FDA Panel Would Strip Ketek of Two Indications

BY ALICIA AULT

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SILVER SPRING, MD. — The antibiotic Ketek (telithromycin) is neither safe nor effective for treating acute exacerbation of chronic bronchitis or acute sinusitis, according to a Food and Drug Administration advisory committee that recommended that the agency remove those indications from the drug's approved

The panel—a joint meeting of the FDA's Anti-Infective Drugs and Drug Safety and Risk Management Advisory committeesconcluded that although Ketek has been marketed since 2004, safety concerns argue against using the drug in two conditions that generally resolve on their own.

The panel voted 16-3 that Ketek should retain its approval for treating mild to moderate community-acquired pneumonia, but as a second- or third-line therapy. Ketek's maker, Sanofi-Aventis, also presented data suggesting that the drug may be effective against multidrug resistant Streptococcus pneumoniae, which was persuasive to the committee.

Although the panel supported keeping Ketek on the market, a majority of panelists recommended that a black box warning be added to the labeling.

"This is a drug that we need, but this is not something I'd reach for, and this is something I'd discourage people from using," said Dr. Margo Smith, a panelist from the Washington Hospital Center.

If the FDA follows the panel's advice, as it normally does, the agency would determine how to educate physicians on the revised uses. Sanofi-Aventis agreed that it would create a medication guide for consumers. The FDA and Sanofi-Aventis would work out the content of the black box warning, which is likely to touch on the potential for liver toxicity, visual disturbances, loss of consciousness, and exacerbations of myasthenia gravis.

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-lovening 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 librates 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 had 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 potential 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 rounds and the patients of the section of the section of the sections of the sections

rescribing recommendations for interacting agents are summarized in the table elow (see also PRECAUTIONS, *Drug Interactions*).

Ing Interactions Associated with Increased Risk of Myopathy/Rhabdomyohsis

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|---|---|
| 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 elevations (a3 x ULN) in serum transaminases was 1.7% overall for patients treated with VYTORIN and appeared to be dose-related with an incidence of 2.6% for patients treated with VYTORIN 10/80. In controlled long-term (44-week) extensions, which included both newly-treated and previously-treated patients, the incidence of consecutive elevations (a5 x ULN) in serum transaminases was 1.8% overall and 3.6% for patients treated with VYTORIN 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 VYTORIN, 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.

ezetimibe in patients with moderate or severe hepatic insufficiency, VYTORIN is not recommended in these patients.

Drug Interactions

Drug Interactions

Drug Interactions

Proposed Interaction

**Prop

Myopathy/Rhabdomio/jscs).

Caution should be exercised when using VYTORIN and cyclosporine concomitantly due to increased exposure to both ezetimibe and cyclosporine. Cyclosporine concentrations should be monitored in patients receiving VYTORIN and cyclosporine. The degree of increase in ezetimibe exposure may be greater in patients with severe renal insufficiency. In patients treated with cyclosporine, the potential effects of the increased exposure to ezetimibe from concomitant use should be carefully weighed against the benefits of alterations in lipid levels provided by ezetimibe. In a pharmacokinetic study in post-renal transplant patients with mildly impaired or normal renal function (creatinine clearance of 2-50 ml/mlm). concomitant cyclosporine administration increased the mean

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 >50 ml/min), concomitant cyclosporine administration increase the mean AUC and C__ of total exetimibe 3.4-fold (range 2.3- to 7.9-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 bailers and comment and comment of the patients prothrombin time should be determined before starting VYTORIN and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once astable prothrombin time has been documented, prothrombin time in a study of 12 healthy adult mal

(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 Wallerian-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 (111) in the in vivo mouse micronucleus test.

**Exetimibe: A 104-week dietary carcinogenicity study with ezetimibe was conducted in rats at doses up to 500 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/m³ 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

Studied in Patients younger than in years or age, not in pre-inelatical gins.

Ceriatric 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

VYTORIN has been evaluated for safety in more than 3800 patients in clinical trials.

VYTORIN has generally well tolerated.

The table below summarizes the frequency of clinical adverse experiences reported in ≥ 2% of patients treated with VYTORIN (r=1256) and at an incidence greater than placedored causality assessment from 3 similarly designed, placebo-controlled trials.

Clinical Adverse Events Occurring in ≥ 2% of Patients Treated with VYTORIN and at an Incidence Greater than Placebo, Regardless of Causality*

Body System/ Placebo (%) Ezettmibe Sirwastatin*(%) VYTORIN*(%)

| Body System/ | Placebo (%) | Ezetimibe | Simvastatin†(%) | VYTORIN [†] (%) | |
|---|--------------------|------------------|--------------------------|--------------------------|--|
| 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-cont | rolled combination | studies in which | the active ingredients e | quivalent to | |
| | | | | | |

YTORIN were coadministered and 1 placebo-controlled study in which VYTORIN was administered

WTTORIN were coadministered and 1 placebo-controlled study in which VYTORIN was administered.

