Sirolimus (Rapamune®)
Manufacturer: Wyeth Pharmaceuticals

Rationale for Labeling Review: On the basis of postmarketing reports, a new boxed warning, the highest level of warning information in labeling, has been created for this drug. The new warning highlights the notification to health care professionals of bronchial anastomotic dehiscence, including fatal cases, found in lung-transplant patients given sirolimus (formerly rapamycin) in combination with tacrolimus and corticosteroids. The safety and efficacy of sirolimus as immunosuppressive therapy have not been established in lung-transplant recipients.

Two health centers reported findings of bronchial anastomotic dehiscence, a severe adverse drug event, in their lung-transplant recipients after the immunosuppressive regimen was begun at the time of transplantation. One health center reported the development of this condition in four of 15 patients enrolled in a study, with three patients ultimately dying. The other health center reported two cases of bronchial anastomotic dehiscence, one of which was fatal.

Indication: Sirolimus, an immunosuppressant agent, has been developed to reduce organ rejection in patients receiving kidney transplants. It is used in combination with cyclosporine and corticosteroids and has been shown to significantly reduce kidney rejection rates. Sirolimus inhibits T-lymphocyte activation and proliferation, which occurs in response to antigenic and cytokine stimulation, but its mechanism is distinct from that of other immunosuppressants.

Sirolimus also inhibits antibody production. In cells, sirolimus binds to the immunophilin, FK-binding protein-12 (FKBP-12), to generate an immunosuppressive complex. This complex binds to and inhibits the activation of the mammalian target of rapamycin (mTOR), a key regulatory kinase. This inhibition suppresses cytokine-driven, T-cell proliferation, thus inhibiting the phase progression of the cell cycle.

Label Change

Boxed Warning
Liver Transplantation: Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis

In a study of de novo liver-transplant recipients, the use of sirolimus in combination with tacrolimus was associated with excess mortality and graft loss. Many patients had evidence of infection at or near the time of death.

In this study and in another study of de novo liver-transplant recipients, the use of sirolimus, in combination with cyclosporine or tacrolimus, was associated with an increased incidence of hepatic artery thrombosis. Most of these cases occurred within 30 days after transplantation, and most led to graft loss or death.

Drug Safety Revisions: FDA Update

Marvin M. Goldenberg, PhD, RPh, MS

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Dr. Goldenberg is Executive Director of Pharmaceutical and Scientific Services for MMG Associates in Westfield, New Jersey, and coordinates the Pharmaceutical-Approval Update and FDA Update columns.
tions of valvulopathy improved with cessation of pergolide therapy. Two patients required valve replacement.

**Indications:** Pergolide mesylate, a dopamine receptor agonist, is used with levodopa or with a carbidopa–levodopa combination to treat patients with Parkinson’s disease, a progressive neurological disorder resulting from the degeneration of neurons in a region of the brain that controls movement. Pergolide mesylate works by stimulating certain parts of the central nervous system that are involved in this disease. In deciding whether or not to use pergolide mesylate, prescribers must weigh the risks associated with the drug against the benefits it confers.

**Warning Label Change**

**Serous Inflammation and Fibrosis**

There have been rare reports of pleuritis, pleural effusion, pleural fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy involving one or more valves, and retroperitoneal fibrosis in patients taking pergolide. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of therapy. Pergolide should be used with caution in patients with a history of these conditions, particularly in patients who experience these events while taking ergot derivatives. Patients with a history of such events should be carefully monitored clinically and with appropriate radiographic and laboratory studies during pergolide therapy.

**Conclusion:** Mayo Clinic physicians have recently issued a report warning that pergolide mesylate, when used to treat Parkinson’s disease, might cause serious damage to the heart valves, similar to the damage caused by the diet drug “Phentermine,” a combination of phentermine with fenfluramine (Pondimin®) or dexfenfluramine (Redux™), both from American Home Products/Wyeth. From this observation, it is recommended that all patients taking pergolide mesylate undergo a thorough cardiovascular examination. The evidence in the report is based on only three patients treated at the clinic, but the physicians consider their evidence sufficient to recommend that patients with heart problems not take pergolide. Pergolide has been used since 1989 to treat the tremors and restlessness that patients with heart problems not take pergolide. Pergolide should be used with caution in patients taking pergolide. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of therapy. Pergolide should be used with caution in patients with a history of these conditions, particularly in patients who experience these events while taking ergot derivatives. Patients with a history of such events should be carefully monitored clinically and with appropriate radiographic and laboratory studies during pergolide therapy.

