产品名称：奥斯他伟酸
产品别名：Oseltamivir (acid)

生物活性：

Description	Oseltamivir acid (GS 4071), the active metabolite of Oseltamivir phosphate, is an orally bioavailable, potent and selective inhibitor of influenza virus neuraminidase (IC50=2 nM) with activity against both influenza A and B viruses[1][2].
IC_{50} & Target	IC50: 2 nM (influenza virus neuraminidase)
In Vitro	Oseltamivir acid inhibits virus replication in vitro and in vivo. Influenza B and A/H1N1 viruses appeare to be sensitive to Oseltamivir (mean B IC50 value: 13 nM; mean H1N1 IC50 value: 1.34 nM), while A/H1N2 and A/H3N2 viruses are more sensitive to Oseltamivir (mean H3N2 IC50 value: 0.67 nM; mean H1N2 IC50 value: 0.9 nM)[3]. In neuraminidases inhibition assays with influenza A viruses, the IC50 of RWJ-270201 (approximately 0.34 nM) is comparable to that of Oseltamivir carboxylate (0.45 nM) For influenza B virus isolates, the IC50 of RWJ-270201 (1.36 nM) is comparable to that of Zanamivir (2.7 nM) and less than that of Oseltamivir carboxylate (8.5 nM)[4].
In Vivo	Oseltamivir (0.1, 1, or 10 mg/kg/day, twice daily by oral gavage) produces a dose-dependent antiviral effect against Vietnam/1203/04 (VN1203/04) virus. The 5-day regimen at 10 mg/kg/day protects 50% of mice; deaths in this treatment group are delayed and indicated the replication of residual virus after the completion of treatment. Eight-day regimens improved Oseltamivir efficacy, and dosages of 1 and 10 mg/kg/day significantly reduced virus titers in organs and provided 60% and 80% survival rates, respectively[5]. In the pharmacokinetic study, after the oral administration of 1,000 mg/kg Oseltamivir, peak plasma concentrations are reached at 2 h postdose for Oseltamivir and 8 h for Oseltamivir carboxylate (OC). Rats are exposed to Oseltamivir over the whole sampling interval and had a ~2.7-fold-higher rate of exposure to OC than Oseltamivir. In CSF, peak concentrations are reached at 2 h postdose for Oseltamivir and 6 h for OC. CSF/plasma exposure ratios (AUC0-8 h) are ~0.07 for Oseltamivir and 0.007 for OC. In perfused brain samples, peak concentrations are reached at 8 h postdose for Oseltamivir and 6 h for OC. Brain/plasma exposure ratios (AUC0-8 h) of ~0.12 for Oseltamivir and 0.01 for OC are recorded. Corresponding CSF/brain exposure ratios ranged between ~0.55 and 0.64 for both analytes. A further group of animals that received a single oral administration of Oseltamivir at a lower dose produced similar results[6].

In Vitro:

DMSO : ≥ 230 mg/mL (808.86 mM)

H2O : ≥ 56 mg/mL (196.94 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	3.5168 mL	17.5840 mL	35.1679 mL
5 mM	0.7034 mL	3.5168 mL	7.0336 mL
10 mM	0.3517 mL	1.7584 mL	3.5168 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

Solvent&Solubility	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: ≥ 5.75 mg/mL (20.22 mM); Clear solution 此方案可获得 ≥ 5.75 mg/mL (20.22 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 57.5 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: ≥ 5.75 mg/mL (20.22 mM); Clear solution 此方案可获得 ≥ 5.75 mg/mL (20.22 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 57.5 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。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 5.75 mg/mL (20.22 mM); Clear solution 此方案可获得 ≥ 5.75 mg/mL (20.22 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 57.5 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Li W, et al. Identification of GS 4104 as an orally bioavailable prodrug of the influenza virus neuraminidase inhibitor GS 4071. Antimicrob Agents Chemother. 1998 Mar;42(3):647-53. [2]. Ghosh GC, et al. Oseltamivir carboxylate, the active metabolite of oseltamivir phosphate (Tamiflu), detected in sewage discharge and river water in Japan. Environ Health Perspect. 2010 Jan;118(1):103-7. [3]. Ferraris O, et al. Sensitivity of influenza viruses to zanamivir and oseltamivir: a study performed on viruses circulating in France prior to the introduction of neuraminidase inhibitors in clinical practice. Antiviral Res. 2005 Oct;68(1):43-8. [4]. Gubareva LV, et al. Comparison of the activities of zanamivir, oseltamivir, and RWJ-270201 against clinical isolates of influenza virus and neuraminidase inhibitor-resistant variants.Antimicrob Agents Chemother. 2001 Dec;45(12):3403-8. [5]. Yen HL, et al. Virulence may determine the necessary duration and dosage of oseltamivir treatment for highly pathogenic A/Vietnam/1203/04 influenza virus in mice. J Infect Dis. 2005 Aug 15;192(4):665-72. [6]. Hoffmann G, et al. Nonclinical pharmacokinetics of oseltamivir and oseltamivir carboxylate in the central nervous system. Antimicrob Agents Chemother. 2009 Nov;53(11):4753-61.

