Not All Breast Cancer Patients Need Radiotherapy

BY BRUCE JANCIN

Denver Bureau

SAN ANTONIO — Lumpectomy and tamoxifen without radiotherapy is a reasonable choice for women aged 70 years or older with early-stage estrogen receptor-positive breast cancer, Dr. Kevin S. Hughes said at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

The supporting evidence comes from a

new 8.2-year update of a large randomized, multicenter, prospective trial. The resultant conclusion—that radiotherapy adds only limited benefit—is identical to the lesson drawn from an earlier 5-year follow-up of the same women (N. Engl. J. Med. 2004;351:971-7). At the time of the earlier analysis, critics insisted that 5 years wasn't long enough to show the benefits of radiation. But at 8.2 years, the case for radiotherapy hasn't grown any stronger, said Dr. Hughes, a surgical oncologist at Massachusetts General Hospital, Boston.

The study, known as Cancer and Leukemia Group B (CALGB) 9343, involved 631 women aged 70 or older who had clinical stage I, node-negative, estrogen receptor-positive breast cancer measuring 2 cm or smaller in size. All underwent lumpectomy and were randomized to receive tamoxifen and radiotherapy, or tamoxifen alone.

By 8.2 years, 20 patients in the tamoxifenonly arm had an ipsilateral breast recur-

rence, compared with 4 patients in the radiotherapy arm. This translates into an absolute 5% reduction in in-breast recurrence. There was also an absolute 0.9% lower incidence of axillary recurrence, for an overall absolute 5.9% decrease in locoregional recurrence in the radiotherapy group.

But this modest benefit didn't confer any clinically meaningful advantages for radiation in this aged population. Radiotherapy had no benefit over tamoxifen alone in terms of rates of ultimate breast

VYTORIN® (ezetimibe/simvastatin) Brief Summary of Prescribing Information CONTRAINDICATIONS

Hypersensitivity to any component of this medication. Active liver disease or unexplained persistent elevations in serum transaminases (see WARNINGS, Liver Enzymes).

of unexplained persistent elevations in serum draisaminases (see warkinings, Luver Enzymes).

Pregnancy and lactation. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as simvastain to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, VYTORIN is contraindicated during pregnancy and in nursing mothers. VYTORIN should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, VYTORIN should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, Pregnancy). WARNINGS.

patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, WTORIN should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, Pregnancy). WARNINGS Myopathy/Rhabdomyolysis: In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with exetimibe compared with the relevant control arm (placebo or HMG-CoA reductase inhibitor alone). However, myopathy and rhabdomyolysis are known adverse reactions to HMG-CoA reductase inhibitors and other lipid-lowering drugs. In dinical trials, the incidence of CK-210 x the upper limit of normal [ULN] was 0.2% for VYTORIN. (See PRECAUTIONS, Skeletal Muscle.) Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase above 10 x ULN. Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitors, the risk of myopathy is increased by high levels of HMG-CoA reductase inhibitors, the risk of myopathy is a same and the sam

merit doser monitoring. Therapy with VYTORIN snould be considered from the constraints of the constraints of

telithromyon is unavoidable, unerapy many constitutions of treatment.

Other drugs: Gemfibrozil, particularly with higher doses of VYTORIN, and other fibrates: The safety and effectiveness of ezetimibe administered with fibrates have not been established. Therefore, the concomitant use of VYTORIN and fibrates

other drugs: Cembriozal, particularly with nigher doses of vrVioRiv, and other fibrates: The safely and effectiveness of ezetimibe administered with fibrates have not been established. Therefore, the concomitant use of VYTORIN and fibrates should be avoided.

There is an increased risk of myopathy when simastatin is used concomitantly with fibrates (especially gemifibrozil). The combined use of simastatin with gemifibrozil should be avoided, unless the benefits are likely to outweigh the increased risks of this drug combination. The dose of simastatin should not exceed 10 mg daily in aphents receiving concomitant medication with gemifibrozil. Therefore, although not recommended, if VYTORIN is used in combination with gemifibrozil, the dose should not exceed 10/10 mg daily. (See PRECAUTIONS, Drug Interactions, Other drug interactions, Fibrates.)

