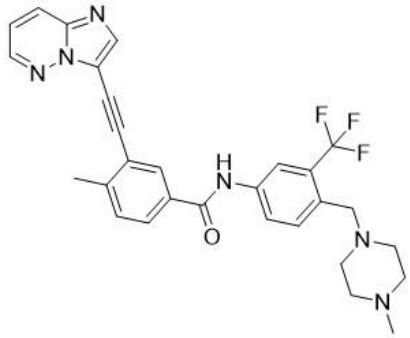
Product data sheet

MedKoo Cat#: 202320 Name: Ponatinib CAS#: 943319-70-8 (free base) Chemical Formula: $C_{29}H_{27}F_3N_6O$ Exact Mass: 532.21984 Molecular Weight: 532.56	
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:

Ponatinib is an orally bioavailable multitargeted receptor tyrosine kinase (RTK) inhibitor with potential antiangiogenic and antineoplastic activities. Multitargeted tyrosine kinase inhibitor AP24534 inhibits unmutated and all mutated forms of Bcr-Abl, including T315I, the highly drug therapy-resistant missense mutation of Bcr-Abl. This agent also inhibits other tyrosine kinases including those associated with vascular endothelial growth factor receptors (VEGFRs) and fibroblast growth factor receptors (FGFRs); in addition, it inhibits the tyrosine kinase receptor TIE2 and FMS-related tyrosine kinase receptor-3 (Flt3).

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	50.0	93.9
Ethanol	25.0	46.9

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	**1 mg**	**5 mg**	**10 mg**
1 mM	1.88	9.39	18.78
5 mM	0.38	1.88	3.76
10 mM	0.19	0.94	1.88
50 mM	0.04	0.19	0.38

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. Chen S, Liu G, Chen J, Hu A, Zhang L, Sun W, Tang W, Liu C, Zhang H, Ke C, Wu J, Chen X. Ponatinib Protects Mice From Lethal Influenza Infection by Suppressing Cytokine Storm. Front Immunol. 2019 Jun 21;10:1393. doi: 10.3389/fimmu.2019.01393. PMID: 31293574; PMCID: PMC6598400.
2. Madonna R, Pieragostino D, Cufaro MC, Doria V, Del Boccio P, Deidda M, Pierdomenico SD, Dessalvi CC, De Caterina R, Mercuro G. Ponatinib Induces Vascular Toxicity through the Notch-1 Signaling Pathway. J Clin Med. 2020 Mar 18;9(3):820. doi: 10.3390/jcm9030820. PMID: 32197359; PMCID: PMC7141219.

In vivo study

1. Chen S, Liu G, Chen J, Hu A, Zhang L, Sun W, Tang W, Liu C, Zhang H, Ke C, Wu J, Chen X. Ponatinib Protects Mice From Lethal Influenza Infection by Suppressing Cytokine Storm. Front Immunol. 2019 Jun 21;10:1393. doi: 10.3389/fimmu.2019.01393. PMID: 31293574; PMCID: PMC6598400.
2. Latifi Y, Moccetti F, Wu M, Xie A, Packwood W, Qi Y, Ozawa K, Shentu W, Brown E, Shirai T, McCarty OJ, Ruggeri Z, Moslehi J, Chen J, Druker BJ, López JA, Lindner JR. Thrombotic microangiopathy as a cause of cardiovascular toxicity from the BCR-ABL1 tyrosine kinase inhibitor ponatinib. Blood. 2019 Apr 4;133(14):1597-1606. doi: 10.1182/blood-2018-10-881557. Epub 2019 Jan 28. PMID: 30692122; PMCID: PMC6450432.

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7. Bioactivity

Biological target:

Ponatinib (AP24534) is a multi-targeted kinase inhibitor with IC50s of 0.37 nM, 1.1 nM, 1.5 nM, 2.2 nM, and 5.4 nM for Abl, PDGFRα, VEGFR2, FGFR1, and Src, respectively.

