studies should be performed to ascertain that the patient's TG levels are consistently abnormal before instituting Lovaza therapy. Every attempt should be made to control serum TG levels with appropriate diet, exercise, weight loss in overweight patients, and control of any medical problems (such as diabetes mellitus and hypothyroidism) that may be contributing to the patient's TG abnormalities. Medications known to exacerbate HTG (such as beta blockers, thiazides, and estrogens) should be discontinued or changed, if possible, before considering TG-lowering drug therapy.

**Continued Therapy:** Laboratory studies should be performed periodically to measure the patient's TG levels during Lovaza therapy. Lovaza therapy should be withdrawn in patients who do not have an adequate response after 2 months of treatment.

##### Information for Patients:

Lovaza should be used with caution in patients with known sensitivity or allergy to fish. Patients should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet.

##### Laboratory Tests:

In some patients, increases in alanine aminotransferase (ALT) levels without a concurrent increase in aspartate aminotransferase (AST) levels were observed. Alanine aminotransferase levels should be monitored periodically during Lovaza therapy.

In some patients, Lovaza increased low-density lipoprotein cholesterol (LDL-C) levels. As with any lipid-regulating product, LDL-C levels should be monitored periodically during Lovaza therapy.

##### Drug Interactions:

**Anticoagulants:** Some studies with omega-3-acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Clinical studies have not been done to thoroughly examine the effect of Lovaza and concomitant anticoagulants. Patients receiving treatment with both Lovaza and anticoagulants should be monitored periodically.

**HMG-CoA reductase inhibitors:** In a 14-day study of 24 healthy adult subjects, daily co-administration of simvastatin 80 mg with Lovaza 4 g did not affect the extent (AUC) or rate (C<sub>max</sub>) of exposure to simvastatin or the major active metabolite, beta-hydroxy simvastatin at steady state.

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**Cytochrome P450-Dependent Monooxygenase Activities:** Omega-3-fatty acid containing products have been shown to increase hepatic concentrations of cytochrome P450 and activities of certain P450 enzymes in rats. The potential of Lovaza to induce P450 activities in humans has not been studied.

##### Carcinogenesis, Mutagenesis, Impairment of Fertility:

In a rat carcinogenicity study with oral gavage doses of 100, 600, 2000 mg/kg/day by oral gavage, males were treated with omega-3-acid ethyl esters for 101 weeks and females for 89 weeks without an increased incidence of tumors (up to 5 times human systemic exposures following an oral dose of 4 g/day based on a body surface area comparison). Standard lifetime carcinogenicity bioassays were not conducted in mice.

Omega-3-acid ethyl esters were not mutagenic or clastogenic with or without metabolic activation in the bacterial mutagenesis (Ames) test with *Salmonella typhimurium* and *Escherichia coli* or in the chromosomal aberration assay in Chinese hamster V79 lung cells or human lymphocytes. Omega-3-acid ethyl esters were negative in the *in vivo* mouse micronucleus assay.

In a rat fertility study with oral gavage doses of 100, 600, 2000 mg/kg/day, males were treated for 10 weeks prior to mating and females were treated for 2 weeks prior to and throughout mating, gestation and lactation. No adverse effect on fertility was observed at 2000 mg/kg/day (5 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

##### Pregnancy Category C:

There are no adequate and well-controlled studies in pregnant women. It is unknown whether Lovaza can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Lovaza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Omega-3-acid ethyl esters have been shown to have an embryocidal effect in pregnant rats when given in doses resulting in exposures 7 times the recommended human dose of 4 g/day based on a body surface area comparison. In female rats given oral gavage doses of 100, 600, 2000 mg/kg/day beginning two weeks prior to mating and continuing through gestation and lactation, no adverse effects were observed in the high dose group (5 times human systemic exposure following an oral dose of 4 g/day based on body surface area comparison).