Niacin (=1 g/day): Caution should be used when prescribing lipid-lowering doses (=1 g/day) of niacin with VYTORIN, as niacin can cause myopathy when given alone. The benefit of further alterations in lipid levels by the combined use of VYTORIN with niacin should be carefully weighed against the optential risks of this drug combination (see PRECAUTIONS, Drug Interactions, Interactions with lipid-lowering drugs that can cause myopathy when given alone.)

Cyclosporine or danazol with higher doses of VYTORIN: The dose of VYTORIN should not exceed 10/10 mg daily in patients receiving concomitant medication with cyclosporine or danazol should be carefully weighed against the risks of these combinations. (See PRECAUTIONS, Drug Interactions). In the patients receiving cyclosporine or danazol should be carefully weighed against the risks of these combinations. (See PRECAUTIONS) are patient of the use of VYTORIN in patients receiving overlay interactions.) Under drug interactions and mindardone in an analysis of clinical trials involving 25,248 patients treated with simusotatin 20 to 80 mg, the incidence of myopathy was higher in patients receiving recommendations for interaction The scribing recommendations for interacting agents are summarized in the table lelow (see also PRECAUTIONS, Drug Interactions), long Interactions Associated with Increased Risk of Myopathy/Rhabdomyohsis

Drug interactions Associated with increased task of Myopathy/Mabbaohnyolysis						
Interacting Agents	Prescribing Recommendations					
Itraconazole Ketoconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone Fibrates*	Avoid VYTORIN					
Cyclosporine Danazol	Do not exceed 10/10 mg VYTORIN daily					
Amiodarone Verapamil	Do not exceed 10/20 mg VYTORIN daily					
Grapefruit juice	Avoid large quantities of grapefruit juice					

VYTORIN® (ezetimibe/simvastatin)
Liver Enzymes
In 3 placebo-controlled, 12-week trials, the incidence of consecutive elevation

Liver Enzymes
In 5 placebo-controlled, 12-week trials, the incidence of consecutive elevations (23 x ULN) in serum transaminases was 1.7% overall for patients treated with VTORIN and appeared to be dose-related with an incidence of 2.6% for patients treated with VTORIN and appeared to be dose-related with an incidence of 2.6% for patients treated with VTORIN 10/80. In controlled long-term (48-week) extensions, which included both newly-treated and previously-treated patients, the incidence of consecutive elevations (23 x ULN) in serum transaminases was 1.8% overall and 3.6% for patients treated with VTORIN 10/80. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment. It is recommended that liver function tests be performed before the initiation of treatment with VTORIN, and thereafter when clinically indicated. Patients titrated to the 10/80-mg dose should receive an additional test prior to titration, 3 months after titration to the 10/80-mg dose, and periodically thereafter (eg, semiannually) for the first year of treatment. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(es) return to normal. Should an increase in AST or ALT of 3 x ULN or greater persist, withdrawal of therapy with VYTORIN is recommended.

VYTORIN should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained persistent transaminase elevations are contraindications to the use of VYTORIN.

PRECAUTIONS

alcohol and/or have a past history of liver disease. Active liver diseases or unexplained persistent transaminase elevations are contraindications to the use of VTTORIN. PRECAUTION. Information for Patients: Patients should be advised about substances they should not take concomitantly with VTTORIN and be advised to report promptly unexplained muscle pain, tenderness, or weakness (see below and WARNINGS, Myopathy/Rhabdarmyoh/sis). Patients should also be advised to inform other physicians prescribing a new medication that they are taking VTTORIN. Skeletal Muscle: In post-marketing experience with ezetimbe, cases of myopathy and habdomyolysis have been reported regardless of causality. Most patients who developed rhabdomyolysis were taking a statin prior to initiating ezetimibe. However, rhabdomyolysis been reported very rarely with ezetimbe monotherapy and very rarely with the addition of ezetimbe to agents known to be associated with increased risk of rhabdomyolysis, such as fibrates. Hepatic Insufficiency: Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, VYTORIN is not recommended in these patients.

regular Instituteity. Due to the inhalown entects of the interessed exposure as preetimble in patients with moderate or severe hepatic insufficiency, VYTORIN is not recommended in these patients.

