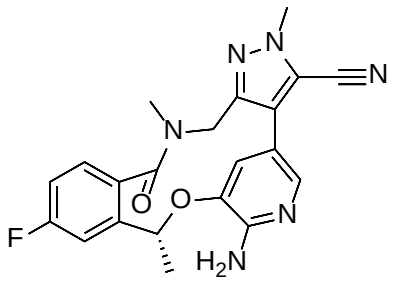
Product data sheet

MedKoo Cat#: 406533 Name: Lorlatinib (PF-06463922) CAS#: 1454846-35-5 (free base) Chemical Formula: $C_{21}H_{19}FN_6O_2$ Exact Mass: 406.1554 Molecular Weight: 406.41	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:
Lorlatinib, also known as PF-06463922, is an orally available, ATP-competitive inhibitor of the receptor tyrosine kinases, anaplastic lymphoma kinase (ALK) and C-ros oncogene 1 (Ros1), with potential antineoplastic activity. Upon administration, ALK/ROS1 inhibitor PF-06463922 binds to and inhibits both ALK and ROS1 kinases. The kinase inhibition leads to disruption of ALK- and ROS1-mediated signaling and eventually inhibits tumor cell growth in ALK- and ROS1-overexpressing tumor cells. In addition, PF-06463922 is able to cross the blood brain barrier.

2. CoA, QC data, SDS, and handling instruction
SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	38.0	93.50
DMF	5.0	12.30
Ethanol	15.50	38.14
Ethanol:PBS (pH 7.2) (1:1)	0.50	1.23

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	**1 mg**	**5 mg**	**10 mg**
1 mM	2.46 mL	12.30 mL	24.61 mL
5 mM	0.49 mL	2.46 mL	4.92 mL
10 mM	0.25 mL	1.23 mL	2.46 mL
50 mM	0.05 mL	0.25 mL	0.49 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator
Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study
In vitro study

1. Infarinato NR, Park JH, Krytska K, Ryles HT, Sano R, Szigety KM, Li Y, Zou HY, Lee NV, Smeal T, Lemmon MA, Mossé YP. The ALK/ROS1 Inhibitor PF-06463922 Overcomes Primary Resistance to Crizotinib in ALK-Driven Neuroblastoma. Cancer Discov. 2016 Jan;6(1):96-107. doi: 10.1158/2159-8290.CD-15-1056. Epub 2015 Nov 10. PMID: 26554404; PMCID: PMC4707106.

In vivo study

1. Infarinato NR, Park JH, Krytska K, Ryles HT, Sano R, Szigety KM, Li Y, Zou HY, Lee NV, Smeal T, Lemmon MA, Mossé YP. The ALK/ROS1 Inhibitor PF-06463922 Overcomes Primary Resistance to Crizotinib in ALK-Driven Neuroblastoma. Cancer Discov. 2016 Jan;6(1):96-107. doi: 10.1158/2159-8290.CD-15-1056. Epub 2015 Nov 10. PMID: 26554404; PMCID: PMC4707106.

7. Bioactivity

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Biological target: Lorlatinib is a ROS1/ALK inhibitor with Kis of <0.025 nM, <0.07 nM, and 0.7 nM for ROS1, wild type ALK, and ALKL1196M, respectively.

In vitro activity

To compare PF-06463922 and crizotinib over a broader range of ALK-driven tumors, their abilities to inhibit growth of a range of cell-lines in vitro were assessed. As shown in Fig. 4 and Table S1, IC50 values measured for PF-06463922 in neuroblastoma cell-lines dependent on R1275Q-mutated ALK were 51-fold (NB-1643) and 19-fold (LAN-5) lower than those measured for crizotinib (Fig. 4A and B) – which themselves were ~310 nM. Importantly, IC50 values for PF-06463922 inhibition of cell-lines driven by the ALK-resistant F1174L ALK variant were also much lower – falling in the range of 12.7 nM to 26.6 nM, which is ~30-fold lower than measured for crizotinib (Fig. 4C–F and Table S1). A similar difference was also seen for Felix cells, driven by the F1245C variant (Fig. 4G). Whereas a small (~3-fold) difference in IC50 appeared to be sufficient to explain the relative crizotinib resistance of tumors and cell-lines driven by F1174L-mutated ALK in neuroblastoma compared with those driven by R1275Q (11), the overall higher potency of PF-06463922 appears to render such differences irrelevant – so that both tumor cell-lines (Fig. 4) and xenografts (Fig. 2) driven by the F1174L variant are sensitive to PF-06463922. The same appears to be true for the F1245C variant. Similar results were seen for NB-1 cells, driven by amplified wild-type ALK – with IC50 values of 256 nM and 5.2 nM for crizotinib and PF-06463922 respectively (Fig. 4H).

Reference: Cancer Discov. 2016 Jan;6(1):96-107. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4707106/

In vivo activity

The in vivo efficacy of PF-06463922 was examined in patient-derived xenografts (PDXs) harboring F1174L or F1245C ALK mutations (COG-N-453x and Felix-PDX respectively), as well as cell line-derived xenografts utilizing SH-SY5Y cells (F1174L) or NB-1643 cells (R1275Q). Treatment with 10 mg/kg/day PF-06463922 (5 mg/kg BID) resulted in rapid (within 2–3 weeks) and sustained complete tumor regression for the duration of treatment in all xenografts (red curves in Fig. 2, and Table 1A). After PF-06463922 treatment was stopped, animals were further monitored for tumor progression by observation and palpation. Mice that had been treated with 10 mg/kg/day PF-06463922 remained in complete remission with no discernible tumor growth for a further 4.8 weeks (COG-N-453x), 7.1 weeks (Felix-PDX), 5 weeks (SH-SY5Y) and 4 weeks (NB-1643), as shown in Fig. S2A–D. Thus, xenografts harboring the ALK F1174L mutation exhibited unprecedented anti-tumor responses to single agent ALK inhibition therapy with PF-06463922, as did a PDX harboring the F1245C mutation.

Reference: Cancer Discov. 2016 Jan;6(1):96-107. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4707106/