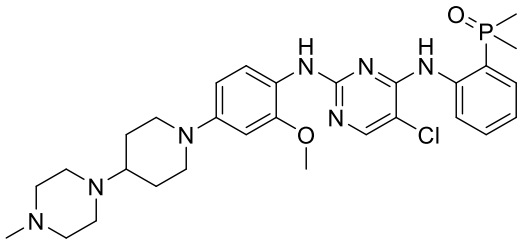
Product data sheet

MedKoo Cat#: 206488 Name: Brigatinib (AP-26113) CAS#: 1197953-54-0 Chemical Formula: $C_{29}H_{39}ClN_7O_2P$ Exact Mass: 583.25914 Molecular Weight: 584.10176	
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:
Brigatinib, also known as AP-26113, is an orally active, potent and selective Dual ALK/EGFR inhibitor. AP26113 binds to and inhibits ALK kinase and ALK fusion proteins as well as EGFR and mutant forms. This leads to the inhibition of ALK kinase and EGFR kinase, disrupts their signaling pathways and eventually inhibits tumor cell growth in susceptible tumor cells. In addition, AP26113 appears to overcome mutation-based resistance. ALK belongs to the insulin receptor superfamily and plays an important role in nervous system development; ALK dysregulation and gene rearrangements are associated with a series of tumors. EGFR is overexpressed in a variety of cancer cell types.

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	3	5.14
Ethanol	10	17.12

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	1.71 mL	8.56 mL	17.12 mL
5 mM	0.34 mL	1.71 mL	3.42 mL
10 mM	0.17 mL	0.86 mL	1.71 mL
50 mM	0.03 mL	0.17 mL	0.34 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. Zhang S, Anjum R, Squillace R, Nadworny S, Zhou T, Keats J, Ning Y, Wardwell SD, Miller D, Song Y, Eichinger L, Moran L, Huang WS, Liu S, Zou D, Wang Y, Mohemmad Q, Jang HG, Ye E, Narasimhan N, Wang F, Miret J, Zhu X, Clackson T, Dalgarno D, Shakespeare WC, Rivera VM. The Potent ALK Inhibitor Brigatinib (AP26113) Overcomes Mechanisms of Resistance to First- and Second-Generation ALK Inhibitors in Preclinical Models. Clin Cancer Res. 2016 Nov 15;22(22):5527-5538. doi: 10.1158/1078-0432.CCR-16-0569. Epub 2016 Oct 25. PMID: 27780853.

2. Siaw JT, Wan H, Pfeifer K, Rivera VM, Guan J, Palmer RH, Hallberg B. Brigatinib, an anaplastic lymphoma kinase inhibitor, abrogates activity and growth in ALK-positive neuroblastoma cells, Drosophila and mice. Oncotarget. 2016 May 17;7(20):29011-22. doi: 10.18632/oncotarget.8508. PMID: 27049722; PMCID: PMC5045374.

In vivo study

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1. Zhang S, Anjum R, Squillace R, Nadworny S, Zhou T, Keats J, Ning Y, Wardwell SD, Miller D, Song Y, Eichinger L, Moran L, Huang WS, Liu S, Zou D, Wang Y, Mohemmad Q, Jang HG, Ye E, Narasimhan N, Wang F, Miret J, Zhu X, Clackson T, Dalgarno D, Shakespeare WC, Rivera VM. The Potent ALK Inhibitor Brigatinib (AP26113) Overcomes Mechanisms of Resistance to First- and Second-Generation ALK Inhibitors in Preclinical Models. Clin Cancer Res. 2016 Nov 15;22(22):5527-5538. doi: 10.1158/1078-0432.CCR-16-0569. Epub 2016 Oct 25. PMID: 27780853.

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7. Bioactivity

Biological target:

Brigatinib (AP-26113) is a highly potent and selective ALK inhibitor, with an IC50 of 0.6 nM.

In vitro activity

The activity of brigatinib against native ALK and a number of non-ALK kinases was next examined in cellular assays (Table 1). Consistent with in vitro kinase data, brigatinib inhibited ALK and ROS1 with similar potencies (IC50, 14 and 18 nmol/L, respectively). Compared with ALK, brigatinib inhibited FLT3 and IGF-1R with about 11-fold lower potency (IC50, 148–158 nmol/L) and inhibited mutant variants of FLT3 and EGFR with 15- to 35-fold lower potency (IC50, 211–489 nmol/L), despite inhibiting some of these kinases (e.g., FLT3, FLT3 [D835Y], and EGFR [L858R]) with potency similar to ALK in in vitro kinase assays. Finally, brigatinib lacked cellular activity against INSR and native EGFR (IC50 > 3,000 nmol/L). Overall, these results suggest that brigatinib is a highly potent and selective ALK and ROS1 inhibitor.In a panel of seven ALCL and NSCLC cell lines that express NPM-ALK or EML4-ALK fusions, the concentration of brigatinib that inhibited growth by 50% (GI50) ranged from 4 to 31 nmol/L, and the concentration that inhibited ALK phosphorylation by 50% (IC50) ranged from 1.5 to 12 nmol/L (Fig. 2A and B). Potent inhibition of downstream signaling was also observed in both ALCL and NSCLC cell lines (Supplementary Fig. S5). Across three ALK-negative ALCL and NSCLC cell lines, the GI50 values for brigatinib ranged from 503 to 2,387 nmol/L. Thus, overall, brigatinib potently inhibited ALK activity and proliferation in all ALK+ cell lines tested and exhibited more than 100-fold selectivity over ALK-negative lines.

Reference: Clin Cancer Res. 2016 Nov 15;22(22):5527-5538. https://clincancerres.aacrjournals.org/content/22/22/5527.long

In vivo activity

The in vivo activity of brigatinib was examined in ALK+ Karpas-299 (ALCL) and H2228 (NSCLC) xenograft mouse models, with oral administration of brigatinib (10, 25, or 50 mg/kg once daily) leading to a dose-dependent inhibition of tumor growth in both models. In the Karpas-299 model, 25 mg/kg inhibited tumor growth by 87% and 50 mg/kg induced near complete tumor regression that was maintained for at least 13 days after treatment (Fig. 2C). Increased efficacy was associated with increased plasma levels of brigatinib and deeper and more sustained inhibition of ALK signaling in the tumor (Supplementary Fig. S6A and S6B). H2228-derived tumors, possibly because of their slower growth rate, were even more sensitive to ALK inhibition than Karpas-299–derived tumors, with 10, 25, or 50 mg/kg brigatinib inducing substantial tumor regression that was maintained for more than 28 days after treatment (Fig. 2C).

Reference: Clin Cancer Res. 2016 Nov 15;22(22):5527-5538. https://clincancerres.aacrjournals.org/content/22/22/5527.long

Note: The information listed here was extracted from literature. MedKoo has not independently retested and confirmed the accuracy of these methods. Customer should use it just for a reference only.