Drug Interactions

VYTORIN: CYP3A4 Interactions: Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of the simwastatin component of VYTORIN. See WARNINGS, Myopathy/Rhabdomyolysis. Intraconazole, ketoconazole, erythromycin, clarithromycin, tellithromycin, HIV protease inhibitors, nefazodone, large quantities of grapefritti juice (>1 quart daily). Interactions with lipid-lowering drugs that can cause myopathy when given alone See WARNINGS, Myopathy/Rhabdomyolysis.

The risk of myopathy is increased by gemifbrozil and to a lesser extent by other fibrates and niacin (nicotinic acid) (-is giday).

Other drug interactions

Danazol: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of danazol particularly with higher doses of VYTORIN (see WARNINGS, Myopathy/Rhabdomyolysis).

Arniodarone or Verapamii: The risk of myopathy/fhabdomyolysis is increased by concomitant administration of amazol particularly with higher doses of VYTORIN (see WARNINGS, Myopathy/Rhabdomyolysis).

Cholestyramine: Concomitant cholestyramine administration decreased the mean AUC of total ezetimbe approximately 55%. The incremental LDL-C reduction due to adding VYTORIN to cholestyramine may be reduced by this interaction.

Cyclosporine: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine particularly with higher doses of VYTORIN (see WARNINGS, Myopathy/Rhabdomyolysis).

Caution should be exercised when using VYTORIN and cyclosporine concomitantly due to increase in exercisine exposure may be greater in patients with severe renal insufficiency. In patients treated with cyclosporine, the potential effects of the increased exposure to exelimible from concomitant use should be carefully weighed against this severe renal insufficiency. In patients

exposure to exeturnise from concomitant use should be Carefully weighed against est sudy in post-renal transplant patients with mildly impaired or normal renal function (creatinine dearance of 2-50 ml/min), concomitant cyclosporine administration increased the mean AUC and C__ of total exetimibe 3.4-fold (range 2.3- to 79-fold) and 3.9-fold (range 3.0- to 4.4-fold), respectively. In a separate study, the total exetimibe exposure increased 12-fold in one renal transplant patient with severe renal insufficiency receiving multiple medications, including cyclosporine. (See WARNINICS, MyopathyRhabdomyolysis.) Digowir: Concomitant administration of a single does of digowin healthy male doubliness receiving simvastatin resulted in a slight elevation (<0.3 ng/ml.) in plasma digowin concentrations compared to concomitant administration of placebo and digowin Patients taking digowin should be monitored appropriately when VYTORIN is initiated. Fibrates have not been established Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, exetimible increased cholesterol in the galliblader bile. Coadministration of Intro Viori Niu with fibrates is not recommended until use in patients is studied. (See WARNINGS, MyopathyRhabdomyolysis). Warfarin: Simvastatin 20-40 mg/day modestly potentiated the effect of comanin anticoagulants: the prothrombin time, reported as international Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in a normal volunteer study and in a hypercholesterolemic patient study, respectively. With other statins, clinically evident bleeding and/or increased prothrombin time has been reported in a few balants that prothrombin time as the mean of prothrombin time cocurs. Once astable prothrombin time has been documented, prothrombin time scan be monitored at the intervals usually recommended for patients on coumann anticoagulants. If the commended of the patients on totaling anticoagulants.

Concomitant administration o

(INR) in patients who had ezetimibe added to warfain. Most of these patients were also on other medications. The effect of VYTORIN on the prothrombin time has not been studied.
Ezetimibe: Fenolibrate: In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold.
Gernifibrozii: In a pharmacokinetic study, concomitant gernifibrozii administration increased total ezetimibe concentrations approximately 1.7-fold.
Sirrusatstin: Propranolol: In healthy male volunteers there was a significant decrease in mean C_{max}, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of simvastatin total and active inhibitors with concomitant administration of single doses of simvastatin total and active inhibitors with concomitant administration of single doses of simvastatin and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.
CNS Toxicity

Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 2 times higher than the mean plasma drug level in humans taking 80 mg/day. Achemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean plasma drug level in humans taking 80 mg/day.

