such as those containing aluminum and magnesium, result in a decrease in the AUC of delavirdine of approximately 41% (ViiV Healthcare, product information, 2012). No data are available on the effect of H_2R antagonists and proton pump inhibitors on delavirdine absorption, but it is safe to assume that they will reduce it. In a study of HIV-infected volunteers with (n = 11) and without (n = 10) gastric hypoacidity, delavirdine exposure (C_{max}, $AUC_{0-\infty}$, and C_{min}) was approximately 50% lower and the extent of delavirdine metabolism was higher in the subjects with gastric hypoacidity (Shelton *et al.*, 2003b). Administration of delavirdine with an acidic solution (orange juice) in the subjects with gastric hypoacidity produced a mean gastric pH lower than that of water and increased delavirdine absorption by 50–70% (Shelton *et al.*, 2003a; Shelton *et al.*, 2003b). In patients with *Helicobacter pylori* infection, eradication of the infection increased delavirdine absorption.

Co-administrations of a single dose of buffered didanosine with delavirdine decreased the *in vivo* exposure of delavirdine and, to a lesser extent, of didanosine (Morse *et al.*, 1997). Drug pharmacokinetics was studied when buffered didanosine tablets (125–200 mg) and delavirdine mesylate (400 mg) were given separately, when the two drugs were given concurrently, and when didanosine was given 1 hour after delavirdine. Co-administration reduced the delavirdine C_{max} by 51% and the $AUC_{0-\infty}$ by 38%. Didanosine pharmacokinetics was also impaired by concurrent administration of delavirdine, with the didanosine C_{max} decreasing by 31% and the $AUC_{0-\infty}$ decreasing by 18% (Morse *et al.*, 1997). In the steady-state situation, co-administration of delavirdine with didanosine appeared to have no significant effect on absorption (Morse *et al.*, 2003b). Although the delavirdine C_{max} was reduced by about 37% by co-administration with didanosine, no significant difference was noted for the delavirdine AUC. In addition, no differences were noted for didanosine pharmacokinetic variables. These authors concluded that patients could co-administer didanosine and delavirdine as part of a combination regimen in an attempt to enhance adherence to treatment (Morse *et al.*, 2003b). Although, taken together, the clinical significance of the interactions between buffered didanosine and delavirdine seem of little clinical consequence, the manufacturer does recommend giving delavirdine at least 1 hour before didanosine (ViiV Healthcare, product information, 2012).

Delavirdine is extensively bound to plasma proteins (approximately 98%), and this proportion remains constant over a wide range of delavirdine concentrations (Chaput *et al.*, 1996; ViiV Healthcare, product information, 2012).

5b. Drug distribution

Over total daily doses of 60–1200 mg the steady-state pharmacokinetics of delavirdine is nonlinear, resulting in a 40-fold decrease in oral clearance and increase in apparent half-life as doses increase (Freimuth, 1996). This is probably due to inhibition of the relevant cytochrome P-450 isoenzymes by delavirdine (see section 5d, Excretion). In dose-ranging studies, trough plasma levels of delavirdine in excess of 10 μM have readily been achieved, these being > 100 times the IC_{90} of delavirdine for wild-type HIV-1 strains. The plasma half-life ($t_{½}$) of delavirdine increases with dose; mean delavirdine $t_{½}$ after administration of 400 mg three times daily (the recommended dose) was 5.8 hours (range: 2–11 hours). Although all studies of delavirdine have used three times daily administration, with a serum $t_{½}$ in this range it would seem at least possible that a twice-daily regimen would be equally effective.

Smith *et al.* (2005) studied the population pharmacokinetics of delavirdine in the AIDS Clinical Trials Group studies ACTG260 and 261. Mean (% coefficient of variation [CV]) population estimates of pharmacokinetic variables for delavirdine were volume of distribution at steady state 67.6 l (100), intrinsic oral clearance 19.8 l/hour (64), concentration at half the maximum velocity of metabolism (V_{max}) 6.3 μmol/l (69), and first-order oral clearance 0.57 l/hour (86). These authors also noted that the pharmacokinetic parameters of delavirdine exhibited large interpatient variability (although it is not clear whether this variability was greater in magnitude than for some other antiretroviral drugs, such as protease inhibitors).

Steady-state concentrations of delavirdine in saliva and semen were 6% and 2% of plasma concentrations, respectively, in persons receiving 400 or 300 mg of delavirdine three times daily. In HIV-infected subjects on a total daily delavirdine dose of 600–1200 mg, levels in the cerebrospinal fluid (CSF) were 0.4% of plasma levels (ViiV Healthcare, product information, 2012).

The pharmacokinetics of delavirdine in children under the age of 16 years or in patients with hepatic impairment has not been investigated. At a dose of 400 mg three times daily, AUC is higher in women (31%) than in men (ViiV Healthcare, product information, 2012).

5c. Clinically important pharmacokinetic and pharmacodynamic features

No clinically important pharmacokinetic/pharmacodynamic features have been described for delavirdine.

5d. Excretion

Delavirdine is metabolized primarily through dealkylation catalyzed by CYP3A4 and CYP2D6 and by pyridine hydroxylation catalyzed by CYP3A4 (Voorman *et al.*, 1998a; Voorman *et al.*, 1998b; Voorman *et al.*, 2001). Further, because delavirdine can partially inhibit CYP2C9, -2C19, -2D6, and -3A4, although the degree of inhibition *in vivo* would be subject to a variety of additional factors, delavirdine inhibits its own metabolism as well as that of a wide variety of other drugs. Delavirdine does not inhibit CYP1A2 or -2E1 (Voorman *et al.*, 2001). In volunteers given ^{14}C-labeled delavirdine, approximately 44% of the radioactivity was recovered in feces and 51% in urine; < 5% of urine radioactivity represented