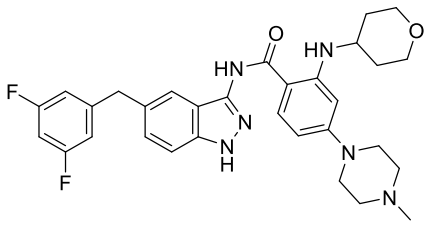
Product data sheet

MedKoo Cat#: 206181 Name: Entrectinib CAS#: 1108743-60-7 Chemical Formula: $C_{31}H_{34}F_2N_6O_2$ Exact Mass: 560.27113 Molecular Weight: 560.64	
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:

Entrectinib, also known as RXDX-101 and NMS-E628, is an oral small molecule inhibitor of TrkA, TrkB and TrkC, as well as ROS1 and ALK, with high potency and selectivity. RXDX-101 has demonstrated potent pharmacological activity in preclinical studies and has the potential to be first-in-class against the Trk family of kinases. PXDX-101 has been well tolerated in patients with advanced solid tumors. PXDX-101 is currently in clinical trials, and is being developed by Ignyta.

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	50.33	89.77
DMF	30.0	53.51
DMF:PBS (pH 7.2) (1:4)	0.2	0.36
Ethanol	50.5	90.08

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	1.78 mL	8.92 mL	17.84 mL
5 mM	0.36 mL	1.78 mL	3.57 mL
10 mM	0.18 mL	0.89 mL	1.78 mL
50 mM	0.04 mL	0.18 mL	0.36 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. Smith KM, Fagan PC, Pomari E, Germano G, Frasson C, Walsh C, Silverman I, Bonvini P, Li G. Antitumor Activity of Entrectinib, a Pan-TRK, ROS1, and ALK Inhibitor, in ETV6-NTRK3-Positive Acute Myeloid Leukemia. Mol Cancer Ther. 2018 Feb;17(2):455-463. doi: 10.1158/1535-7163.MCT-17-0419. Epub 2017 Dec 13. PMID: 29237803.
2. Ardini E, Menichincheri M, Banfi P, Bosotti R, De Ponti C, Pulci R, Ballinari D, Ciomei M, Texido G, Degrassi A, Avanzi N, Amboldi N, Saccardo MB, Casero D, Orsini P, Bandiera T, Mologni L, Anderson D, Wei G, Harris J, Vernier JM, Li G, Felder E, Donati D, Isacchi A, Pesenti E, Magnaghi P, Galvani A. Entrectinib, a Pan-TRK, ROS1, and ALK Inhibitor with Activity in Multiple Molecularly Defined Cancer Indications. Mol Cancer Ther. 2016 Apr;15(4):628-39. doi: 10.1158/1535-7163.MCT-15-0758. Epub 2016 Mar 3. PMID: 26939704.

In vivo study

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1. Fischer H, Ullah M, de la Cruz CC, Hunsaker T, Senn C, Wirz T, Wagner B, Draganov D, Vazvaei F, Donzelli M, Paehler A, Merchant M, Yu L. Entrectinib, a TRK/ROS1 inhibitor with anti-CNS tumor activity: differentiation from other inhibitors in its class due to weak interaction with P-glycoprotein. Neuro Oncol. 2020 Jun 9;22(6):819-829. doi: 10.1093/neuonc/noaa052. PMID: 32383735; PMCID: PMC7283026.
2. Iyer R, Wehrmann L, Golden RL, Naraparaju K, Croucher JL, MacFarland SP, Guan P, Kolla V, Wei G, Cam N, Li G, Hornby Z, Brodeur GM. Entrectinib is a potent inhibitor of Trk-driven neuroblastomas in a xenograft mouse model. Cancer Lett. 2016 Mar 28;372(2):179-86. doi: 10.1016/j.canlet.2016.01.018. Epub 2016 Jan 18. PMID: 26797418; PMCID: PMC4792275.

7. Bioactivity

Biological target:

Entrectinib (NMS-E628) is a CNS-active pan-Trk, ROS1, and ALK inhibitor.

In vitro activity

Entrectinib treatment potently blocked cellular proliferation in NTRK fusion–positive AML patient-derived cell lines (Fig. 1C) and resulted in rapid apoptotic cell death in a dose- and time-dependent manner (Fig. 2). Cell death was preceded by rapid reduction in TRK autophosphorylation at Y764/Y765 in the kinase activation loop and Y785, the PLCγ interaction site, and by reduced phosphorylation of downstream signaling partners, PLCγ, ERK, and STAT3 (Fig. 1E and F). TRK kinase inhibition was also accompanied by a reduction in ETV6–TRKC fusion protein levels (Fig. 1F). Similar reductions in PML–RARA fusion protein stability after retinoic acid/arsenic trioxide treatment or estrogen receptor after fulvestrant treatment have been described. Altered protein stability upon entrectinib treatment may be a novel mechanism of action against TRKC fusion proteins as reduced TRK fusion protein levels have not been seen after entrectinib treatment of patient-derived cell lines carrying TRKA fusions or Ba/F3 cells expressing ETV6–NTRK1.

Reference: Mol Cancer Ther. 2018 Feb;17(2):455-463. https://mct.aacrjournals.org/content/17/2/455.long

In vivo activity

Significant tumor growth inhibition was observed with entrectinib treatment compared to vehicle ($p<0.0001$, Fig. 3A). Entrectinib treated mice also demonstrated a significantly prolonged EFS ($p<0.0001$, Fig. 3B). Analysis of the tumors harvested at different time points after treatment (1, 4 and 6 hr, respectively) showed inhibition of TrkB phosphorylation in tumors treated with entrectinib compared to vehicle controls. Inhibition of phosphorylation was also seen for p-PLCγ, p-Akt and p-Erk in entrectinib treated tumors (Fig. 3C). Densitometric analysis of Western blot images was also performed to indicate the statistical significance of phosphoprotein expression in xenografts upon entrectinib treatment (Fig. S2). Actin levels were unchanged indicating that there is no global inhibition of protein. These results show that entrectinib significantly inhibited the growth of SY5Y-TrkB xenograft as well as Trk phosphorylation in vivo.

Reference: Cancer Lett. 2016 Mar 28; 372(2): 179–186. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4792275/