VYTORIN* (ezetimibe/simvastatin)
also produced vestibulocochiear Walleinan-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose. CNS vascular lesions, characterized by penkascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels were seen in dogs treated with simmastatin at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.
There were cataracts in female rats after 2 years of treatment with 50 and 100 mg/kg/day (22 and 25 times the human ALC at 80 mg/day, respectively) and in dogs after 3 months at 90 mg/kg/day (19 times) and at 2 years at 50 mg/kg/day (5 times). Caranogenesis, Mutagenesis, Impairment of Fertility
VYTOR/IN: No animal cartonogenicity or fertility studies have been conducted with the combination of ezetimibe and simvastatin. The combination of ezetimibe with simvastatin did not show evidence of mutagenicity in vitro in a microbial mutagenicity (Ames) test with Salmonella typhimurium and Escherichia coli with or without metabolic activation. There was no evidence of genotoxicity at doses up to 600 mg/kg with the combination of ezetimibe and simvastatin with or without metabolic activation. There was no evidence of genotoxicity at doses up to 600 mg/kg with the combination of ezetimibe and simvastatin with or without metabolic activation. There was no evidence of genotoxicity at doses up to 500 mg/kg with exe mobination of ezetimibe and simvastatin (11) in the in vivo mouse micronucleus test.

**Exetimibe: A 104-week dietary carcinogenicity study with ezetimibe was conducted in rats at doses up to 1500 mg/kg/day (Tis0 times the human exposure at 10 mg daily based on AUC₀₋₃₄₄ for total ezetimibe). A 104-week dietary carcinogenicity st

in a 2-year study in rats at 25 mg/kg/day, inser we seposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC).

Asecond 2-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasma appears to be consistent with findings from other HMG-CoA reductase inhibitors. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80-mg daily dose. No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an in vitro alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, anin vitro of monosome abenation study in CHO cells, or an in vivo chromosomal abenation assay in mouse bone marrow. There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day), however, this effect was not observed during a subsequent fertility study in winch simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testse of rats from either study. At 180 mg/kg/day (which produces exposure levels 22 times higher than those in humans tak

exposures. Reproductive findings occur at lower doses in coadministration therapy compared to monotherapy.
Sirmostatin: Sirmostatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses up to 10 mg/kg daily. These doses resulted in 3 times (rat) or 3 times (rabb) the human exposure based on mg/m² surface area. However, in studies with another structurally-related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice.
Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review of approximately 100 prospectively followed prepanancies in women exposed to simmastatin or another structurally related HMG-CoA reductase inhibitors. In a review of approximately 100 prospectively followed prepanancies in women exposed to simmastatin or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, pontaneous abortions and fetal deathy/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3- to 4-fold increase in congenital anomalies over the background incidence. In 9890 of the prospectively followed pregnancies, drug teathment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.
Labor and Delivery

The effects of ViTORIN on labor and delivery in pregnant women are unknown.
Mursing Mothers

Labor and Delivery
The effects of WTORIN on labor and delivery in pregnant women are unknown.
Nursing Mothers
In rat studies, exposure to ezetimibe in nursing pups was up to half of that observed

WTORIN® (ezetimibe/simvastatin)

in maternal plasma. It is not known whether ezetimibe or simvastatin are excreted into human breast milk. Because a small amount of another drug in the same class as simvastatin is excreted in human milk and because of the potential for senous adverse reactions in nursing infants, women who are nursing should not take VYTORIN (see CONTRAINDICATIONS).

