Delavirdine

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1. DESCRIPTION

Delavirdine mesylate, formerly known as U-90152, is a member of the bisheteroarylpiperazine (BHAP) class of nonnucleoside reverse transcriptase inhibitors discovered at UpJohn Laboratories in Kalamazoo, Michigan (Romero *et al.*, 1991; Adams *et al.*, 1998). Like other members of its class, it is an inhibitor of the HIV-1 reverse transcriptase but is inactive against HIV-2 or other retroviruses. Atevirdine (U-87201E) is a closely related compound of the same class (χ). Manufactured and previously marketed by Pfizer it is now marketed by ViiV Healthcare under the brand name Rescriptor.

The chemical name of delavirdine is 1-[3-[(1-methylethyl)amino]-2-pyridinyl]-4-[[5-[(methylsulfonyl) amino]-1H-indol-2-yl] carbonyl]-piperazine, monomethanesulfonate. The molecular formula of delavirdine is $C_{22}H_{28}N_6O_3S$, and the molecular weight is 456.565. The chemical structure is shown in Figure 237.1. Delavirdine is available as 100- and 200-mg tablets; there is no parenteral formulation.

Although delavirdine is approved for the treatment of HIV infection in many countries, it is now very rarely used in any country because of the need for three times daily administration as well as its low barrier for the development of resistance.

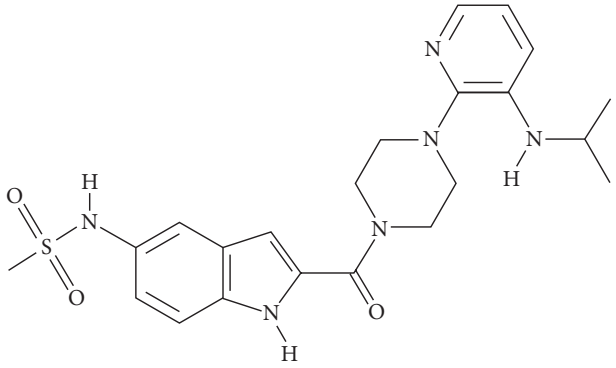

Figure 237.1. Chemical structure of delavirdine.

2. ANTIMICROBIAL ACTIVITY

2a. Routine susceptibility

Like other nonnucleoside reverse transcriptase inhibitors, delavirdine is active against HIV-1 but not HIV-2. The subtype O (outlier) of HIV-1 may not be inhibited by delavirdine (ViiV Healthcare, product information, 2012).

The antiretroviral activity of delavirdine has been evaluated in HIV-1-infected peripheral blood mononuclear cells, T-cell lines, and monocyte-derived macrophages and in acutely infected brain microglial cells (Dueweke *et al.*, 1993a; Nottet *et al.*, 1994; Peterson *et al.*, 1994; Freimuth *et al.*, 1996). The delavirdine half-maximal inhibitory concentration (IC_{50}) for inhibition of purified HIV-1 reverse transcriptase activity was 0.26–0.29 μM (Dueweke *et al.*, 1993a; Fan *et al.*, 1995a). Delavirdine inhibits replication of clinical isolates of HIV-1 (including isolates that are resistant to other classes of antiretrovirals) in peripheral blood mononuclear cells with a mean IC_{50} of 0.06 μM (range: < 0.0010.69 μM) and an IC_{90} of 0.1 μM (Dueweke *et al.*, 1993a; Nottet *et al.*, 1994; Freimuth, 1996; see Table 237.1). In acutely infected macrophage cultures, delavirdine inhibits HIV replication with an IC_{50} ranging from 0.02 to 0.1 μM (Dueweke *et al.*, 1993a).

2b. Emerging resistance and cross-resistance

Like all nonnucleoside reverse transcriptase inhibitors, delavirdine has a low genetic barrier to resistance, and the common mutations associated with resistance are common with nevirapine and efavirenz.

When passaged in cell culture in the presence of delavirdine, HIV-1 rapidly develops resistance to the drug, and the resulting HIV-1 strains are 10 to 100 times less susceptible to delavirdine than the parental strain (Balzarini *et al.*, 1993a; Balzarini *et al.*, 1993b). Combining delavirdine with nevirapine