# 产品名称：PF-06463922
# 产品别名：Lorlatinib ；劳拉替尼

## 生物活性：

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| **Description** | Lorlatinib (PF-06463922) is a selective, orally active, brain-penetrant and ATP-competitive ROS1/ALK inhibitor. Lorlatinib has Kis of <0.025 nM, <0.07 nM, and 0.7 nM for ROS1, wild type ALK, and ALKL1196M, respectively. Lorlatinib has anticancer activity[1][2]. |
| **$IC_{50}$ & Target** | Ki: < 0.02 nM (ROS1), < 0.07 nM (ALK WT), 0.7 nM (ALK L1196M) |
| **In Vitro** | Lorlatinib (PF-06463922) demonstrates significant cell activity against ALK and a large set of ALK clinical mutations with IC50 ranging from 0.2 nM-77 nM[1]. Lorlatinib significantly inhibits cell proliferation and induces cell apoptosis in the HCC78 human NSCLC cells harboring SLC34A2-ROS1 fusions and the BaF3-CD74-ROS1 cells expressing human CD74-ROS1. Lorlatinib also shows potent growth inhibitory activity and induces apoptosis in the NSCLC cells harboring either non-mutant ALK or mutant ALK fusions[2]. |
| **In Vivo** | In rats, Lorlatinib (PF-06463922) displays low plasma clearance, a moderate volume of distribution, a reasonable half-life, low propensity for p-glycoprotein 1-mediated efflux and a bioavailability of 100%[1]. In vivo, Lorlatinib shows cytoreductive antitumor efficacy in the NIH3T3 xenograft models expressing human CD74-ROS1 and Fig-ROS1 via inhibition in ROS1 phosphorylation and the downstream signaling molecules, as well as inhibition of the cell cycle protein Cyclin D1 in tumors. Lorlatinib also demonstrates marked antitumor activity in mice bearing tumor xenografts expressing EML4-ALK, EML4-ALK-L1196M, EML4-ALK-G1269A, EML4-ALK-G1202R or NPM-ALK[2]. |
| **Solvent&Solubility** | ***In Vitro:***<br>**DMSO : ≥ 28 mg/mL (68.90 mM)**<br>**H2O : < 0.1 mg/mL (insoluble)**<br>* "≥" means soluble, but saturation unknown. |

| Preparing Stock Solutions | Solvent / Mass / Concentration | 1 mg | 5 mg | 10 mg |
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| | 1 mM | 2.4606 mL | 12.3028 mL | 24.6057 mL |
| | 5 mM | 0.4921 mL | 2.4606 mL | 4.9211 mL |
| | 10 mM | 0.2461 mL | 1.2303 mL | 2.4606 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 (6.15 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (6.15 mM，饱和度未知) 的澄清溶液。

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| | 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。<br><br>2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline)<br>Solubility: 2.5 mg/mL (6.15 mM); Suspended solution; Need ultrasonic<br>此方案可获得 2.5 mg/mL (6.15 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。<br>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。<br><br>3.请依序添加每种溶剂： 10% DMSO →90% corn oil<br>Solubility: ≥ 2.5 mg/mL (6.15 mM); Clear solution<br>此方案可获得 ≥ 2.5 mg/mL (6.15 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。<br>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]. Johnson TW, et al. Discovery of (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile (PF-06463922), a macrocyclic inhibitor of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) with preclinical brain exposure and broad-spectrum potency against ALK-resistant mutations. J Med Chem. 2014 Jun 12;57(11):4720-44.<br>[2]. Zou HY, et al. PF-06463922 is a potent and selective next-generation ROS1/ALK inhibitor capable of blocking PF-02341066-resistant ROS1 mutations. Proc Natl Acad Sci U S A. 2015 Mar 17;112(11):3493-8 |

**实验参考：**

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| **Cell Assay** | Cells are seeded in 96-well plates in growth medium containing 10% FBS and are cultured overnight at 37°C. The following day, serial dilutions of Lorlatinib or appropriate controls are added to the designated wells, and cells are incubated at 37°C for 72 h. A CellTiter-Glo assay is performed to determine the relative cell numbers. $IC_{50}$ values are calculated by concentration-response curve fitting using a four-parameter analytical method. [2] |
| **Animal Administration** | De novoGBM tumorigenesis is initiated in LSL-FIG-ROS1;Cdkn2a−/−;LSL-Luc mice through intracranial stereotactic injections of Adeno-Cre as described previously. Tumor development is monitored using BLI as described below. Once tumors reach a given size ($10^7$ $p^{-1}·s^{-1}·cm^{-2}·sr^{-1}$), animals are randomLy enrolled into vehicle control or 3-, 7-, or 14-d treatment with the indicated doses of Lorlatinib. Drug is administered through s.c. implanted Alzet osmotic pumps. After treatment, mice are killed, GBM tumors are microdissected, and tissues are flash-frozen in liquid $N_2$. The remaining brains are processed for histology. [2] |
| **References** | [1]. Johnson TW, et al. Discovery of (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile (PF-06463922), a macrocyclic inhibitor of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) with preclinical brain exposure and broad-spectrum potency against ALK-resistant mutations. J Med Chem. 2014 Jun 12;57(11):4720-44.<br>[2]. Zou HY, et al. PF-06463922 is a potent and selective next-generation ROS1/ALK inhibitor capable of blocking PF-02341066-resistant ROS1 mutations. Proc Natl Acad Sci U S A. 2015 Mar |

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