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产品名称: **OSI-906 (Linsitinib)**
产品别名: **Linsitinib**

生物活性:				
Description	Linsitinib (OSI-906) is a dual inhibitor of the IGF-1 receptor and IR with IC50s of 35 and 75 nM, respectively.			
IC ₅₀ & Target	IC50: 35 nM (IGF-1R), 75 nM (InsR)			
In Vitro	Linsitinib inhibits IGF-1R autophosphorylation and activation of the downstream signaling proteins Akt, ERK1/2 and S6 kinase with IC50 of 0.028 to 0.13 μ M. Linsitinib enables an intermediate conformation of the target protein through interactions with the C-helix. Linsitinib displays favorable metabolic stability in liver microsomes. Linsitinib fully inhibits both IR and IGF-1R phosphorylation at a concentration of 1 μ M. Linsitinib inhibits proliferation of several tumor cell lines including non-small-cell lung cancer and colorectal cancer (CRC) tumor cell line with EC50 of 0.021 to 0.810 μ M[1].			
In Vivo	Linsitinib inhibits tumor growth in an IGF-1R-driven xenograft mouse model, with 100% TGI and 55% regression at a dose of 75 mg/kg and 60% TGI and no regression at a dose of 25 mg/kg. Linsitinib administration induces different elimination half-lives of itself in dog, rat and mice, the elimination half-lives are 1.18 hours, 2.64 hours and 2.14 hours, respectively. Linsitinib administration at different single dose once-daily in femal Sprague-Dawley rat and femal CD-1 mouse reveal that the Vmax is not dose-proportional to Linsitinib dose. Linsitinib elevates the blood glucose levels at a dose of 25 mg/kg after 12 days administration. Linsitinib administration at a single dose of 75 mg/kg in IGF-1R-driven full-length human IGF-1R (LISN) xenograft mouse model achieve maximal inhibition of IGF-1R phosphorylation (80%) between 4 and 24 hours with plasma drug concentrations of 26.6-4.77 μ M[1]. Linsitinib administered as a single dose of at 60 mg/kg in NCI-H292 xenografts mice inhibits uptake of glucose at 2, 4, and 24 hours post-treatment in vivo. Linsitinib inhibits the growth of tumors in NCI-H292 xenograft mouse model[2].			
Solvent&Solubility	In Vitro: DMSO : 62.5 mg/mL (148.28 mM; Need ultrasonic)			
		Solvent Concentration	Mass Concentration	
	Preparing	1 mM	2.3725 mL	11.8627 mL
	Stock Solutions	5 mM	0.4745 mL	2.3725 mL
		10 mM	0.2373 mL	1.1863 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				



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	<p>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 (4.93 mM); Clear solution</p> <p>此方案可获得 ≥ 2.08 mg/mL (4.93 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 (4.93 mM); Clear solution</p> <p>此方案可获得 ≥ 2.08 mg/mL (4.93 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>
References	<p>[1]. Mulvihill MJ, et al. Discovery of OSI-906: a selective and orally efficacious dual inhibitor of the IGF-1 receptor and IR. Future Med Chem. 2009 Sep;1(6):1153-71.</p> <p>[2]. McKinley ET, et al. 18FDG-PET predicts pharmacodynamic response to OSI-906, a dual IGF-1R/IR inhibitor, in preclinical mouse models of lung cancer. Clin Cancer Res. 2011 May 15;17(10):3332-40.</p> <p>[3]. Li W, et al. Effectiveness of inhibitor rapamycin, saracatinib, linsitinib and JNJ-38877605 against human prostate cancer cells. Int J Clin Exp Med. 2015 Apr 15;8(4):6563-7.</p>
实验参考:	
Cell Assay	<p>For assays of cell proliferation, cells are seeded into 96-well plates in appropriate media containing FCS 10% and incubated for 3 days in the presence of Linsitinib at various concentrations. Inhibition of cell growth is determined by luminescent quantitation of intracellular ATP content using CellTiterGlo. Data is presented as a fraction of maximal proliferation, calculated by dividing the cellular density in the presence of varying concentrations of Linsitinib by the cellular density of control cells treated with vehicle (DMSO) only. [1]</p>
Animal Administration	<p>Cells are harvested from cell culture flasks during exponential cell growth, washed twice with sterile PBS to a suitable concentration before subcutaneous implantation on the right flank of female nu/nu CD-1 mice. Tumors are established to 200\pm50 mm³ in size before randomization into treatment groups of eight mice each for efficacy studies. Linsitinib or vehicle is administered orally as indicated. The %TGI values indicated are the median %TGI over the entire dosing period. TGI of at least 505 is considered significant. Growth delay is calculated as T-C where T and C are the times in days for mean tumor size in the treated (T) and control (C) groups to reach 400% of the initial tumor volume. Cures are excluded from this calculation. [1]</p>
Kinase Assay	<p>Protein kinase assays are either performed in-house by ELISA-based assay methods (IGF-1R, IR, EGFR and KDR) or by a radiometric method with ATP at 100 μM concentration. In-house ELISA assays use poly(Glu:Tyr) as the substrate bound to the surface of 96-well assay plates and phosphorylation is detected using an antiphosphotyrosine antibody conjugated to horseradish peroxidase. The bound antibody is quantified using ABTS as the peroxidase substrate by measuring absorbance at 405/490 nm. All assays use purified recombinant kinase catalytic domains. Recombinant enzymes of human IGF-1R or EGFR are expressed as an NH₂-terminal glutathione</p>



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	<p>S-transferase fusion protein in insect cells and are purified in house. IC50 values are determined from the sigmoidal dose-response plot of percent inhibition versus log10 compound concentration. A minimum of three measurements, performed in duplicate, are carried out with in-house assays unless otherwise indicated. Linsitinib at a concentration of 1 μM is profiled versus a panel of kinases using the ProfilerProTM Kinase Selectivity Assay Kit. [1]</p>
References	<p>[1]. Mulvihill MJ, et al. Discovery of OSI-906: a selective and orally efficacious dual inhibitor of the IGF-1 receptor and IR. Future Med Chem. 2009 Sep;1(6):1153-71.</p> <p>[2]. McKinley ET, et al. 18FDG-PET predicts pharmacodynamic response to OSI-906, a dual IGF-1R/IR inhibitor, in preclinical mouse models of lung cancer. Clin Cancer Res. 2011 May 15;17(10):3332-40.</p> <p>[3]. Li W, et al. Effectiveness of inhibitor rapamycin, saracatinib, linsitinib and JNJ-38877605 against human prostate cancer cells. Int J Clin Exp Med. 2015 Apr 15;8(4):6563-7.</p>

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