Pediatric Use
WTORIN** There are insufficient data for the safe and effective use of VYTORIN in pediatric patients. (See **Zetimibe** en hepharmacokinetics of zetimibe** in the pediatric Use wTORIN** there are insufficient data for the safe and effective use of VYTORIN in pediatric patients. (See **Zetimibe** en hepharmacokinetics of zetimibe** in each setimibe** in the pediatric population is limited to 4 patients (9 to 17 years) with homozygous stosterolemia and 5 patients (11 to 17 years) with HoFH. Treatment with ezetimibe in children (<10 years) is not recommended. **Simvastatin** Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholestrolemia have been evaluated in a controlled dirincal trial in adolescent boys and in girls who were at least 1 year post-menarche. Patients treated with placebo. **Doses > 40 mg have not been studied in this population. In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length ingirls. Adolescent females should be courseled on appropriate contraceptive methods while on therapy with simwastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls. **Geriatric Use**

Of the patients who received VYTORIN in clinical studies, 792 were 65 and older (this

studied in patients younger than 10 years of age, nor in pre-menarchal girls.
Certaint Use**
Of the patients who received VYTORIN in clinical studies, 792 were 65 and older (this included 176 who were 75 and older). The safety of VYTORIN was similar between these patients and younger patients. Greater sensitivity of some older individuals cannot be ruled out. (See ADVERSE REACTIONS.)
ADVERSE REACTIONS.
WYTORIN has been evaluated for safety in more than 3800 patients in clinical trials. VYTORIN was generally well tolerally net 150 patients. The table below summarizes the frequency of clinical adverse experiences reported in \$\times 2\% of patients treated with VYTORIN (n=1256) and at an incidence greater than placeborographics of causality assessment from 3 similarly designed, placebo-controlled trials.
**Clinical Adverse Events Occurring in \$\times 2\% of Patients Treated with VYTORIN and at an Incidence Greater than Placebo, Regardless of Causality*

BOdy System/ Placebo (%) Ezettmibe Sinwastatin (%) VYTORIN (%)

Body System/	Placebo (%)	Ezetimibe	Simvastatin [†] (%)	VYTORIN¹(%)			
Organ Class		10 mg (%)					
Adverse Event	n=311	n=302	n=1234	n=1236			
Body as a whole – general disorders							
Headache	6.4	6.0	5.9	6.8			
Infection and infestations							
Influenza	1.0	1.0	1.9	2.6			
Upper respiratory	2.6	5.0	5.0	3.9			
tract infection							
Musculoskeletal and connective tissue disorders							
Myalgia	2.9	2.3	2.6	3.5			
Pain in extremity	1.3	3.0	2.0	2.3			
* Includes 2 placebo-controlled combination studies in which the active ingredients equivalent to							

WTORIN were coadministered and I placebo-controlled study in which VYTORIN was administered. I All doses.

*Post-marketing Experience: The adverse reactions reported for VYTORIN are consistent with those previously reported with exterimible and/or sinwastatin.

*Eetimible: Other adverse experiences reported with zeetimible in placebo-controlled studies, regardless of causality assessment. *Body as a whole – general disorders: fatigue; *Castraintestinal system disorders: abdominal pain, diarthea; Infection and infectations: infection viral, pharyngitis, sinusitis; *Musculoskeletal system disorders: arthralgia, back pain, *Respiratory system disorders: adominal pain, diarthea; Infection and infectations: infection viral, pharyngitis, sinusitis; *Musculoskeletal system disorders: arthralgia, plevations: infection viral, pharyngitis, sinusitis; *Musculoskeletal system disorders: arthralgia, plevations in liver transaminases, pepatitis; thrombocytopenia, pancreatitis; nausea; cholelthitasis; cholesystitis; elevated creatine phosphokinase; and, very rarely, myopathy/rhabdomyolysis (see WARNINGS, Myopathy/Rhabdomyolysis).

Simvastatin: Other adverse experiences reported with simvastatin in placebo-controlled clinical studies, regardless of causality assessment. Body as a whole – general disorders: asthenia; *Eye disorders:* cataract; *Castrointestinal system disorders:* abdominal pain, constipation, diarrhea, dyspepsia, lifatulence, nausea; *Sim and subcutaneous tissue disorders:* eczerna, pruntus, rash.