In pregnant rats given oral gavage doses of 1000, 3000, 6000 mg/kg/day from gestation day 6 through 15, no adverse effects were observed (14 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

In pregnant rats given oral gavage doses of 100, 600, 2000 mg/kg/day from gestation day 14 through lactation day 21, no adverse effects were seen at 2000 mg/kg/day (5 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, decreased live births (20% reduction) and decreased survival to postnatal day 4 (40% reduction) were observed in a dose-ranging study using higher doses of 3000 mg/kg/day (7 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

In pregnant rabbits given oral gavage doses of 375, 750, 1500 mg/kg/day from gestation day 7 through 19, no findings were observed in the fetuses in groups given 375 mg/kg/day (2 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, at higher doses, evidence of maternal toxicity was observed (4 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

##### Nursing Mothers:

It is not known whether omega-3-acid ethyl esters are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Lovaza is administered to a woman who is breastfeeding.

##### Pediatric Use:

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

##### Geriatric Use:

A limited number of patients over 65 years of age were enrolled in the clinical studies. Safety and efficacy findings in subjects over 60 years of age did not appear to differ from those of subjects less than 60 years of age.

#### ADVERSE REACTIONS

Treatment-emergent adverse events reported in at least 1% of patients treated with Lovaza 4 g per day or placebo during 8 randomized, placebo-controlled, double-blind, parallel-group studies for HTG are listed in Table 3. Adverse events led to discontinuation of treatment in 3.5% of patients treated with Lovaza and 2.6% of patients treated with placebo.

Table 3: Adverse Events in Randomized, Placebo-Controlled, Double-Blind, Parallel-Group Studies for Very High TG Levels (≥ 500 mg/dL) that Used LOVAZA 4 g per Day

BODY SYSTEM Adverse Event	LOVAZA (N = 226)		Placebo* (N = 228)	
	n	%	n	%
Subjects with at least 1 adverse event	80	35.4	63	27.6
Body as a whole				
Back pain	5	2.2	3	1.3
Flu syndrome	8	3.5	3	1.3
Infection	10	4.4	5	2.2
Pain	4	1.8	3	1.3
Cardiovascular				
Angina pectoris	3	1.3	2	0.9
Digestive				
Dyspepsia	7	3.1	6	2.6
Eructation	11	4.9	5	2.2
Skin				
Rash	4	1.8	1	0.4
Special senses				
Taste perversion	6	2.7	0	0.0

Adverse events were coded using COSTART, version 5.0. Subjects were counted only once for each body system and for each preferred term.

\*Placebo was corn oil for all studies.

Additional adverse events reported by 1 or more patients from 22 clinical studies for HTG are listed below:

**BODY AS A WHOLE:** Enlarged abdomen, asthenia, body odor, chest pain, chills, suicide, fever, generalized edema, fungal infection, malaise, neck pain, neoplasm, rheumatoid arthritis, and sudden death.

**CARDIOVASCULAR SYSTEM:** Arrhythmia, bypass surgery, cardiac arrest, hyperlipemia, hypertension, migraine, myocardial infarct, myocardial ischemia, occlusion, peripheral vascular disorder, syncope, and tachycardia.

**DIGESTIVE SYSTEM:** Anorexia, constipation, dry mouth, dysphagia, colitis, fecal incontinence, gastritis, gastroenteritis, gastrointestinal disorder, increased appetite, intestinal obstruction, melena, pancreatitis, tenesmus, and vomiting.

**HEMATOLOGIC-LYMPHATIC SYSTEM:** Lymphadenopathy.

**INFECTIONS AND INFESTATIONS:** Viral infection.

**METABOLIC AND NUTRITIONAL DISORDERS:** Edema, hyperglycemia, increased ALT, and increased AST.

**MUSCULOSKELETAL SYSTEM:** Arthralgia, arthritis, myalgia, pathological fracture, and tendon disorder.

**NERVOUS SYSTEM:** Central nervous system neoplasia, depression, dizziness, emotional lability, facial paralysis, insomnia, vasodilatation, and vertigo.

**RESPIRATORY SYSTEM:** Asthma, bronchitis, increased cough, dyspnea, epistaxis, laryngitis, pharyngitis, pneumonia, rhinitis, and sinusitis.

**SKIN:** Alopecia, eczema, pruritus, and sweating.

**SPECIAL SENSES:** Cataract.

**UROGENITAL SYSTEM:** Cervix disorder, endometrial carcinoma, epididymitis, and impotence.

#### DRUG ABUSE AND DEPENDENCE

Lovaza does not have any known drug abuse or withdrawal effects.

