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产品名称: **Pimodivir**
产品别名: **VX-787**

生物活性:				
Description	Pimodivir (VX-787) is an orally bioavailable inhibitor of influenza A virus polymerases through interaction with the viral PB2 subunit.			
In Vitro	Pimodivir rescues macrophages from virus-mediated death at non-cytotoxic concentrations 24 hpi. The EC ₅₀ value for Pimodivir are 8 and 12 nM for A(H1N1) and A(H3N2) strains, respectively, whereas the CC ₅₀ values are >1 μM, giving selectivity indexes (SI) > 125 and > 83 for A(H1N1) and A(H3N2) strains, respectively. Pimodivir significantly attenuates the transcription of viral M1 RNA in macrophages, which are infected with A(H1N1) or A(H3N2) strains for 8 h. Pimodivir inhibits the transcription of viral but not cellular genes. Pimodivir allows some activation of IAV-mediated expression of several cellular genes, which are involved in tryptophan and nucleotide metabolism. Pimodivir possesses excellent anti-IAV but not immuno/metabolo-modulating effect ^[2] . Pimodivir (VX-787) is very potent against influenza A strains, including pandemic 2009 H1N1 and avian H5N1 ^[3] . Pimodivir (VX-787) shows potent activity against all influenza A virus strains tested, with an EC ₅₀ range of 0.13 to 3.2 nM. Pimodivir-selected PB2 variant viruses maintain susceptibility to neuraminidase inhibitors in vitro ^[4] .			
In Vivo	Pimodivir (2, 6, and 20 mg/kg/day, p.o.) and oseltamivir (20 mg/kg/day) completely prevent death in the H1N1pdm virus infection in mice. Pimodivir (20 mg/kg/day) is more effective than oseltamivir (20 mg/kg/day) in improving body weight and reducing the severity of lung infection ^[1] . Moreover, Pimodivir (VX-787) shows 100% survival in a +48 h delay to treatment mouse influenza model at 10, 3 and 1 mpk (BID × 10 days) whereas the SOC, oseltamivir, provide no survival benefit in this model at 10 mpk ^[3] . Pimodivir (VX-787; 1, 3, or 10 mg/kg, bid) provided complete survival, with a dose-dependent reduction in BW loss of the mice ^[4] .			
Solvent&Solubility	In Vitro: DMSO : 100 mg/mL (250.38 mM; Need ultrasonic)			
		Solvent Mass Concentration	1 mg	5 mg
	Preparing	1 mM	2.5038 mL	12.5191 mL
	Stock Solutions	5 mM	0.5008 mL	2.5038 mL
		10 mM	0.2504 mL	1.2519 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				



	<p>1.请依序添加每种溶剂: 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline</p> <p>Solubility: ≥ 2.5 mg/mL (6.26 mM); Clear solution</p> <p>此方案可获得 ≥ 2.5 mg/mL (6.26 mM, 饱和度未知) 的澄清溶液。</p> <p>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。</p> <p>2.请依序添加每种溶剂: 10% DMSO→ 90% (20% SBE-β-CD in saline)</p> <p>Solubility: ≥ 2.5 mg/mL (6.26 mM); Clear solution</p> <p>此方案可获得 ≥ 2.5 mg/mL (6.26 mM, 饱和度未知) 的澄清溶液。</p> <p>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。</p> <p>3.请依序添加每种溶剂: 10% DMSO →90% corn oil</p> <p>Solubility: ≥ 2.5 mg/mL (6.26 mM); Clear solution</p> <p>此方案可获得 ≥ 2.5 mg/mL (6.26 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。</p> <p>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。</p>
References	<p>[1]. Smee DF, et al. Activities of JNJ63623872 and oseltamivir against influenza A H1N1pdm and H3N2 virus infections in mice. Antiviral Res. 2016 Dec;136:45-50.</p> <p>[2]. Fu Y, et al. JNJ872 inhibits influenza A virus replication without altering cellular antiviral responses. Antiviral Res. 2016 Sep;133:23-31.</p> <p>[3]. Boyd MJ, et al. Isosteric replacements of the carboxylic acid of drug candidate VX-787: Effect of charge on antiviral potency and kinase activity of azaindole-based influenza PB2 inhibitors. Bioorg Med Chem Lett. 2015 May 1;25(9):1990-4.</p> <p>[4]. Byrn RA, et al. Preclinical activity of VX-787, a first-in-class, orally bioavailable inhibitor of the influenza virus polymerase PB2 subunit. Antimicrob Agents Chemother. 2015 Mar;59(3):1569-82.</p>
实验参考:	
Cell Assay	<p>The compound cytotoxicity and efficacy testing is performed in 96-well plates with macrophages at 95% confluence. The compounds are added to the medium, and 30 min later, the cells are infected with virus or non-infected. The cell viability is analyzed with the Cell Titer Glo assay at 24 hpi. The luminescence is read with a PHERAstar FS plate reader. [2]</p>
Animal Administration	<p>The mice are anesthetized by intraperitoneal injection of ketamine/xylazine (50/5 mg/kg), and the animals are infected intranasally with a 90-μL suspension of influenza virus. The virus challenge is approximately four 50% mouse lethal infectious doses. Treatments are given twice a day (at 12 h intervals) for 10 days starting 2 h before virus challenge. Parameters for assessing the infection are survival, mean day of death, body weight changes, and lung infection parameters (hemorrhage score, weight, and virus titer). Animals are weighed individually every other day through day 21 of the infection. Initially, there are 15 mice per group treated with compound and 25 placebos. Five mice in each group are subsequently sacrificed for determination of lung infection parameters. A larger number of placebos are used than compound-treated mice to achieve greater statistical</p>



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	<p>power, especially if some animals in that group survive the infection. One mouse that dies during the treatment period is presumed to have died from treatment trauma because its death occurs well before other mice die from influenza. It is excluded from the total counts. Animals that die during infection are accounted for in the tabular data. [1]</p>
References	<p>[1]. Smee DF, et al. Activities of JNJ63623872 and oseltamivir against influenza A H1N1pdm and H3N2 virus infections in mice. <i>Antiviral Res.</i> 2016 Dec;136:45-50.</p> <p>[2]. Fu Y, et al. JNJ872 inhibits influenza A virus replication without altering cellular antiviral responses. <i>Antiviral Res.</i> 2016 Sep;133:23-31.</p> <p>[3]. Boyd MJ, et al. Isosteric replacements of the carboxylic acid of drug candidate VX-787: Effect of charge on antiviral potency and kinase activity of azaindole-based influenza PB2 inhibitors. <i>Bioorg Med Chem Lett.</i> 2015 May 1;25(9):1990-4.</p> <p>[4]. Byrn RA, et al. Preclinical activity of VX-787, a first-in-class, orally bioavailable inhibitor of the influenza virus polymerase PB2 subunit. <i>Antimicrob Agents Chemother.</i> 2015 Mar;59(3):1569-82.</p>

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