*He following effects have been reported with other HMG-CoA reductase inhibitors. Not all the effects listed below have necessarily been associated with simvastatin therapy.

The following effects have been reported with other HIMC-LOA reductase inhibitors. Not all the effects listed below have necessarily been associated with simwastatin therapy. Musculokeletal system disorders: muscle cramps, myalgia, myopathy, rhabdomyolysis, and the control of algias. Ous system disorders: dysfunction of certain cranial nerves (including alteration of taste,

arthralgas.

Nervous system disorders: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-cular movement, facial paresis), tremor, dizziness, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances.

Ear and labyninh disorders: vertigo.

Psychiatric disorders: amolety, insomnia, depression, loss of libido.

Psychiatric disorders: amolety, leser, disorders: anaphylaxis, anguedema, lupus erythematous-like syndrome, polymalgia rehumalica, dermatomycosis, vasculikis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticana, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multirome, induding Stevens-Johnson syndrome.

Gastrointestinal system disorders: pancreatitis, vomitting.

Hepatabiliary disorders: hepatistis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, currhosis, fulminant hepatic necrosis, and hepatoma.

Skin and subcutaneous tissue disorders anoresis.

Skin

Laboratory Tests
Marked persistent increases of serum transaminases have been noted (see WARNINGS, Liver Enzymes). About 5% of patients taking simvastatin had elevations of CK levels of 3 or more times the normal value on 1 or more occasions. This was attributable to the noncardiac traction of CK. Muscle pain or dysfunction usually was not reported (see WARNINGS, Myopathy/Rhabdomyolysis).

ARNINGS, Myopathy/Khabdomyopyss), oncomitant Lipid-Lowering Therapy controlled clinical studies in which simvastatin was administered concomitantly with olestyramine, no adverse reactions peculiar to this concomitant treatment were observed, e adverse reactions that occurred were limited to those reported previously with simvastatin

or cholestyramine. Adolescent Patients (ages 10-17 years) In a 48-week controlled study in adolescent boys and girls who were at least 1 year post-menarche, 10-17 years of age with heterozygous familial hypercholesterolemia (n=175), the stelly and tolerability profile of the group treated with simusatian (10-40 mg daily) was generally similar to that of the group treated with placebo, with the most common adverse experiences observed in both groups being upper respiratory infection, headache, abdominal pain, and nausea (see PRECAUTIONS, Pediatric Use).

MERCK / Schering-Plough Pharmaceuticals

ctured for: MERCK/Schering-Plough Pharmaceuticals

Manufactured for Michael School (1997)

North Wales, PA 19454, USA

Copyright ©Merck/Schering-Plough Pharmaceuticals, 2006. All rights reserved.

20607955(2)(607)-VVT

preservation, distant metastases, death from breast cancer, or all-cause mortality.

Of the study participants, 29% were dead by 8.2 years, but only six in the radiotherapy arm and five in the no-radiotherapy arm actually died of breast cancer.

"In this population, breast cancer is not the major issue these people are facing," Dr. Hughes noted.

Audience member Dr. Laura J. Esserman hailed CALGB 9493 as "a great study." "I hope everyone heard the results and is offering these choices to their patients," added Dr. Esserman, professor of surgery and director of the breast care center at the University of California, San Francisco.

Meditation Eases Stress in Breast Cancer Survivors

SAN ANTONIO — The mindfulnessbased stress reduction program developed by Jonathan Kabat-Zinn, Ph.D., appears to be beneficial to patients with early-stage breast cancer in the immediate posttreatment period as they transition to survivorship, Cecile Lengacher, Ph.D., reported at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

This transition is an underappreciated period of high risk for emotional distress. Many patients experience fear of recurrence while also coming to grips with changes in body image, and concern for their children and other family members, explained Dr. Lengacher of the Lee Moffitt Cancer Center and Research Institute, University of South Florida, Tampa.

Dr. Lengacher and her coworkers conducted a nonrandomized pilot feasibility study of mindfulness-based stress reduction, the structured program developed by Dr. Kabat-Zinn of the University of Massachusetts, Worcester. The program is designed to teach patients to self-regulate their arousal to stress through awareness of their thoughts and feelings during stressful circumstances. The program emphasizes regular practice of four meditation techniques: sitting meditation, body scan, gentle Hatha yoga, and walking meditation. The formal program entails eight 2-hour weekly group sessions, along with a minimum of 45 minutes per day 6 days per week practicing the various forms of meditation individually outside of class.

Investigators offered the program to 58 women who had undergone lumpectomy plus radiotherapy and/or chemotherapy. Thirty-one agreed to attend an orientation session. Nineteen of the 31 consented to participate in the program, and 17 completed the classes.

Compliance was excellent. Fifteen of the 17 patients reported that they found the program beneficial, and 13 said they had a greater ability to handle stress and improved coping skills. Measures of anxiety, depression, and pain were obtained, but the results haven't yet been analyzed.

Patients found the 8-week course too great a time burden, though, so investigators have condensed it to 6 weeks. The shorter version has been well accepted. A randomized trial is planned.

—Bruce Jancin

Another surgeon observed that if the more generous lumpectomies that are

now standard had been the norm in the 1990s when study participants had their surgery, their locoregional recurrence rate tamoxifen alone would likely be even lower than it was in the study.



But other audience members noted that the overview analysis presented by the Oxford, England-based Early Breast Cancer Trialists' Collaborative Group at the San Antonio meeting 2 years ago concluded

'In this population [of women aged 70 years and older], breast cancer is not the major issue these people are facing.'

DR. HUGHES

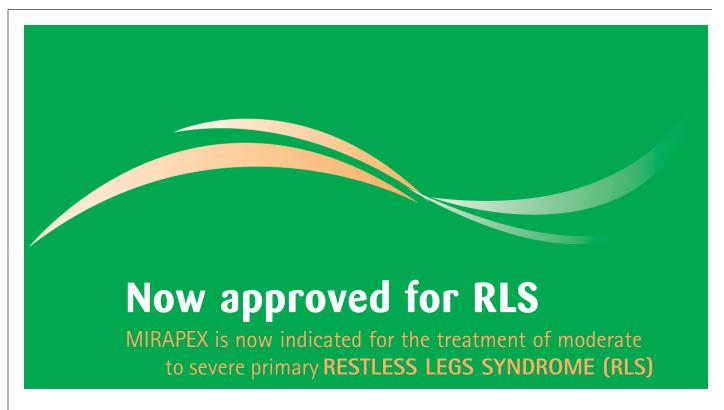
vantage for radiotherapy becomes significant at 15 years. What good are 8.2-year followup data, they asked, when a physician is faced with an otherwise healthy 70year-old who might

that a survival ad-

well live for another 15-20 years?

"We have to look at physiologic age as well as chronologic age," Dr. Hughes replied. "As patients are physiologically older, I think we'd all agree that radiation becomes unnecessary. What we argue about is, [at what point do] patients become physiologically older.

He added that he's not convinced the overview analysis findings apply to the type of patients in CALBG 9493. "What critics have brought up before is the idea that, as we [do more] follow-up, we'll see more and more in-breast recurrences in the group that didn't have radiotherapy. I think it's just as likely we'll see more inbreast recurrences in the arm that had radiation. I don't think we can predict what will happen beyond this point."





IMPORTANT SAFETY INFORMATION ABOUT MIRAPEX:

Patients have reported falling asleep without perceived warning signs during activities of daily living, including operation of a motor vehicle. Hallucinations and postural (orthostatic) hypotension may occur. The most commonly reported adverse events in clinical trials for RLS were nausea, headache, fatigue, and somnolence.

Patients and caregivers should be informed that impulse control disorders/compulsive behaviors may occur while taking medicines, including pramipexole, to treat Parkinson's disease and RLS.

Please see Brief Summary on adjacent pages.



www.mirapex.com

Copyright © 2006, Boehringer Ingelheim Pharmaceuticals, Inc. All rights reserved Printed in U.S.A. (11/06) MRLS-11452R0E