Letermovir

Cat. No.: HY-15233

CAS No.: 917389-32-3

Molecular Formula: $C_{29}H_{28}F_4N_4O_4$

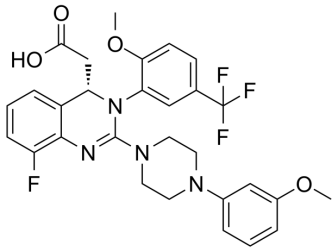
Molecular Weight: 572.55

Target: CMV

Pathway: Anti-infection

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (174.66 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.7466 mL	8.7329 mL	17.4657 mL
5 mM	0.3493 mL	1.7466 mL	3.4931 mL
10 mM	0.1747 mL	0.8733 mL	1.7466 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (4.37 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.37 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.37 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Letermovir (AIC246) is a potent inhibitor of CMV, which targets the viral terminase complex and remains active against virus resistant to DNA polymerase inhibitors.

In Vitro

AIC246 has consistent antiviral efficacy, and there is remarkable selectivity of AIC246 for human cytomegaloviruses[1]. AD169 mutant strains and designated rAIC246-1 and rAIC246-2 are highly resistant to Letermovir (AIC246), with EC_{50}s of 5.6 nM, 1.24 μM, 0.37 μM, respectively. Letermovir inhibits HCMV replication through a specific antiviral mechanism that involves the viral

	gene product UL56. Letermovir inhibits HCMV replication in cell culture by interfering with the proper cleavage/packaging of HCMV progeny DNA[2]. Letermovir inhibits the current gold standard GCV by more than 400-fold with respect to EC_{50}s (mean, 4.5 nM versus 2 μM) and by more than 2,000-fold with respect to EC_{90} values (mean, 6.1 nM versus 14.5 μM)[3]. Letermovir in conbination with anti-HCMV drugs causes additive antiviral effects, but there is no interaction between letermovir and anti-HIV drugs[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Letermovir (10-100 mg/kg/day, p.o.) leads to a dose-dependent reduction of the HCMV titer in transplanted cells compared to that of the placebo-treated control group using the mouse xenograft model[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	Briefly, 5×10^3 AD169-infected NHDF cells/well are seeded into the wells of 30 96-well microtiter plates. The infection is allowed to proceed under the exposure of 50 nM AIC246 ($10\times EC_{50}$) until a CPE developed in one or more of the compound-treated wells (indicative of resistant virus breakthrough). Noninfected and nontreated cells serve as controls on each plate. Mutant virus amplification is accomplwashed after cultures achieved maximum CPE by the passage of cell-free supernatant virus in the presence of 50 nM AIC246. The resultant AIC246-resistant progeny virus mutants are plaque purified three times by limiting dilutions in the presence of AIC246. The stability of resistance is tested by serially passaging plaque-purified viruses without selective pressure (8 to 10 times). MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3]	Mice (18 to 25 g body weight) are anesthetized, and the Gelfoam sponges are implanted subcutaneously in the dorsoscapular area. After transplantation, mice are randomized and grouped in 10 animals per treatment group. Starting 4 h after transplantation, mice are treated once daily with letermovir for nine consecutive days. Drugs are applied per os by oral gavage. Total administration volume is 10 mL/kg. Mice are sacrificed after 9 days of treatment, and the Gelfoam implants are removed and digested with collagenase at 37°C. After 2 to 3 h, human cells are recovered by centrifugation and resuspended in GM. Subsequently, the isolated cell suspensions are serially diluted and mixed with uninfected NHDF indicator cells and PFU are determined by plaque assays as described above. Virus titers determined from isolated cells are given as PFU/mL. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Antiviral Res. 2022 Jun 8;105361.
- Antiviral Res. 2018 Oct;158:255-263.
- Antiviral Res. 2018 Sep;157:128-133.
- Antiviral Res. 2017 Dec;148:1-4.
- PLoS Pathog. 2017 Feb 27;13(2):e1006202.

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REFERENCES

[1]. Marschall M, et al. In vitro evaluation of the activities of the novel anticytomegalovirus compound AIC246 (letermovir) against herpesviruses and other human pathogenic viruses. Antimicrob Agents Chemother. 2012 Feb;56(2):1135-7.

[2]. Goldner T, et al. The novel anticytomegalovirus compound AIC246 (Letermovir) inhibits human cytomegalovirus replication through a specific antiviral mechanism that

involves the viral terminase. J Virol. 2011 Oct;85(20):10884-93.

[3]. Lischka P, et al. In vitro and in vivo activities of the novel anticytomegalovirus compound AIC246. Antimicrob Agents Chemother. 2010 Mar;54(3):1290-7.

[4]. Wildum S, et al. In vitro drug combination studies of Letermovir (AIC246, MK-8228) with approved anti-human cytomegalovirus (HCMV) and anti-HIV compounds in inhibition of HCMV and HIV replication. Antimicrob Agents Chemother. 2015;59(6):3140-8.

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