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产品名称: **GDC-0068 (dihydrochloride)**

产品别名: **Ipatasertib dihydrochloride; RG-7440 dihydrochloride**

生物活性:																												
Description	Ipatasertib dihydrochloride (GDC-0068 dihydrochloride) is a highly selective pan-Akt inhibitor targeting Akt1/2/3 with IC ₅₀ of 5/18/8 nM, 620-fold selectivity over PKA.																											
IC₅₀ & Target	Akt1	Akt2	Akt3	PKA																								
	5 nM (IC ₅₀)	18 nM (IC ₅₀)	8 nM (IC ₅₀)	3100 nM (IC ₅₀)																								
In Vitro	Ipatasertib shows more than 600 and more than 100-fold selectivity for Akt1 in IC ₅₀ against the closely related kinases PKA and p70S6K, respectively. When tested at 1 μM in a panel of 230 protein kinases, which includes 36 human AGC family members, Ipatasertib inhibits only 3 other kinases by more than 70% at 1 μM concentration (PRKG1α, PRKG1β, and p70S6K). IC ₅₀ s measured for these 3 kinases are 98, 69, and 860 nM, respectively. Thus, with the exception of PKG1 (relative to which Ipatasertib is >10-fold more selective for Akt1), Ipatasertib displays a more than 100-fold selectivity for Akt1 over the next most potently inhibited non-Akt kinase, p70S6K, in the screening kinase panel. The relationship between pharmacokinetics (PK) and pharmacodynamics (PD) of Ipatasertib is investigated in 3 xenograft models that showed dose-dependent response to drug treatment: MCF7-neo/HER2, TOV-21G.x1, and LNCaP. The mean cell viability IC ₅₀ of Ipatasertib in these 3 cell lines is 2.56, 0.44, and 0.11 μM, respectively ^[2] .																											
In Vivo	Ipatasertib is typically efficacious in xenograft models in which Akt is activated because of genetic alterations including PTEN loss, PIK3CA mutations/amplifications, or HER2 overexpression. In these models, tumor growth delay, stasis, or regression is achieved at or below 100 mg/kg daily oral dose, which is the maximum dose tested in immunocompromised mice that is well tolerated. When tested in vivo, daily dosing of Ipatasertib in combination with Docetaxel induces tumor regression and stasis in the PC-3 and MCF7-neo/HER2 xenograft models, at doses where each single agent is ineffective or only causes modest tumor growth delay. Similarly, increased TGI is observed in the OVCAR3 ovarian cancer xenograft model when Ipatasertib is combined with Carboplatin. The combination of Ipatasertib with Docetaxel or Carboplatin is tolerated with less than 5% body weight loss when compared with treatment with each chemotherapeutic agent alone ^[2] .																											
<p>In Vitro: DMSO : 125 mg/mL (235.44 mM; Need ultrasonic) H₂O : ≥ 41 mg/mL (77.22 mM)</p> <table border="1"> <thead> <tr> <th rowspan="2">Preparing</th> <th>Solvent</th> <th>Mass</th> <th rowspan="2">1 mg</th> <th rowspan="2">5 mg</th> <th rowspan="2">10 mg</th> </tr> <tr> <th colspan="2">Concentration</th> </tr> </thead> <tbody> <tr> <td rowspan="3">Stock Solutions</td> <td colspan="2">1 mM</td> <td>1.8835 mL</td> <td>9.4176 mL</td> <td>18.8352 mL</td> </tr> <tr> <td colspan="2">5 mM</td> <td>0.3767 mL</td> <td>1.8835 mL</td> <td>3.7670 mL</td> </tr> <tr> <td colspan="2">10 mM</td> <td>0.1884 mL</td> <td>0.9418 mL</td> <td>1.8835 mL</td> </tr> </tbody> </table> <p>*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。</p> <p>In Vivo:</p>					Preparing	Solvent	Mass	1 mg	5 mg	10 mg	Concentration		Stock Solutions	1 mM		1.8835 mL	9.4176 mL	18.8352 mL	5 mM		0.3767 mL	1.8835 mL	3.7670 mL	10 mM		0.1884 mL	0.9418 mL	1.8835 mL
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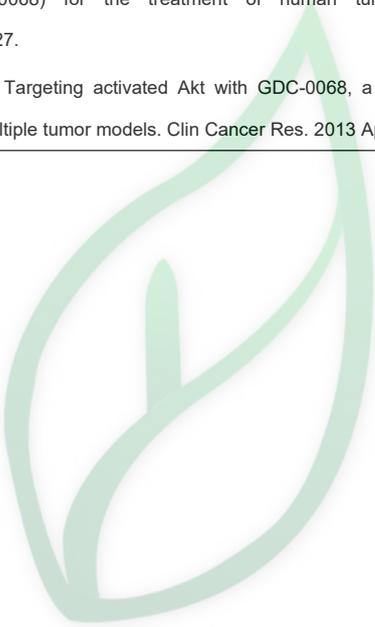


