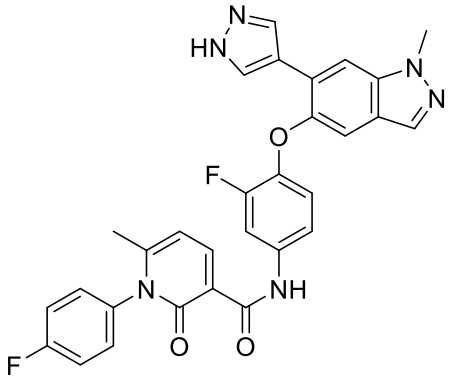
Product data sheet

MedKoo Cat#: 205526 Name: Merestinib (LY2801653) CAS#: 1206799-15-6 (free base) Chemical Formula: $C_{30}H_{22}F_2N_6O_3$ Exact Mass: 552.17215 Molecular Weight: 552.53	
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:

Merestinib, also known as LY2801653, is an orally available, small molecule inhibitor of the proto-oncogene c-Met (mesenchymal-epithelial transition, also known as hepatocyte growth factor receptor [HGFR]) with potential antineoplastic activity. c-Met inhibitor LY2801653 selectively binds to c-Met, thereby inhibiting c-Met phosphorylation and disrupting c-Met signal transduction pathways. This may induce cell death in tumor cells overexpressing c-Met protein or expressing constitutively activated c-Met protein. This agent has potent anti-tumor efficacy in mono- and combination therapy in a broad range of cancers.

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	66.0	119.45

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	1.81 mL	9.05 mL	18.10 mL
5 mM	0.36 mL	1.81 mL	3.62 mL
10 mM	0.18 mL	0.90 mL	1.81 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. Konicek BW, Capen AR, Credille KM, Ebert PJ, Falcon BL, Heady GL, Patel BKR, Peek VL, Stephens JR, Stewart JA, Stout SL, Timm DE, Um SL, Willard MD, Wulur IH, Zeng Y, Wang Y, Walgren RA, Betty Yan SC. Merestinib (LY2801653) inhibits neurotrophic receptor kinase (NTRK) and suppresses growth of NTRK fusion bearing tumors. Oncotarget. 2018 Feb 13;9(17):13796-13806. doi: 10.18632/oncotarget.24488. PMID: 29568395; PMCID: PMC5862616.
2. Kosciuczuk EM, Saleiro D, Kroczynska B, Beauchamp EM, Eckerdt F, Blyth GT, Abedin SM, Giles FJ, Altman JK, Platanias LC. Merestinib blocks Mnk kinase activity in acute myeloid leukemia progenitors and exhibits antileukemic effects in vitro and in vivo. Blood. 2016 Jul 21;128(3):410-4. doi: 10.1182/blood-2016-02-698704. Epub 2016 Jun 15. PMID: 27307295; PMCID: PMC4957163.

In vivo study

1. Konicek BW, Capen AR, Credille KM, Ebert PJ, Falcon BL, Heady GL, Patel BKR, Peek VL, Stephens JR, Stewart JA, Stout SL, Timm DE, Um SL, Willard MD, Wulur IH, Zeng Y, Wang Y, Walgren RA, Betty Yan SC. Merestinib (LY2801653) inhibits neurotrophic receptor kinase (NTRK) and suppresses growth of NTRK fusion bearing tumors. Oncotarget. 2018 Feb 13;9(17):13796-13806. doi: 10.18632/oncotarget.24488. PMID: 29568395; PMCID: PMC5862616.

2. