



上海源叶生物科技有限公司
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产品名称: **Cobimetinib (hemifumarate)**
产品别名: 考比替尼半富马酸盐; **GDC-0973 hemifumarate; XL-518 hemifumarate**

生物活性:				
Description	Cobimetinib hemifumarate is a novel selective MEK1 inhibitor, and the IC ₅₀ value against MEK1 is 4.2 nM.			
IC₅₀ & Target	MEK1			
	4.2 nM (IC ₅₀)			
In Vitro	The EC ₅₀ values of Cobimetinib (GDC-0973) for 888MEL and A2058 cells are 0.2 μM, 10 μM, respectively. Melanoma cells are treated with EC ₅₀ concentration of MEK and PI3K inhibitors for 24 hours (888MEL: 0.05 μM GDC-0973, 2.5 μM GDC-0941; A2058: 2.5 μM GDC-0973, 2.5 μM GDC-0941)[1]. Mitochondrial OXPHOS limits cell death induced by cobimetinib (100 nM) in melanoma with constitutive MAPK activation in A375 cells[4].			
In Vivo	In the NCI-H2122 KRASG12C mutant non-small cell lung carcinoma (NSCLC) xenograft model, treatment with up to 5 mg/kg Cobimetinib (GDC-0973) lead to moderate TGI and at 10 mg/kg approaches tumor stasis[1]. GDC-0973 and GDC-0941 are administered to A2058 tumor-bearing mice daily (QD) or every third day (Q3D) either as single agents or in combination. The population rate constants associated with tumor growth inhibition for GDC-0973 and GDC-0941 are 0.00102 and 0.000651 μM ⁻¹ h ⁻¹ , respectively[2]. Following single doses of GDC-0973 (1, 3, or 10 mg/kg, p.o.) estimated in vivo IC ₅₀ values of %pERK decrease based on tumor concentrations in xenograft mice are 0.78 (WM-266-4) and 0.52 μM (A375)[3].			
Solvent&Solubility	In Vitro: DMSO : 50 mg/mL (77.23 mM; Need ultrasonic)			
	Preparing Stock Solutions	Solvent	Mass	
		Concentration		
			1 mg	5 mg
			10 mg	
		1 mM	1.5447 mL	7.7234 mL
		5 mM	0.3089 mL	1.5447 mL
		10 mM	0.1545 mL	0.7723 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 (3.86 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (3.86 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			



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	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$\rightarrow$ 90% (20% SBE-β-CD in saline) Solubility: $\geq$ 2.5 mg/mL (3.86 mM); Clear solution 此方案可获得 $\geq$ 2.5 mg/mL (3.86 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 $\rightarrow$90% corn oil Solubility: $\geq$ 2.5 mg/mL (3.86 mM); Clear solution 此方案可获得 $\geq$ 2.5 mg/mL (3.86 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]. Hoeflich KP, et al. Intermittent administration of MEK inhibitor GDC-0973 plus PI3K inhibitor GDC-0941 triggers robust apoptosis and tumor growth inhibition. Cancer Res. 2012 Jan 1;72(1):210-9. [2]. Choo EF, et al. PK-PD modeling of combination efficacy effect from administration of the MEK inhibitor GDC-0973 and PI3K inhibitor GDC-0941 in A2058 xenografts. Cancer Chemother Pharmacol. 2013 Jan;71(1):133-43. [3]. Wong H, et al. Bridging the gap between preclinical and clinical studies using pharmacokinetic-pharmacodynamic modeling: an analysis of GDC-0973, a MEK inhibitor. Clin Cancer Res. 2012 Jun 1;18(11):3090-9. [4]. Corazao-Rozas P, et al. Mitochondrial oxidative phosphorylation controls cancer cell's life and death decisions upon exposure to MAPK inhibitors. Oncotarget. 2016 Feb 29. doi: 10.18632/oncotarget.7790.
实验参考:	
Animal Administration	5 million WM-266-4 melanoma cells are resuspended in Hank balanced salt solution and implanted intradermally into the hind flank of female NCR nude mice. On days 11 or 13 after the implantation, xenograft mice with tumor volumes of approximately 100 to 120 mm³ are randomly assigned to 8 groups (n=27 per group), 4 single dose groups and 4 multiple dose groups. One day after randomization and group assignment, mice in the single dose groups are given a single oral dose of vehicle (water for injection USP), 1, 3, or 10 mg/kg of Cobimetinib (GDC-0973, expressed as free base equivalents). Mice in the multiple dose groups are given daily oral doses of vehicle (water for injection USP), 1, 3, or 10 mg/kg of GDC-0973 for 14 days. Plasma and tumor samples (n=3 per time point) are collected from euthanized mice predose and at 2, 4, 8, 16, 24, 72, 120, and 168 hours postdose on day 1 (single dose groups) or day 14 (multiple dose groups). Samples are stored at -80°C until analysis. GDC-0973 concentrations in plasma and tumor lysates are determined using liquid chromatography/tandem mass spectrometry (LC/MS-MS). The dynamic range of the assay is 0.004 to 35 μM. [3]
	[1]. Hoeflich KP, et al. Intermittent administration of MEK inhibitor GDC-0973 plus PI3K inhibitor GDC-0941 triggers robust apoptosis and tumor growth inhibition. Cancer Res. 2012 Jan 1;72(1):210-9.



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- [2]. Choo EF, et al. PK-PD modeling of combination efficacy effect from administration of the MEK inhibitor GDC-0973 and PI3K inhibitor GDC-0941 in A2058 xenografts. Cancer Chemother Pharmacol. 2013 Jan;71(1):133-43.
- [3]. Wong H, et al. Bridging the gap between preclinical and clinical studies using pharmacokinetic-pharmacodynamic modeling: an analysis of GDC-0973, a MEK inhibitor. Clin Cancer Res. 2012 Jun 1;18(11):3090-9.
- [4]. Corazao-Rozas P, et al. Mitochondrial oxidative phosphorylation controls cancer cell's life and death decisions upon exposure to MAPK inhibitors. Oncotarget. 2016 Feb 29. doi: 10.18632/oncotarget.7790.



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