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产品名称：Letermovir
产品别名：莱莫维韦 ；AIC246

生物活性：

Description	Letermovir is a novel 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 EC50s 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 EC50s (mean, 4.5 nM versus 2 μM) and by more than 2,000-fold with respect to EC90 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].
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].
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

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 In Vitro 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶

1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline

Solubility: ≥ 2.5 mg/mL (4.37 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (4.37 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。

	2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline) Solubility: ≥ 2.5 mg/mL (4.37 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.37 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (4.37 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.37 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
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.

实验参考：

Cell Assay	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). [2]
Animal Administration	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. [3]
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.