

Amiodarone - Simvastatin

Simvastatin is used to treat hyperlipidemia. It is primarily metabolized by CYP3A4 and has a very low bioavailability (<5%) due to extensive enterocyte and hepatic first-pass clearance. It is very sensitive to inhibitors of CYP3A4, especially if the inhibitor is administered orally near to the administration time of simvastatin. Amiodarone is an antiarrhythmic drug that inhibits the activity CYP3A4 in addition to several other cytochrome P450 enzymes. A metabolite of amiodarone, desethyamiodarone, appears to be a more potent inhibitor of CYP3A4 than the parent drug. Due to the long half-lives of amiodarone and desethyamiodarone, maximal inhibition of CYP3A4 may require several weeks.

Dose of Simvastatin ¹	Less than or equal to 20 mg/day	Dose greater than 20 mg/day
Increased simvastatin side effects likely	■ ²	◆ ³

○ = No special precautions. ■ = Assess risk and take action if necessary. ◆ = Use only if benefit outweighs risk

Footnotes:

- 1 It is preferable to simply avoid this drug combination. Alternative statins not metabolized by CYP3A4 include pravastatin, rosuvastatin, and pitavastatin.
2. Several case reports of amiodarone-simvastatin interactions have been reported, some resulting in rhabdomyolysis. Chouhan et al. *Ann Pharmacother.* 2005;38:1760-1.; Roten L et al. *Ann Pharmacother.* 2004;38:978-81. Amiodarone 400 mg daily for 3 days has been reported to increase the AUC of simvastatin lactone (73%) and its active metabolite simvastatin acid (78%) when administered together compared to simvastatin alone (Bacquemont L et al. *Clin Pharmacol Ther.* 2007;81:679-84.)
3. Patients taking simvastatin doses above 20 mg daily may be at greater risk of adverse outcomes during concurrent amiodarone administration.