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FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury

This information has been updated in the December 15, 2011, FDA Drug Safety Communication: Revised dose limitation for Zocor (simvastatin) when taken with amiodarone.

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Safety Announcement

[06-08-2011] The U.S. Food and Drug Administration (FDA) is recommending limiting the use of the highest approved dose of the cholesterol-lowering medication, simvastatin (80 mg) because of increased risk of muscle damage. Simvastatin 80 mg should be used only in patients who have been taking this dose for 12 months or more without evidence of muscle injury (myopathy). Simvastatin 80 mg should not be started in new patients, including patients already taking lower doses of the drug. In addition to these new limitations, FDA is requiring changes to the simvastatin label to add new contraindications (should not be used with certain medications) and dose limitations for using simvastatin with certain medicines.

Patients taking simvastatin 80 mg daily have an increased risk of myopathy compared to patients taking lower doses of this drug or other drugs in the same class. This risk appears to be higher during the first year of treatment, is often the result of interactions with certain medicines, and is frequently associated with a genetic predisposition toward simvastatin-related myopathy. Patients with myopathy generally have muscle pain, tenderness or weakness, and an elevation of a muscle enzyme in the blood (creatinine kinase, or CK). The most serious form of myopathy, called rhabdomyolysis, can damage the kidneys and lead to kidney failure which can be fatal. Rhabdomyolysis is rare; hospitalized rhabdomyolysis occurs in 4.9 people out of every 100,000 people exposed to simvastatin for one full year (the average incidence for hospitalized rhabdomyolysis for atorvastatin, pravastatin, or simvastatin is 4.4 people out of every 100,000 people exposed to the drugs for one full year).¹

FDA has revised the drug labels for simvastatin and Vytorin to include the new dosing restriction for the 80-mg dose. The labels for simvastatin, Vytorin, and Simcor were also revised to include new dosing recommendations when these drugs are used with certain medicines that interact with simvastatin to increase the level of simvastatin in the body. Increasing the levels of simvastatin in the body can increase the risk for myopathy (see Simvastatin Dose Limitations below).

In March 2010, FDA announced it was reviewing the safety of simvastatin in the Agency's Ongoing safety review of high-dose Zocor (simvastatin) and increased risk of muscle injury

Facts about simvastatin

- Sold as a single-ingredient generic medication and under the brand-name Zocor. It is also sold in combination with ezetimibe as Vytorin, and niacin as Simcor.
- Used together with diet and exercise to reduce the amount of low-density lipoprotein (LDL) cholesterol ("bad cholesterol") in the blood to decrease the risk of heart attack, stroke, and cardiovascular death.
- The 80-mg dose lowers the LDL cholesterol by an additional 6% over simvastatin 40 mg
- It is estimated that approximately 2.1 million patients in the U.S. were prescribed a product containing 80-mg simvastatin in year 2010.

Additional Information for Patients

Patients currently taking 80-mg simvastatin-containing medicines should:

- Not stop taking their medicine unless told to by their healthcare professional.
- Review their medical history with their healthcare professional, the currently prescribed dose of simvastatin, and a list of their other current medications to determine if the medicines they are taking are appropriate. Know that certain medications should never be taken with simvastatin (see Simvastatin Dose Limitations below).
- Immediately contact their healthcare professional if they experience muscle pain, tenderness or weakness, dark or red colored urine, or unexplained tiredness.
- Talk to their healthcare professional about any questions or concerns they have about simvastatin-containing medicines.
- Report side effects from the use of simvastatin-containing medicines to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of this page.

Additional Information for Healthcare Professionals

FDA recommends that healthcare professionals should:

- Maintain patients on simvastatin 80 mg only if they have been taking this dose for 12 or more months without evidence of muscle toxicity.
- Not start new patients on simvastatin 80 mg.
- Place patients who do not meet their LDL cholesterol (LDL-C) goal on simvastatin 40 mg on alternative LDL-C lowering treatment(s) that provides greater LDL-C lowering (see Relative LDL-lowering Efficacy of Statin and Statin-based Therapies below).
- Follow the recommendations in the simvastatin-containing medicines labels regarding drugs that may increase the risk for muscle injury when used with simvastatin (see Simvastatin Dose Limitations below).
- Switch patients who need to be initiated on a drug that interacts with simvastatin to an alternative statin with less potential for the drug-drug interaction.
- Report adverse events involving simvastatin-containing medicines to the FDA MedWatch program using the information in the "Contact Us" box at the bottom of this page.

Data Summary

The new changes to the drug labels for simvastatin-containing medicines are based on FDA's review of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial and other data described in the Agency's March 2010 Ongoing safety review of high-dose Zocor (simvastatin) and increased risk of muscle injury.

SEARCH was a seven-year, randomized, double-blind clinical trial comparing the efficacy and safety of simvastatin 80 mg to simvastatin 20 mg, with or without vitamin B12 and folate, in survivors of myocardial infarction.