#### OVERDOSAGE

In the event of an overdose, the patient should be treated symptomatically, and general supportive care measures instituted, as required.

#### Rx only

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## Part B Premium Up 3.1% for Most Beneficiaries

The standard monthly Medicare Part B premium will increase to \$96.40 next year, up 3.1% from the current \$93.50, Kerry Weems, the administrator of the Centers for Medicare and Medicaid Services announced in a teleconference with reporters.

That amount will be paid by individuals with an annual income of \$82,000 or less or couples with \$160,000 or less a year, approximately 95% of all Medicare beneficiaries, according to the agency.

Next year, Part B premiums again will be tied to beneficiary income as required by the Medicare Modernization Act. As income goes up, so does the premium and the amount of increase. For example, beneficiaries in the top bracket (those with annual income of more than \$205,000 or more than \$410,000 for couples), the amount will increase to \$238.40, by \$77 or 48%, from this year's \$161.40. The Part B deductible also will increase to \$135 from the current \$131.

The increases are a result of growth in certain areas of Medicare's fee-for-service program, including home health services and independent lab and physician-administered drugs, and in the Medicare Advantage program, as well as the need to increase contingency reserves in the Part B trust fund, Mr. Weems said.

Dr. Edward Langston, who is the chair of the American Medical Association Board of Trustees, expressed concern that government is cutting payment to doctors who care for the majority of Medicare patients who are in effect "helping subsidize overpayments to private insurance companies [providing Medicare Advantage plans], while only one in five Medicare patients participates," he said in a statement.

The AMA is calling on Congress to eliminate overpayments to Medicare Advantage plans.

CMS also announced increases in the Medicare Part A deductible and in the premium for those who must "buy in" for coverage. Beneficiaries who have less than 30 quarters of coverage would have to pay \$432, up \$13 from the current \$419. The Part A deductible, payable at first hospital admission, will increase to \$1,024, up \$32 from the current \$992.

—Renée Matthews

## Insurance Premium Increase Slows

Employer-sponsored health insurance premiums rose on average 6.1% in 2007, reflecting a continuing slowdown in premium increases. The 2007 premium increase is the smallest hike since 1999, according to an employer survey by the Kaiser Family Foundation and the Health Research and Educational Trust. But experts say the slowdown is likely temporary and isn't providing relief to individuals or employers. In fact, the 6.1% increase is higher than the average increase in wages (3.7%) and in the overall inflation rate (2.6%). In 2007, the average premium for family coverage in the United States is \$12,106, with work-

ers paying about \$3,281 for their share of the policy. The market continues to be dominated by preferred provider organizations, which insure about 57% of covered workers; consumer-driven plans account for only about 5%. For details, visit [www.kff.org/insurance/7672](http://www.kff.org/insurance/7672).

## N.J. Task Force Examines MD Gifts

The New Jersey Attorney General's Advisory Task Force on Physician Compensation, which met for the first time in September, is examining the potential impact of payments and gifts to physicians from the drug and device industry. The task force will also consider possible

public disclosure of gifts, direct disclosure to patients, and limits on payments to physicians. Vermont, Maine, Minnesota, West Virginia, and the District of Columbia have passed laws requiring some form of reporting of payments made to physicians by pharmaceutical and medical device companies. In response to the formation of the task force, the Pharmaceutical Research and Manufacturers of America issued a statement citing its 2002 Code on Interactions with Healthcare Professionals as an important safeguard. The code declares all forms of entertainment to be inappropriate and says that any gifts given to physicians should sup-

port medical practice and be valued at less than \$100.

## Taxing Health Benefits

Proposals to cap the tax deductions employers and employees can take regarding health insurance could spell the end of employer-based health benefits, according to a new report from the Employee Benefit Research Institute. Under the current system, employers are allowed to deduct the cost of the health insurance coverage they provide to their workers with no limits and workers are not taxed on the value of the health coverage they receive. Capping these tax exclusions could cause young, healthy workers to seek insurance outside of their employers' offering, leaving the employer-based pool with an older, sicker group of patients, the EBRI report said. The organization also examined the potential effect of offering tax credits as a way to reduce the number of uninsured Americans. But even a sizable tax credit is unlikely to be enough to offset the high costs of health insurance, the report noted. The full report is available online at [www.ebri.org](http://www.ebri.org).