In vitro activity

This study aimed to determine the mechanisms of ponatinib-induced vascular toxicity, defining associated signaling pathways and identifying potential rescue strategies. Human umbilical endothelial cells (HUVECs) were exposed to ponatinib or vehicle in the presence or absence of the neutralizing factor anti-Notch-1 antibody for exposure times of 0–72 h. Although HUVECs treated with 1.7 nM of ponatinib showed signs of cellular distress compared to vehicle (DMSO)-treated cells already after 17 h of incubation, the analysis of cell proliferation showed no significant differences in the incorporation rate of CyQUANTR NF fluorochrome, suggesting the maintenance of cells in the cell cycle at 1.7 nM of ponatinib (Figure 1A,B). On the contrary, the proliferation curves of PBMNCs treated with 1.7 nM of ponatinib showed an almost immediate toxicity of the drug, in terms of cell morphology, cell detachment from culture monolayer and block of the incorporation of the fluorochrome, compared to PBMNC treated with vehicle, suggesting a greater toxicity of ponatinib in this type of cells (data not shown). At 24 and 48 h, the HUVECs treated with 1.7 nM of ponatinib showed a significant reduction in the fluorochrome incorporation rate compared to DMSO, and a worsening of the morphological signs of cell suffering, suggesting the block of cell proliferation and the appearance of frank cytotoxicity of the drug. These effects were reverted by the co-incubation of the cells with 1 µg/mL neutralizing factor anti-Notch-1 antibody, suggesting that ponatinib acts on HUVECs via Notch-1 and the blocking of this signaling pathway can revert the endothelial drug toxicity (Figure 1A,B). After 72 h of treatment, HUVECs showed a complete and irreversible block of cell proliferation, which could not be reversed by the Notch-1 receptor blockage, suggesting the appearance of nonspecific cytotoxicity by ponatinib (Figure 1A,B). These results show the concentration-dependent effects of ponatinib on endothelial cell viability and greater sensitivity of PBMNC to ponatinib compared to HUVECs. This demonstrated that ponatinib significantly increased endothelial toxicity in vitro. Importantly, the AKT/eNOS and Notch-1 pathways have been identified as key targets of ponatinib. It has been shown that the Notch-1 pathway likely mediates, at least in part, the vascular toxicity associated with this agent.

J Clin Med. 2020 Mar; 9(3): 820. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7141219/

In vivo activity

Ponatinib was tested for a therapeutic effect on mouse influenza model infected by H1N1 influenza PR8 virus. Twenty-five mg/kg/d of ponatinib was set as the maximal drug dose administered in PR8-infected mice. As shown in Figure 2A, the placebo-treated mice started dying from day 9 and by day 11 and 90% of them had succumbed to infection. The mice treated with 15 mg/kg/d of ponatinib showed the highest survivalrate (50%) and had the least decline in body weight during the early stage (days 3 to 5) of influenza A virus infection (Figures 2A,C). The mice treated with 5 mg/kg/d of ponatinib showed lowest survive rate (20%), and the improvement in body weight loss decreased significantly compared to the middle dose group (Figures 2A,D). However, mice in the high dose group (25 mg/kg/d) also showed low survive rate (30%), and improvement of body weight loss was not observed at all (Figures 2A,B). To explore the optimal time to start ponatinib treatment, we performed the in vivo experiments with drug administration started on days 1, 2, 3, or 4 post-infection (Figure 3A). The mice treated with ponatinib starting on days 3 and 4 had higher survival rates than those treated starting on days 1 and 2 (Figure 3B). The body weight loss of the mice slowed down significantly after the delayed administration of ponatinib (Figures 3C–F). Unlike current antivirals that need to be administered early after virus infection, ponatinib works better when administered starting at days 3 and 4 post-infection when mice have developed obvious clinical symptoms, including piloerection, hunched posture, reduced movement, and labored breathing concomitant with a significant decrease in body weight. There were fewer inflammatory infiltrates observed in the lungs in ponatinib-treated mice than in the lungs of mice treated with placebo (Figure 4A). The cell infiltrates in the BALFs of mice treated with ponatinib or placebo were statistically analyzed for cell numbers and types (Figure 4B). Ponatinib greatly reduced the infiltration of neutrophils, which have been proven to contribute to acute lung injury in influenza pneumonia, while monocyte infiltration was not affected. Therefore, ponatinib has potential as an immunomodulator for the treatment of severe influenza.

Front Immunol. 2019; 10: 1393. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6598400/