At the end of the trial, the incidence of major vascular events was 25.7% in the 20-mg group versus 24.5% in the 80-mg group [RR=0.094, 95% CI (0.88, 1.01); p=0.10]. Due in part to greater use of off-study LDL-C lowering medication in the simvastatin 20 mg group versus the 80-mg group, the difference in mean levels of LDL-C between the two treatment groups was 13 mg/dL. Instead of the expected difference of 20 mg/dL. Nonetheless, the 6% reduction in relative risk for major vascular events observed in SEARCH is consistent with the 13 mg/dL lower level of LDL-C in the 80-mg group.

Fifty-two patients (0.9%) in the 80-mg group versus one patient (0.02%) in the 20-mg group developed myopathy (defined as unexplained muscle weakness or pain with a serum CK >10 times the upper limit of normal [ULN]). This was higher than the labeled risk (based on clinical trial data) of 0.53%. Twenty-two patients (0.4%) in the 80-mg group versus no patient in the 20-mg group developed rhabdomyolysis (defined as unexplained muscle weakness or pain with serum CK >40 times ULN). There were no fatalities related to rhabdomyolysis.

The risks for myopathy and rhabdomyolysis with simvastatin 80 mg were highest in the first 12 months of treatment, 5 per 1000 person-years and 2 per 1000 person-years, respectively, and decreased to 1 per 1000 person-years and 0.4 per 1000 person-years after that.

Older age and female sex both increased the risk of myopathy. In SEARCH, the risk of myopathy was approximately doubled in patients taking a calcium channel blocker, in particular diltiazem. Approximately 60% of the cases of myopathy were associated with a genetic variant which affects the coding of the transporter responsible for simvastatin uptake into the liver. This variant increases the plasma concentration of simvastatin, thus increasing the risk of myopathy.

The findings from the SEARCH trial are supported by analyses of the FDA's Adverse Event Reporting System (AERS) database, which show that the level of reporting of fatal rhabdomyolysis associated with the 80-mg dose of simvastatin has been higher in comparison with lower doses of simvastatin or lower doses of most other statins. In addition, clinical trial data from other long-term statin trials show higher overall rates of myopathy and rhabdomyolysis in patients treated with simvastatin 80 mg versus lower doses of simvastatin or other statins.

Simvastatin Dose Limitations

When used with simvastatin, the following medications can raise the levels of simvastatin in the body and increase the risk of myopathy. Taking no more than the recommended dose of simvastatin with these medications will help keep simvastatin levels in the body at a safer level.

Previous simvastatin label	New simvastatin label
Avoid simvastatin with: <ul style="list-style-type: none">ItraconazoleKetoconazoleErythromycinClarithromycinTelithromycinHIV protease inhibitorsNefazodone	Contraindicated with simvastatin: <ul style="list-style-type: none">ItraconazoleKetoconazolePosaconazole (New)ErythromycinClarithromycinTelithromycinHIV protease inhibitorsNefazodoneGemfibrozilCyclosporineDanazol
Do not exceed 10 mg simvastatin daily with: <ul style="list-style-type: none">GemfibrozilCyclosporineDanazol	Do not exceed 10 mg simvastatin daily with: <ul style="list-style-type: none">AmiodaroneVerapamilDiltiazem <p>(Note: These drugs are contraindicated with Simcor as Simcor is only available with 20 mg or 40 mg of simvastatin.)</p>
Do not exceed 20 mg simvastatin daily with: <ul style="list-style-type: none">AmiodaroneVerapamil	Do not exceed 20 mg simvastatin daily with: <ul style="list-style-type: none">Amlodipine (New)Ranolazine (New)
Do not exceed 40 mg simvastatin daily with: <ul style="list-style-type: none">Diltiazem	
Avoid large quantities of grapefruit juice (>1 quart daily)	Avoid large quantities of grapefruit juice (>1 quart daily)

Relative LDL-lowering Efficacy of Statin and Statin-based Therapies

Atorva	Fluva	Pitava	Lova	Prava	Rosuva	Vytorin*	Simva	% _L LDL-C
-----	40 mg	1 mg	20 mg	20 mg	-----	-----	10 mg	30%
10 mg	80 mg	2 mg	40 or 80 mg	40 mg	-----	-----	20 mg	38%
20 mg	-----	4 mg	80 mg	80 mg	5 mg	10/10 mg	40 mg	41%
40 mg	-----	-----	-----	-----	10 mg	10/20 mg	80 mg	47%
80 mg	-----	-----	-----	-----	20 mg	10/40 mg	-----	55%
-----	-----	-----	-----	-----	40 mg	10/80 mg	-----	63%

Atorva=Atorvastatin; Fluva=Fluvastatin; Pitava= Pitavastatin; Lova=Lovastatin; Prava=Pravastatin; Rosuva=Rosuvastatin; Simva=Simvastatin.

*No incremental benefit of Vytorin on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.

References

- Graham DJ, Staffa JA, Shalin D, Andrade SE, Schech SD, La Grenade L. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA. 2004;292:2585-90.

Related Information

- Simvastatin (marketed as Zocor) Information
- FDA: Limit Use of 80 mg Simvastatin
Consumer Update 6/8/2011
- FDA announces new safety recommendations for high-dose simvastatin
6/8/2011
- FDA Drug Safety Podcast for Healthcare Professionals: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury
6/9/2011
- FDA Drug Safety Communication: Ongoing safety review of high-dose Zocor (simvastatin) and increased risk of muscle injury
3/19/2010

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