Dolutegravir

Keith A. Pappa, Mark A. Wainberg, Andrew R. Zolopa

1. DESCRIPTION

Dolutegravir is a human immunodeficiency virus (HIV) integrase strand–transfer inhibitor (INSTI), consisting of a chiral nonracemic tricyclic carbamoyl pyridone–containing heterocycle core and a benzyl carboxamide moiety. Dolutegravir was discovered using a pharmacophore-based design approach to construct a bioisostere of the integrase phosphodiester substrate. As such, dolutegravir was designed to bind two divalent magnesium ions within the integrase catalytic active site, which effectively prevents the productive integration of viral and host deoxyribonucleic acid (DNA) substrates through inhibition of the second biochemical step catalyzed by HIV integrase known as strand transfer. Dolutegravir has no appreciable inhibition of the first biochemical step catalyzed by integrase known as 3′ processing, which is consistent with the two-metal binding mechanism of action (Johns *et al.*, 2013). Dolutegravir is a specific inhibitor of HIV-1 and HIV-2 and has some antiviral activity against select non-HIV viruses, as described in section 2a, Routine susceptibility.

Formerly known as GSK1349572 with the generic name dolutegravir, the drug is marketed under the brand name of Tivicay and is also marketed as part of a fixed-dose combination of dolutegravir–abacavir–lamivudine (Triumeq) by ViiV Healthcare. In addition, GlaxoSmithKline and Shionogi scientists were an integral part of the discovery and development program. Dolutegravir is administered orally as a film-coated tablet.

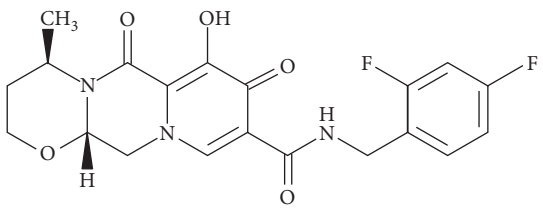

Figure 251.1. Chemical structure of dolutegravir.

The molecular formula of dolutegravir is $C_{20}H_{19}F_2N_3O_5$, having a parent molecular weight of 419 g/mol although dolutegravir is dosed at its corresponding sodium (Na^+) salt (molecular weight = 441 g/mol). The chemical name for dolutegravir sodium is sodium (4R,12aS)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1′,2′:4,5]pyrazino[2,1-b][1,3]oxazin-7-olate. The chemical structure of dolutegravir is shown in Figure 251.1.

2. ANTIMICROBIAL ACTIVITY

2a. Routine susceptibility

HUMAN IMMUNODEFICIENCY VIRUS

Dolutegravir has low nanomolar activity against wild-type HIV-1 and HIV-2 in a variety of cells lines, regardless of subtype. Against laboratory strains of wild-type HIV-1, dolutegravir exhibited antiviral activity with mean 50% effective concentration (EC_{50}) values of 0.5 nM (0.21 ng/ml) to 2.1 nM (0.85 ng/ml) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells, respectively (Kobayashi *et al.*, 2011). Using the integrase coding region from clinical isolates, dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC_{50} value of 0.52 nM in a viral integrase susceptibility assay (Underwood *et al.*, 2010). In addition, dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates (three in each group of M clades A, B, C, D, E, F, and G and three in group O), with mean EC_{50} values against group M subtypes A–G from 0.22 to 0.62 nM, group O mean of 0.87 nM, and HIV-2 mean of 0.29 nM in PBMCs (Underwood *et al.*, 2010). The EC_{50} values ranged from 0.02to 2.14 nM for HIV-1; against HIV-2 clinical isolates in PBMC assays, dolutegravir EC_{50} values ranged from 0.09 to 0.61 nM. In monocyte-derived macrophage assays using 4 clade B isolates, the geometric mean EC_{50} was 0.87 nM, and values ranged from 0.37 to 1.98 nM. Mean EC_{50} values for each of these categories are listed in Table 251.1. In 72 additional nonsubtype B isolates