## One-Third of Americans Uninsured

According to a September report by Families USA, almost 35% of Americans had no health care coverage for at least part of 2006-2007, up from about 30% in 1999-2000. Of these, 19% were uninsured for the entire period and 19% were uninsured for longer than 1 year; more than half were uninsured for longer than 6 months. Of the 89.6 million individuals who lacked health care coverage, 71% were employed full time and another nearly 9% were working part time; only 17% were unemployed. The states with the highest percentage of uninsured residents under the age of 65 were Texas (46%), New Mexico (44%), and Arizona (42%). The numbers in the report are substantially larger than those published by the U.S. Census Bureau (which cites 47 million uninsured in 2006, or 16%), because Census Bureau statistics include only those who were uninsured for a full year. The report is available at [www.familiesusa.org](http://www.familiesusa.org).

## Required Audits of Limited Value

The Centers for Medicare and Medicaid Services did not meet the audit requirement for private insurers participating in Medicare for the contract years 2001-2005, nor did it attempt to recover overpayments to the insurers that should have been channeled back to the beneficiaries and government, according to a report by the Government Accountability Office. The Balanced Budget Act of 1997 required the CMS to conduct annual audits of at least one-third of the participating insurers. During 2001-2005, between 19% and 23% of organizations were audited, and only 14% were audited in 2006. In 2003, 49 of 220 participating plans were audited; a contractor identified errors for 41 of those, which would have translated into \$59 million that could have covered additional benefits or offset costs for beneficiaries. The CMS claimed that it does not have legal authority to pursue such financial recoveries, but the GAO asserted that the CMS has the authority but did not exercise it.

—Leanne Sullivan

## ADVERSE REACTIONS

**Clinical Trials Experience.** The overall incidence of side effects reported in patients receiving sitagliptin and metformin was similar to that reported with patients receiving placebo and metformin.

In a 24-week placebo-controlled trial of sitagliptin 100 mg administered once daily added to a twice-daily metformin regimen, there were no adverse reactions reported regardless of investigator assessment of causality in  $\geq 5\%$  of patients and more commonly than in patients given placebo. Discontinuation of therapy due to clinical adverse reactions was similar to the placebo treatment group (sitagliptin and metformin, 1.9%; placebo and metformin, 2.5%).

The overall incidence of adverse reactions of hypoglycemia in patients treated with sitagliptin and metformin was similar to patients treated with placebo and metformin (100 mg sitagliptin and metformin, 1.3%; placebo and metformin, 2.1%). Adverse reactions of hypoglycemia were based on all reports of hypoglycemia; a concurrent glucose measurement was not required. The incidence of selected gastrointestinal adverse reactions in patients treated with sitagliptin and metformin was also similar to placebo and metformin: nausea (sitagliptin and metformin, 1.3%; placebo and metformin, 0.8%), vomiting (1.1%, 0.8%), abdominal pain (2.2%, 3.8%), and diarrhea (2.4%, 2.5%).

No clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed with the combination of sitagliptin and metformin.

The most common adverse experience in sitagliptin monotherapy reported regardless of investigator assessment of causality in  $\geq 5\%$  of patients and more commonly than in patients given placebo was nasopharyngitis.

The most common ( $>5\%$ ) established adverse reactions due to initiation of metformin therapy are diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache.

### Laboratory Tests.

**Sitagliptin.** The incidence of laboratory adverse reactions was similar in patients treated with sitagliptin and metformin (7.6%) compared to patients treated with placebo and metformin (8.7%). In most but not all studies, a small increase in white blood cell count (approximately 200 cells/microL difference in WBC vs placebo; mean baseline WBC approximately 6600 cells/microL) was observed due to a small increase in neutrophils. This change in laboratory parameters is not considered to be clinically relevant.