实验参考：

	Mice[3] Female 6-week-old BALB/c mice are anesthetized with isofluorane and intranasally inoculated with 50 μL of 10-fold serial dilutions of VN1203/04 virus in PBS. The mouse lethal dose (MLD50) is

Animal Administration	calculated after a 16-day observation period. Oseltamivir is administered by oral gavage twice daily for 5 or 8 days to groups of 10 mice at dosages of 0.1, 1, and 10 mg/kg/day. Control (infected but untreated) mice received sterile PBS (placebo) on the same schedule. Four hours after the first dose of Oseltamivir, the mice are inoculated intranasally with 5 MLD50 of VN1203/04 virus in 50 μL of PBS. Survival and weight change are observed for 24 days. Virus titers in the mouse organs are determined on days 3, 6, and 9 after inoculation. Three mice from each experimental and placebo group are killed, and the lungs and brains are removed. The organs are homogenized and suspended in 1 mL of PBS. The cellular debris is cleared by centrifugation at 2000 g for 5 min. The limit of virus detection is 0.75 log10 EID50. For calculation of the mean, samples with a virus titer <0.75 log10 EID50/mL are assigned a value of 0. Virus titers in each organ are calculated by use of the method of Reed and Muench and are expressed as mean log10 EID50/mL±SE. Rats[4] Several studies are performed to characterize the pharmacokinetics of Oseltamivir and OC in the plasma, cerebrospinal fluid (CSF), and brain of Sprague-Dawley rats following single-dose bolus administration of Oseltamivir (intravenous [i.v.] and oral) and OC (i.v.). In the i.v. studies, nonfasted adult rats (two groups of 35 animals for each test substance) received a dose of 30 mg/kg body weight of either Oseltamivir or Oseltamivir carboxylate (OC) in aqueous solution with sodium chloride (0.9%; pH 4.0) via slow injection into the tail vein over 20 to 30 s. In both i.v. studies, pharmacokinetic sampling took place at 5 min and at 0.25, 0.5, 1, 2, 4, and 8 h postdose (four or five rats/time point).
References	[1]. Li W, et al. Identification of GS 4104 as an orally bioavailable prodrug of the influenza virus neuraminidase inhibitor GS 4071. Antimicrob Agents Chemother. 1998 Mar;42(3):647-53. [2]. Ghosh GC, et al. Oseltamivir carboxylate, the active metabolite of oseltamivir phosphate (Tamiflu), detected in sewage discharge and river water in Japan. Environ Health Perspect. 2010 Jan;118(1):103-7. [3]. Ferraris O, et al. Sensitivity of influenza viruses to zanamivir and oseltamivir: a study performed on viruses circulating in France prior to the introduction of neuraminidase inhibitors in clinical practice. Antiviral Res. 2005 Oct;68(1):43-8. [4]. Gubareva LV, et al. Comparison of the activities of zanamivir, oseltamivir, and RWJ-270201 against clinical isolates of influenza virus and neuraminidase inhibitor-resistant variants.Antimicrob Agents Chemother. 2001 Dec;45(12):3403-8. [5]. Yen HL, et al. Virulence may determine the necessary duration and dosage of oseltamivir treatment for highly pathogenic A/Vietnam/1203/04 influenza virus in mice. J Infect Dis. 2005 Aug 15;192(4):665-72. [6]. Hoffmann G, et al. Nonclinical pharmacokinetics of oseltamivir and oseltamivir carboxylate in the central nervous system. Antimicrob Agents Chemother. 2009 Nov;53(11):4753-61.