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**Salmeterol Xinafoate Inhalation Aerosol (Serevent®)**

**Manufacturer:** GlaxoSmithKline

**Rationale for Labeling Revision:** An interim analysis of a large safety study—the Salmeterol Multicenter Asthma Research Trial (SMART)—of the approved asthma drug salmeterol xinafoate inhalation aerosol suggested that this drug might be associated with an increased risk of life-threatening asthma episodes or asthma-related deaths. The analysis did not show a statistically significant result for the primary endpoint—a combination of respiratory-related deaths or intubations (or ventilation failure). There was a trend, however, toward an increased number of asthma deaths and serious asthma episodes when all patients in the study were considered, although this trend did not reach statistical significance.

On further analysis, the risk appeared to be greater in African-American patients. In white patients (71% of the study population), there were no significant differences between treatment groups for primary events and asthma-related events. In African-Americans (17% of the trial’s enrollees), the study showed a statistically significant greater number of primary events and asthma-related events, including deaths, in patients taking salmeterol than in those taking placebo; however, fewer than 1% of all African-Americans enrolled in the study experienced such events during the 28-week trial. In addition, patients who were not taking inhaled corticosteroids at the time of enrollment appeared to be at greater risk for serious adverse outcomes than those who were taking inhaled corticosteroids.

**Indication:** In 1994, salmeterol xinafoate inhalation aerosol was approved to treat asthma. This approval was later extended to treat chronic obstructive pulmonary disease (COPD), including emphysema and chronic bronchitis. The drug belongs to the class of asthma medications known as β₂-receptor agonists (commonly called beta agonists).

**Label Change**

**Warnings:** None exist at this time. Further review of the SMART interim analysis data is ongoing, and the FDA is discussing these findings with GlaxoSmithKline. The manufacturer and the FDA are also reviewing potential changes to the labeling that will reinforce guidance on appropriate and safe prescribing.

**Current Warning Label:** Salmeterol xinafoate inhalation aerosol therapy should not be initiated in patients with significantly or acutely worsening asthma, a potentially life-threatening condition. Serious acute respiratory events, including fatalities, have been reported in both the U.S. and worldwide after initiation of aerosol therapy in this situation. Although it is unclear whether salmeterol xinafoate inhalation aerosol therapy contributed to these adverse effects or simply was unable to relieve the worsening asthma, its use in this setting is inappropriate. Usage guidelines are as follows:

- Inform patients that the aerosol should not be used to treat acute symptoms. Instead, prescribe an inhaled, short-acting β₂-agonist for this purpose, and warn patients that their need to increase the use of inhaled β₂-agonists is a signal of worsening asthma.
- Do not prescribe salmeterol xinafoate inhalation aerosol as a substitute for inhaled or oral corticosteroids. The corticosteroids should be continued at the same dose, not stopped or reduced, when treatment with the inhalation aerosol is initiated.
- Do not introduce this aerosol as a therapy for acutely worsening asthma. This aerosol formulation is intended for the maintenance treatment of asthma. Prescribe an inhaled, short-acting β₂-agonist to relieve acute asthma or COPD symptoms.
- Watch for increasing use of inhaled, short-acting β₂-agonists, a marker of worsening asthma. Do not use this aerosol as a substitute for oral or inhaled corticosteroids.
- Do not exceed the recommended dosage of this drug.
Salmeterol xinafoate inhalation aerosol therapy can produce paradoxical bronchospasm, immediate hypersensitivity reactions, and upper respiratory symptoms such as laryngeal spasm, irritation, and swelling.

**Conclusion:** The National Asthma Education and Prevention Program (NAEPP) Guidelines recommend that patients who require more than as-needed, short-acting $\beta_2$-agonists take regular and adequate doses of an inhaled anti-inflammatory asthma medication, such as inhaled corticosteroids, for optimal benefits in the management of their asthma.\(^1\)

Consistent with these guidelines and reinforced by trends seen in the interim analysis of the SMART data, the manufacturer recommends that patients using salmeterol xinafoate inhalation aerosol therapy for asthma also receive regular and adequate doses of an effective asthma-control medication, such as inhaled corticosteroids.

GlaxoSmithKline and the FDA agree on the need to reiterate and reinforce advice for the management of patients, including African-Americans, as established in the label for salmeterol xinafoate inhalation aerosol and in the national asthma management guidelines. Given the similar basic mechanisms of action of all $\beta_2$-agonists, the findings observed in the SMART study might be consistent with a class effect.

**REFERENCE**