**Metformin hydrochloride.** In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B<sub>12</sub> levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B<sub>12</sub> absorption from the B<sub>12</sub>-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B<sub>12</sub> supplementation [see *Warnings and Precautions*].

**Postmarketing Experience.** The following additional adverse reactions have been identified during postapproval use of sitagliptin, one of the components of JANUMET. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria.

## DRUG INTERACTIONS

**Cationic Drugs.** Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of JANUMET and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

**Digoxin.** There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (C<sub>max</sub>, 18%) of digoxin with the coadministration of 100 mg sitagliptin for 10 days. These increases are not considered likely to be clinically meaningful. Digoxin, as a cationic drug, has the potential to compete with metformin for common renal tubular transport systems, thus affecting the serum concentrations of either digoxin, metformin or both. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or JANUMET is recommended.

**Glyburide.** In a single-dose interaction study in type 2 diabetes patients, coadministration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C<sub>max</sub> were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

**Furosemide.** A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration. Furosemide increased the metformin plasma and blood C<sub>max</sub> by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C<sub>max</sub> and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

**Nifedipine.** A single-dose, metformin-nifedipine drug interaction study in normal healthy

volunteers demonstrated that coadministration of nifedipine increased plasma metformin C<sub>max</sub> and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T<sub>max</sub> and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

**The Use of Metformin with Other Drugs.** Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving JANUMET the patient should be closely observed to maintain adequate glycemic control.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

## USE IN SPECIFIC POPULATIONS

### Pregnancy

#### Pregnancy Category B.

**JANUMET.** There are no adequate and well-controlled studies in pregnant women with JANUMET or its individual components; therefore, the safety of JANUMET in pregnant women is not known. JANUMET should be used during pregnancy only if clearly needed.

Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to JANUMET while pregnant. Health care providers are encouraged to report any prenatal exposure to JANUMET by calling the Pregnancy Registry at (800) 986-8999.

No animal studies have been conducted with the combined products in JANUMET to evaluate effects on reproduction. The following data are based on findings in studies performed with sitagliptin or metformin individually.

**Sitagliptin.** Reproduction studies have been performed in rats and rabbits. Doses of sitagliptin up to 125 mg/kg (approximately 12 times the human exposure at the maximum recommended human dose) did not impair fertility or harm the fetus. There are, however, no adequate and well-controlled studies with sitagliptin in pregnant women.

Sitagliptin administered to pregnant female rats and rabbits from gestation day 6 to 20 (organogenesis) was not teratogenic at oral doses up to 250 mg/kg (rats) and 125 mg/kg (rabbits), or approximately 30 and 20 times human exposure at the maximum recommended human dose (MRHD) of 100 mg/day based on AUC comparisons. Higher doses increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100 times human exposure at the MRHD.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 decreased body weight in male and female offspring at 1000 mg/kg. No functional or behavioral toxicity was observed in offspring of rats.

Placental transfer of sitagliptin administered to pregnant rats was approximately 45% at 2 hours and 80% at 24 hours postdose. Placental transfer of sitagliptin administered to pregnant rabbits was approximately 66% at 2 hours and 30% at 24 hours.

**Metformin hydrochloride.** Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

**Nursing Mothers.** No studies in lactating animals have been conducted with the combined components of JANUMET. In studies performed with the individual components, both sitagliptin and metformin are secreted in the milk of lactating rats. It is not known whether sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when JANUMET is administered to a nursing woman.

**Pediatric Use.** Safety and effectiveness of JANUMET in pediatric patients under 18 years have not been established.

**Geriatric Use.** **JANUMET.** Because sitagliptin and metformin are substantially excreted by the kidney and because aging can be associated with reduced renal function, JANUMET should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function [see *Warnings and Precautions*].

**Sitagliptin.** Of the total number of subjects (N=3884) in Phase II and III clinical studies of sitagliptin, 725 patients were 65 years and over, while 61 patients were 75 years and over. No overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this and other reported clinical experience have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

**Metformin hydrochloride.** Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin should only be used in patients with normal renal function. The initial and maintenance dosing of metformin should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dose adjustment should be based on a careful assessment of renal function [see *Contraindications; Warnings and Precautions*].



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