产品名称：Lanabecestat
产品别名：Lanabecestat

生物活性：

Description	Lanabecestat (AZD3293) is a potent, highly permeable, orally active and blood-brain barrier penetrating **BACE1** inhibitor with a K_i of 0.4 nM.
IC_{50} & Target	Ki: 0.4 nM (BACE1)[1]
In Vitro	Lanabecestat acts as a full inhibitor of BACE1 in vitro, with a competitive and reversible mechanism of action towards the hBACE1 active site. Lanabecestat displays a very high target affinity and a markedly slow target off-rate. The off-rate of lanabecestat has an estimated t1/2 of approximately 9h. Lanabecestat displays pM potency in primary neuron cultures from mice and guinea pigs and in SH-SY5Y cells over-expressing AβPP (IC50=610 pM, 310 pM, and 80 pM, respectively). The in vitro plasma protein binding of lanabecestat is determined by equilibrium dialysis using mouse, rat, guinea pig, dog, and human plasma. The compound is stable in the plasma of these species for at least the duration of the in vitro incubation period. The unbound fractions are 1.3% to 1.8% for mice, 4.2% to 5.9% for rats, 8.3% to 10.3% for guinea pigs, 9.4% to 10.3% for dogs, and 7.7% to 9.4% for human plasma. The mean blood:plasma ratio of 0.7 in human blood indicates no significant association with red blood cells. The free fraction in the brain tissue binding assay is 4.5%[1].
In Vivo	In mice, guinea pigs, and dogs, lanabecestat displays significant dose- and time-dependent reductions in plasma, cerebrospinal fluid, and brain concentrations of Aβ40, Aβ42, and sAβPPβ[1].
Solvent&Solubility	***In Vitro:*** **DMSO : ≥ 100 mg/mL (242.41 mM)** * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.4241 mL	12.1203 mL	24.2407 mL
	5 mM	0.4848 mL	2.4241 mL	4.8481 mL
	10 mM	0.2424 mL	1.2120 mL	2.4241 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 (6.06 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (6.06 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；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% (20% SBE-β-CD in saline) Solubility: ≥ 2.5 mg/mL (6.06 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.06 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 →90% corn oil Solubility: ≥ 2.5 mg/mL (6.06 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.06 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]. Eketj?ll S, et al. AZD3293: A Novel, Orally Active BACE1 Inhibitor with High Potency and Permeability and Markedly Slow Off-Rate Kinetics. J Alzheimers Dis. 2016;50(4):1109-23.

实验参考：

Cell Assay	Cells are incubated with different lanabecestat concentrations for 5 to 16h, and the release of sAβPPβ, Aβ1-40, Aβ1-42, or sAβPPα into the medium is analyzed using kits. Cytotoxic effect of lanabecestat is evaluated in the cell plates using cell proliferation/cytotoxicity kit[1].
Animal Administration	Female 7- to 14-week-old C57BL/6 mice (n=6 per treatment group and timepoint) receive vehicle or lanabecestat solution at 50, 100, or 200 μmol/kg (20, 41, or 82 mg/kg) as a single dose via oral gavage. Mice and guinea pigs are anesthetized 1.5, 2, 3, 4, 6, 8, 16, 24, or 48 h after the (last) administration of vehicle or drug and are then kept under isoflurane anesthesia. Cerebrospinal fluid (CSF) is aspirated from the cisterna magna, and plasma is isolated from blood collected by cardiac puncture into EDTA tubes. The animals are then sacrificed by decapitation, and the brains are dissected into hemispheres[1].
References	[1]. Eketj?ll S, et al. AZD3293: A Novel, Orally Active BACE1 Inhibitor with High Potency and Permeability and Markedly Slow Off-Rate Kinetics. J Alzheimers Dis. 2016;50(4):1109-23.