上海源叶生物科技有限公司
Shanghai yuanye Bio-Technology Co., Ltd
电话：021-61312973　　传真：021-55068248
网址：www.shyuanye.com
邮箱：shyysw@sina.com

产品名称：Zauritegrast
产品别名： CT7758

生物活性：

Description	Zauritegrast (CT7758) is a potent and oral-effective α_4-integrin inhibitor.
IC_{50} & Target	α_4-integrin[1]
In Vitro	CDP323 is an ethyl ester prodrug of CT7758, a potent carboxylic acid antagonist of $\alpha_4\beta_1$ (very late antigen-4, VLA-4) and, to a lesser extent, $\alpha_4\beta_7$ integrins. CDP323 is developed as a VLA-4 antagonist prodrug for the treatment of multiple sclerosis[2].
In Vivo	CDP323 is a potent and effective α_4 inhibitor that is well tolerated at oral doses up to 1000 mg twice daily (bid). Relative to placebo, all dosages of Zauritegrast (CDP-323) significantly decreased the capacity of lymphocytes to bind vascular adhesion molecule-1 (VCAM-1) and the expression of α_4-integrin on VCAM-1-binding cells. CDP323 at daily doses of 1000 or 2000 mg induced significant increases in total lymphocyte count and suppressed VCAM-1 binding by reducing unbound very late antigen-4 expression on lymphocytes[1]. After oral administration of CDP323, CT7758 is by far the most abundant circulating plasma component, peaking between 0.5 and 1.5 hours irrespective of the species. These data suggested that CDP323 is rapidly absorbed and efficiently hydrolyzed into CT7758. Plasma exposure of CT7758 showed a large species variability with dog>rat=mice>cynomolgus monkey. In the tested dose range of 25-50 mg/kg, the estimated oral bioavailability (i.e., based on intravenous administration of CT7758 and assuming linear PK) is 29, 27, 8, and 0.3% in mice, rat, dog, and cynomolgus monkey, respectively. CDP323 increased the absorption of CT7758 by 5- to 10-fold in rodents, whereas no significant increase is observed in dog and monkey[3].

Solvent&Solubility

In Vitro:

DMSO : 100 mg/mL (191.79 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.9179 mL	9.5894 mL	19.1788 mL
	5 mM	0.3836 mL	1.9179 mL	3.8358 mL
	10 mM	0.1918 mL	0.9589 mL	1.9179 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: ≥ 3.25 mg/mL (6.23 mM); Clear solution

	此方案可获得 ≥ 3.25 mg/mL (6.23 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 32.5 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: ≥ 3.25 mg/mL (6.23 mM); Clear solution 此方案可获得 ≥ 3.25 mg/mL (6.23 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 32.5 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。
References	[1]. Wolf C, et al. Pharmacodynamic consequences of administration of VLA-4 antagonist CDP323 to multiple sclerosis subjects: a randomized, double-blind phase 1/2 study. PLoS One. 2013;8(3):e58438. [2]. Chanteux H, et al. In Vitro Hydrolysis and Transesterification of CDP323, an α4β1/α4β7 Integrin Antagonist Ester Prodrug. Drug Metab Dispos. 2014 Jan;42(1):153-61. [3]. Chanteux H, et al. Cross-Species Differences in the Preclinical Pharmacokinetics of CT7758, an α4β1/α4β7 Integrin Antagonist. Drug Metab Dispos. 2015 Sep;43(9):1381-91.

实验参考：

Animal Administration	Mice[3] Male Wistar rats (250-320 g) and CD-1 mice (20-25 g), Non-naive male Beagle dogs weighing 10 kg, and non-naive male cynomolgus monkeys weighing 3 kg are used. For plasma pharmacokinetic studies, CT7758 is administered orally (5-10 mL/kg, 30 mg/kg) or intravenously (2 mL/kg, 3 mg/kg) as a solution in 10 mM phosphate buffer. CDP323 is administered orally as a 1% methylcellulose suspension containing 0.1% Tween 80 (same dosage volume as CT7758). Compounds are delivered to fasted animals with the food returned 4 hours postdose. Blood samples are collected at the designated time points. Plasma is prepared by centrifugation, collected, and stored at −20°C until analysis by liquid chromatography-tandem mass spectrometry (LC-MS/MS).
References	[1]. Wolf C, et al. Pharmacodynamic consequences of administration of VLA-4 antagonist CDP323 to multiple sclerosis subjects: a randomized, double-blind phase 1/2 study. PLoS One. 2013;8(3):e58438. [2]. Chanteux H, et al. In Vitro Hydrolysis and Transesterification of CDP323, an α4β1/α4β7 Integrin Antagonist Ester Prodrug. Drug Metab Dispos. 2014 Jan;42(1):153-61. [3]. Chanteux H, et al. Cross-Species Differences in the Preclinical Pharmacokinetics of CT7758, an α4β1/α4β7 Integrin Antagonist. Drug Metab Dispos. 2015 Sep;43(9):1381-91.