1 All doses:
Post-marketing Experience: The adverse reactions reported for VYTORIN are consistent with those previously reported with exterimible and/or sinwastatin.
Exelimible: Other adverse experiences reported with zertimible in placebo-controlled studies, regardless of causality assessment: Body as a whole – general disorders: fatigue;
Castraintestinal system disorders: addominal pain, diarthea; Infection and infection or
post-marketing parelines: The following adverse reactions have been reported in post-marketing experience; regardless of causality assessment: Hypersensitivity reactions,
including anaphylaxis, angioedema, rash, and urticaria; arthralgia; elevations in liver
transaminases hepatitis; thrombocytopenia; pancreatitis; nausea; cholelthitasis; cholesystis;
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; Skin and subcutaneous tissue
disorders: eczema, pruntus, rash.
The 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, dermadomycosis, 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

Ketek was under scrutiny during most of 2006. Senator Chuck Grassley (R-Iowa) has alleged that the drug was approved on the basis of a fraudulent trial, known as study 3014. On the eve of the 2-day FDA panel meeting, Sen. Grassley released results—so far—of his Finance Committee's Ketek investigation. He alleged that FDA managers failed to notify the Anti-Infective Drugs Advisory Committee when it met in 2003 that the agency had concerns about study 3014's integrity.

The panel recommended approval at that time. The agency later held a closed-door meeting with the panel to discuss problems with study 3014, but Sen. Grassley alleges that the committee members still were not given a complete story.

In making the original approval decision, the agency determined that it could toss out tainted data from study 3014 and instead rely on postmarketing data col-

Although Ketek is a drug that we need, 'this is not something I'd reach for, and this is something I'd discourage people from using.' lected on about 4 million patient exposures in Europe, said Dr. Janice Soreth, director of the FDA's division of anti-infective and ophthalmology products, at the December 2 meeting.

S e v e r a l speakers at the FDA meeting—

including a recently departed reviewer from the Ketek team—expressed outrage over the agency's reliance on postmarketing data instead of a prospective safety study for approval.

The panel did not seem as concerned.

The older postmarketing safety information—combined with updated surveillance reports from Europe and postmarketing data collected in the United States since Ketek's introduction—was presented at length.

FDA staffers disagreed on the incidence and import of side effects, as did the FDA and Sanofi-Aventis. Sanofi estimated that to date, the reporting rate in Europe for serious hepatic reactions is 4-10 cases/million courses of therapy. According to the FDA, from 2004 to 2006 there were 12 cases of acute liver failure among 5 million U.S. prescriptions, for a reporting rate of 23 per 10 million prescriptions. By comparison, the antibiotic Trovan (trovafloxacin) had a rate of 58 per 10 million in its first year on the market. The drug was subsequently recalled.

The FDA asked several experts from the Drug-Induced Liver Injury Network to take a closer look at 53 reports of hepatic toxicity associated with Ketek use. The network is a cooperative funded by the National Institute of Diabetes, Digestive, and Kidney Disorders.

One of those experts, Dr. William Lee, director of the clinical center for liver diseases at the University of Texas at Dallas, said that of the 53 patients, 44 were hospitalized, 5 died, and 2 had liver transplants. The cases had similar clinical features, including rapid onset, prominent fever, joint aches, and right upper quadrant pain

Dr. Lee said he believed that 28 of the

53 cases were very likely or probably caused by Ketek, 17 were possibly related, and 8 had insufficient data to make a ruling. He said the hospitalization rate was probably 1 in 20,000 or 1 in 30,000 for liver toxicity and 1 in 150,000 for acute liver failure. Ketek's profile would be worse if it was a chronic medication, he said.

"The severity may be limited simply because the drug exposure is quite short," Dr. Lee said.

Sanofi maintained that the hepatotoxicity was similar to that of other antibiotics. The panel was split on whether Ketek was an outlier.

Committee members were more con-

cerned about exacerbations of myasthenia gravis, a neurologic condition affecting about 35,000-70,000 Americans. Many individuals aren't aware they have the condition and might unwittingly take Ketek. The FDA's review found 33 reports of exacerbations of myasthenia gravis since 2004. Of those, seven were life threatening. Twelve patients required a ventilator or intubation.

There were 71 cases of vision disorders and 23 cases of disturbances in consciousness with serious outcomes. In one case, an 18-year-old passed out while driving and struck and killed a pedestrian.

Sanofi-Aventis stuck to its data showing

that Ketek was no different from other drugs in the class. "Overall, we believe that the safety risks with telithromycin appear to be similar to widely prescribed antibiotics," said Dr. Bruno Leroy, head of the company's internal medicine franchise.

Some FDA staffers were not convinced. "Ketek stands out among the macrolides in its unique and notable toxicity," said Dr. Rosemary Johann-Liang, deputy director of the division of drug risk evaluation at FDA's Center for Drug Evaluation and Research.

Ketek has been prescribed to 6 million U.S. patients since 2004, according to Sanofi-Aventis.





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.



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