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Maribavir

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1. DESCRIPTION

Maribavir is an orally bioavailable benzimidazole L-riboside antiviral drug, with a spectrum of activity essentially limited to human cytomegalovirus (CMV) and Epstein-Barr virus (EBV). It is a potent and specific inhibitor of the CMV *UL97* kinase. Maribavir is the generic name for 5,6-dichloro-2-(isopropylamino)-1-beta-L-ribofuranosylbenzimidazole, with the chemical structure as shown in Figure 223.1. The molecular weight is 376.24. Investigational drug code names include (BW)1263W94, GW257406X, VP41263, and SHP620 reflecting sequential changes in corporate ownership. Over the past 20 years, maribavir has undergone various clinical trials as an experimental CMV antiviral drug. Earlier phase I and II trials showed anti-CMV activity with an acceptable adverse effect profile. Unsuccessful phase III trials of low-dose maribavir for prevention of CMV infection in transplant patient populations ended in 2009, followed a few years later by phase II CMV treatment trials at higher doses, which were announced as successful in 2015. There is continued clinical interest in this compound because of its distinct antiviral target, oral bioavailability and favorable toxicity profile, although its optimal therapeutic role remains to be determined.

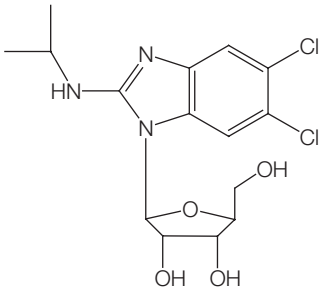

Figure 223.1. Chemical structure of maribavir.

2. ANTIMICROBIAL ACTIVITY

2a. Routine susceptibility

The published literature on antiviral susceptibility usually reports drug concentrations in micromolar (μM) units, whereas the pharmacology literature usually uses μg/ml (1 μM = 0.376 μg/ml).

HUMAN CYTOMEGALOVIRUS

Clinical isolates and laboratory strains of CMV are susceptible to maribavir, but inhibitory concentrations vary, depending on strains, cell culture conditions, and methods (Biron *et al.*, 2002; Williams *et al.*, 2003; Chou *et al.*, 2006). No generally accepted standards have been established either for testing methods or susceptible cut-off drug levels. In traditional plaque reduction assays, the drug concentration required for 50% reduction of CMV growth (EC_{50}) ranged from 0.54 μM (Biron *et al.*, 2002; Lalezari *et al.*, 2002) to 19 μM (Williams *et al.*, 2003) for the same laboratory strain, AD169. Lowering the cell culture incubation temperature from 37° to 34°C reduced the EC_{50} value from 19 to 3 μM (Williams *et al.*, 2003). When viral growth inhibition is measured by DNA hybridization and viral infectivity yield reduction assays, the EC_{50} values are generally lower, ranging from 0.06 to 0.12 μM for strain AD169 (Biron *et al.*, 2002; Chou *et al.*, 2004); by a flow cytometric assay, it was 0.2 μM (McSharry *et al.*, 2001); and by a reporter-based yield reduction assay, it was 0.14 μM in lung fibroblasts and 13 μM in skin fibroblasts (Chou *et al.*, 2006), illustrating the strong impact of cell culture conditions. Another laboratory strain, Towne, was reported to have plaque reduction EC_{50} values ranging from 0.3 to > 44 μM (Evers *et al.*, 2002; Williams *et al.*, 2003; Drew *et al.*, 2006), likely reflecting cell culture differences. Numerous clinical CMV isolates have been tested and found to be susceptible to maribavir, with EC_{50} values similar to those of the laboratory strains (McSharry *et al.*, 2001; Biron *et al.*, 2002; Lalezari *et al.*, 2002; Williams *et al.*, 2003; Drew *et al.*, 2006).

EPSTEIN-BARR VIRUS

The replication of EBV DNA was inhibited when assessed in a Burkitt lymphoma cell line (Akata) latently infected with the virus, with EC_{50} values estimated at 0.15–1.1 μM (Zacny