

## Fluconazole - 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. Fluconazole is used as prophylaxis and treatment of fungal infections. Fluconazole is an inhibitor of CYP3A4, especially at doses of 200 mg/day or more.

Dose of Simvastatin	Less than or equal to 20 mg/day		Dose greater than 20 mg/day	
Dose of Fluconazole	Less than 200 mg/day	Greater or equal 200 mg/day	Less than 200 mg/day	Greater or equal 200 mg/day
Increased simvastatin side effects unlikely	○ <sup>1</sup>			
Increased simvastatin side effects likely		■	■ <sup>2</sup>	◆

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

### Footnotes:

1. Fluconazole doses less than 200 mg daily have a limited effect on CYP3A4 activity. Low doses of fluconazole may increase simvastatin concentrations by up to 2-fold. Varhe A et al. Br J Clin Pharmacol. 1996;42:465-70; Lopez-Gil JA. Ann Pharmacother. 1993;27:427-30; Kruger HU et al. J Antimicrob Chemother. 1989;24:781-6; Vanakoski J et al. Internat J Clin Pharm Ther. 1995;33:518-23.
2. Patients taking simvastatin doses above 20 mg daily may be at greater risk of adverse outcomes during concurrent fluconazole administration.