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Letermovir

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1. DESCRIPTION

Letermovir is the first representative of the nonnucleoside 3,4 dihydro-quinazoline class of human cytomegalovirus (HCMV) viral terminase complex inhibitors (Verghese and Schleiss, 2013). Originally developed by Bayer AG (Wuppertal, Germany), with further preclinical and clinical development through phase II by AiCuris GmbH & Co. KG (Wuppertal, Germany), letermovir is now under development by Merck & Co. (Kenilworth, NJ, USA). Letermovir is now in phase III development for the prevention of HCMV infection in allogeneic hematopoietic cell transplant (HCT) recipients (clinical trials NCT02137772). Owing to its development history, letermovir is variously known as BAY 73-6327, AIC246, and MK-8228. The chemical name of letermovir is 2-((4S)-8-fluoro-2-(4-(3-methoxyphenyl)piperazin-1-yl)-3-(2-methoxy-5)-trifluoromethyl)phenyl)-4H-quinazolin-4-yl)acetic acid (PubChem Open Chemistry Database, 2016), the molecular formula is $C_{29}H_{28}F_4N_4O_4$, and its molecular weight is 572.55 g/mol. The chemical structure is shown in Figure 220.1.

The group of 3,4 dihydro-quinazolines were initially identified as a potential anti-HCMV compounds through high-throughput screening, with letermovir discovered following detailed analysis of structure–activity relationships (Lischka *et al.*, 2010). Letermovir has a unique mechanism of action, targeting proteins of the terminase complex (pUL56). Letermovir is currently available for investigational use as a 240-mg film-coated tablet. Due to poor solubility, an intravenous formulation solubilized in hydroxypropyl beta-cyclodextrin (HPβCD) was developed and is available for use in phase III trials (Kropeit *et al.*, 2013a). An oral solution was evaluated in phase I trials and is in continued development for pediatric use (Kropeit *et al.*, 2010).

Letermovir has been granted US Food and Drug Administration (FDA) fast track status for the treatment of HCMV infection in the USA, and it has orphan drug designation in both the USA and European Union for the treatment and the prevention of HCMV. Early phase II results for letermovir

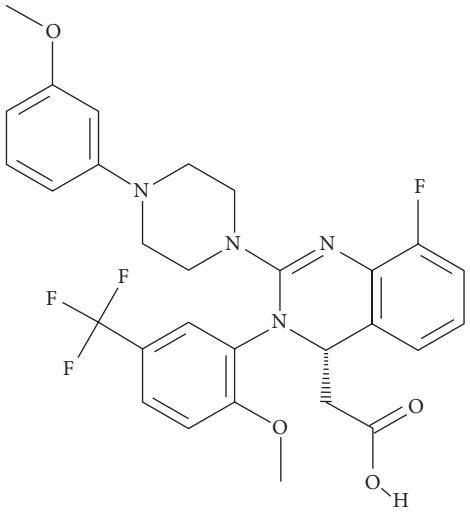

Figure 220.1. Chemical structure of letermovir.

as a treatment and prophylactic against HCMV in transplant recipients are promising in terms of both its efficacy and especially its safety profile (Chemaly *et al.*, 2014; Stoelben *et al.*, 2014). Depending on the results of the ongoing, large-scale phase III trial, preengraftment prophylaxis in HCT patients may be possible, and it is likely that letermovir will not have the associated, and in some cases treatment-limiting, toxicities of ganciclovir (Chemaly *et al.*, 2014) and may even allow preengraftment use in HCT recipients (Griffiths and Emery, 2014).

2. ANTIMICROBIAL ACTIVITY

2a. Routine susceptibility

HUMAN CYTOMEGALOVIRUS

Letermovir is highly active against clinical and laboratory strains of HCMV (AD169 and Davis) with 50% effective concentration (EC_{50}) values of 4–5 nM (Lischka *et al.*, 2010;