产品名称：**Midostaurin (PKC412)**
产品别名：**Midostaurin CGP 41251；米哚妥林**

生物活性：

Description	Midostaurin (PKC412; CGP 41251) is a multi-targeted protein kinase inhibitor which inhibits PKCα/β/γ, Syk, Flk-1, Akt, PKA, c-Kit, c-Fgr, c-Src, FLT3, PDFRβ and VEGFR1/2 with **IC_{50}** ranging from 22-500 nM.			
IC_{50} & Target	cPKC-α	cPKC-γ	cPKC-β1	cPKC-β2
	22 nM (IC_{50})	24 nM (IC_{50})	30 nM (IC_{50})	31 nM (IC_{50})
	nPKC-δ	nPKC-η	nPKC-ε	aPKC-ζ
	33 nM (IC_{50})	160 nM (IC_{50})	1250 nM (IC_{50})	465000 nM (IC_{50})
	PPK	KDR	c-Syk	cdk1/cycB
	38 nM (IC_{50})	86 nM (IC_{50})	95 nM (IC_{50})	570 nM (IC_{50})
	Protein kinase A	c-Fgr	c-Src	Flt-1
	570 nM (IC_{50})	790 nM (IC_{50})	800 nM (IC_{50})	912 nM (IC_{50})
	EGF-R	Myosin-light chain kinase	Flk-1	c-Lyn
	1100 nM (IC_{50})	1900 nM (IC_{50})	3900 nM (IC_{50})	4300 nM (IC_{50})
	P70S6 kinase	CSK		
	5000 nM (IC_{50})	8000 nM (IC_{50})		
In Vitro	Midostaurin (PKC412) shows a broad antiproliferative activity against various tumor and normal cell lines in vitro, and is able to reverse the Pgp-mediated multidrug resistance of tumor cells in vitro. Exposure of cells to Midostaurin (PKC412) results in a dose-dependent increase in the G2/M phase of the cell cycle concomitant with increased polyploidy, apoptosis and enhanced sensitivity to ionizing radiation[1]. Midostaurin (PKC412) induces substantial inhibition of KIT-, Lyn-, and STAT5 activity, but does not suppress Btk in HMC-1 cells and primary neoplastic mast cells[2]. Midostaurin (PKC412) inhibits EN fusion tyrosine kinase in hematopoietic Ba/F3 cells. Midostaurin (PKC412) significantly inhibits EN phosphorylation in M0-91 and IMS-M2 cells in a dose-dependent manner[3].			
In Vivo	Midostaurin (PKC412) strongly inhibits retinal neovascularization as well as laser-induced choroidal neovascularization in murine models[1]. Midostaurin (PKC412) (25 mg/kg, i.p.) protects mouse livers of the K18 Arg90Cys-overexpressing transgenic mice from Fas-induced apoptosis[4].			
	In Vitro: **DMSO : ≥ 50 mg/mL (87.62 mM)** **H_2O : < 0.1 mg/mL** (insoluble) * "≥" means soluble, but saturation unknown.			
Preparing Stock Solutions	**Solvent / Mass / Concentration**	**1 mg**	**5 mg**	**10 mg**
	1 mM	1.7524 mL	8.7621 mL	17.5242 mL
	5 mM	0.3505 mL	1.7524 mL	3.5048 mL

Solvent&Solubility		10 mM	0.1752 mL	0.8762 mL	1.7524 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: 2.08 mg/mL (3.65 mM); Suspended solution; Need ultrasonic 此方案可获得 2.08 mg/mL (3.65 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。 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。 2.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.08 mg/mL (3.65 mM); Clear solution 此方案可获得 ≥ 2.08 mg/mL (3.65 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 20.8 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。				
References	[1]. Fabbro D, et al. PKC412--a protein kinase inhibitor with a broad therapeutic potential. Anticancer Drug Des. 2000 Feb;15(1):17-28. [2]. Gleixner KV, et al. Synergistic growth-inhibitory effects of Midostaurin (PKC412) on neoplastic mast cells carrying KIT D816V. Haematologica. 2013 Sep;98(9):1450-7. [3]. Chi HT, et al. ETV6-NTRK3 as a therapeutic target of small molecule inhibitor PKC412. Biochem Biophys Res Commun. 2012 Dec 7;429(1-2):87-92. [4]. Kwan R, et al. PKC412 normalizes mutation-related keratin filament disruption and hepatic injury in mice by promoting keratin-myosin binding. Hepatology. 2015 Dec;62(6):1858-69. [5]. Fabbro D, et al. Inhibitors of protein kinases: CGP 41251, a protein kinase inhibitor with potential as an anticancer agent. Pharmacol Ther. 1999 May-Jun;82(2-3):293-301.				

实验参考：

Cell Assay	Proliferation is determined by trypan blue dye exclusion test. Cells in suspension are seeded in six-well plates at a density of 1×10^5 cells/mL in the presence of different concentrations of PKC412 for 3 days. In control wells, DMSO instead of Midostaurin (PKC412) is added. After the treatment, 10 μL of the cell suspension is mixed with 10 μL of 0.4% trypan blue, and alive cells are counted manually using a hemacytometer. Results are calculated as the percentage of the values measured when cells are grown in the absence of the reagent. All experiments are performed in triplicate[3].
	K8-deficient, K18-deficient, and human K18 R90C-overexpressing mice with age of 6-8 weeks are used in the assay. Age and sex matched mice are treated with Midostaurin (25 mg/kg), daily for 4 d or with an equal volume of DMSO as vehicle (both administered intraperitoneally). On day 5

Animal Administration	post-treatment, apoptosis is induced by intraperitoneal injection of Fas ligand (Fas-L) (0.15 μg/g body weight). Mice are fasted overnight before Fas Ab injection, and 18 mice are used per DMSO or Midostaurin (PKC412) group for the Fas-treated mice while 6 mice are used per DMSO or Midostaurin (PKC412) group for the control non-Fas-treated mice. Mice are sacrificed by CO_2 inhalation 6 h after Fas Ab injection. Blood is collected by intracardiac puncture, and livers are harvested for hematoxylin and eosin (HE) staining (after fixation in 10% formalin) or frozen in optimum cutting temperature compound for immunofluorescence staining[4].
References	[1]. Fabbro D, et al. PKC412--a protein kinase inhibitor with a broad therapeutic potential. Anticancer Drug Des. 2000 Feb;15(1):17-28. [2]. Gleixner KV, et al. Synergistic growth-inhibitory effects of Midostaurin (PKC412) on neoplastic mast cells carrying KIT D816V. Haematologica. 2013 Sep;98(9):1450-7. [3]. Chi HT, et al. ETV6-NTRK3 as a therapeutic target of small molecule inhibitor PKC412. Biochem Biophys Res Commun. 2012 Dec 7;429(1-2):87-92. [4]. Kwan R, et al. PKC412 normalizes mutation-related keratin filament disruption and hepatic injury in mice by promoting keratin-myosin binding. Hepatology. 2015 Dec;62(6):1858-69. [5]. Fabbro D, et al. Inhibitors of protein kinases: CGP 41251, a protein kinase inhibitor with potential as an anticancer agent. Pharmacol Ther. 1999 May-Jun;82(2-3):293-301.