

**BACKGROUND PACKAGE FOR  
JANUARY 8, 2003 ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE**

**ERRATUM**

Table 5-12, page 61 of the original document included geometric means for the telithromycin data and arithmetic means for the clarithromycin data. For consistency, the geometric means for the clarithromycin data are included (see second row of Table 5-12 on page 61).

This page also includes clarification regarding the data from Studies 1065 and 1067 which indicates that, because the data was submitted to the NDA in December 2002, it has not been evaluated by FDA.

The revised page is attached.

Simvastatin is a CYP 3A4 substrate and is sensitive to blockage of this enzyme. This is due to a high intestinal first-pass metabolism of this drug. Other mild CYP3A4 inhibitors also have an effect on the exposures of simvastatin. The data from a new study (Study 1067) using clarithromycin (see table below) was submitted to the NDA in December 2002 and has not been evaluated by the FDA. A few examples of this effect are shown below.

**Table 5-12. Fold increase due to CYP3A4 inhibition**

Inhibitor	N	Simvastatin		Simvastatin acid	
		C <sub>max</sub>	AUC	C <sub>max</sub>	AUC
Telithromycin <sup>a</sup>	30	5.3	8.9	15	12
Clarithromycin <sup>a, b</sup>	12	8.2	7.9	14.3	13.9
Grapefruit juice	10	9	16	7	7
Itraconazole	10	10	10	17	19

Source: *Telithromycin, Study 1048; grapefruit juice, Lijja et al., 1998 [29]; itraconazole, Neuvonen et al., 1998 [41]*

<sup>a</sup> Fold increase based on geometric means.

<sup>b</sup> *Clarithromycin, Study 1067, data finalized, final report not yet available.*

The data from a new recently completed study (Study 1065) was submitted to the NDA in December 2002 and has not been evaluated by the FDA. This study indicates that the magnitude of interaction between telithromycin and simvastatin can be reduced by more than 50% when the two are administered 12 hours apart, as shown in the table below.

**Table 5-13. Effect of telithromycin on CYP3A4 inhibitor simvastatin**

Parameter	Fold increase in simvastatin exposure <sup>a</sup> (90% confidence interval)	
	Telithromycin 800 mg qd concomitant N=14	Telithromycin 800 mg qd 12 hours apart N=14
Simvastatin	C <sub>max</sub>	7.7 (6.3-9.5)
	AUC	8.4 (5.9-11.9)
Simvastatin acid	C <sub>max</sub>	10.0 (8.3-12.1)
	AUC	9.4 (7.4-11.9)

<sup>a</sup> After 40 mg single dose of simvastatin; Study 1065, data finalized, final report not yet available.

In summary, it can be seen that the effect on all CYP3A4 substrates is similar between telithromycin and clarithromycin. Telithromycin has the added advantage that its duration of administration for certain RTIs is less compared with macrolides and, as shown earlier, its multiple elimination pathways.

#### CYP2D6 substrates

- **Paroxetine:** Co-administration of telithromycin with paroxetine did not alter the pharmacokinetics of paroxetine (Study 1022).
- **Metoprolol:** Co-administration of telithromycin slightly increased the bioavailability of metoprolol (1.4-fold increase for both C<sub>max</sub> and AUC) without affecting elimination, suggesting a minor first-pass effect from CYP2D6 inhibition (Study 1061).

#### Other drugs

- **Theophylline:** AUC<sub>(0-12)<sub>ss</sub></sub> and C<sub>max,ss</sub> values of theophylline both increased by approximately 1.2-fold after co-administration of telithromycin (Study 1011).