Solvent&Solubility	<p>请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 In Vitro 方式配制澄清的储备液，再依次添加助溶剂：</p> <p>——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用；以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶</p> <p>1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline</p> <p>Solubility: ≥ 2.08 mg/mL (3.92 mM); Clear solution</p> <p>此方案可获得 ≥ 2.08 mg/mL (3.92 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例，取 100 μL 20.8 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: ≥ 2.08 mg/mL (3.92 mM); Clear solution</p> <p>此方案可获得 ≥ 2.08 mg/mL (3.92 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例，取 100 μL 20.8 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水溶液中，混合均匀。</p> <p>3.请依序添加每种溶剂： 10% DMSO →90% corn oil</p> <p>Solubility: ≥ 2.08 mg/mL (3.92 mM); Clear solution</p> <p>此方案可获得 ≥ 2.08 mg/mL (3.92 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 20.8 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]. Blake JF, et al. Discovery and preclinical pharmacology of a selective ATP-competitive Akt inhibitor (GDC-0068) for the treatment of human tumors. J Med Chem. 2012 Sep 27;55(18):8110-27.</p> <p>[2]. Lin J, et al. Targeting activated Akt with GDC-0068, a novel selective Akt inhibitor that is efficacious in multiple tumor models. Clin Cancer Res. 2013 Apr 1;19(7):1760-72.</p>
实验参考：	
Cell Assay	<p>The 384-well plates are seeded with 2,000 cells per well in a volume of 54 μL per well followed by incubation at 37°C under 5% CO₂ overnight (~16 hours). Compounds (e.g., Ipatasertib) are diluted in DMSO to generate the desired stock concentrations then added in a volume of 6 μL per well. All treatments are tested in quadruplicates. After 4 days incubation, relative numbers of viable cells are estimated using CellTiter-Glo and total luminescence is measured on a Wallac Multilabel Reader. The concentration of drug resulting in IC₅₀ is calculated from a 4-parameter curve analysis (XLfit) and is determined from a minimum of 3 experiments. For cell lines that failed to achieve an IC₅₀, the highest concentration tested (10 μM) is listed^[2].</p>
	<p>Mice^[2]</p> <p>In vivo efficacy is evaluated in multiple tumor cell line- and patient-derived xenograft models. Cells or tumor fragments are implanted subcutaneously into the flank of immunocompromised mice. Female or male nude (nu/nu) or severe combined immunodeficient mice (SCID)/beige mice are used. For the MCF7-neo/HER2 model, 17β-estradiol pellets (0.36 mg/pellet, 60-day release) are</p>



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Animal Administration	implanted into the dorsal shoulder before cell inoculation. The LuCaP35V patient-derived primary tumors are obtained; male mice are castrated before implantation of tumor fragments. After implantation of tumor cells or fragments into mice, tumors are monitored until they reached mean tumor volumes of 180 to 350 mm ³ and distributed into groups of 8 to 10 animals/group. Ipatasertib is formulated in 0.5% methylcellulose/0.2% Tween-80 (MCT) and administered daily (QD), via oral (per os; PO) gavage. Docetaxel is formulated in 3% EtOH/97% saline and dosed intravenously (IV) every week (QW) at 2.5 or 7.5 mg/kg. Carboplatin is formulated in saline and dosed intraperitoneally (IP) weekly at 50 mg/kg.
References	<p>[1]. Blake JF, et al. Discovery and preclinical pharmacology of a selective ATP-competitive Akt inhibitor (GDC-0068) for the treatment of human tumors. <i>J Med Chem.</i> 2012 Sep 27;55(18):8110-27.</p> <p>[2]. Lin J, et al. Targeting activated Akt with GDC-0068, a novel selective Akt inhibitor that is efficacious in multiple tumor models. <i>Clin Cancer Res.</i> 2013 Apr 1;19(7):1760-72.</p>



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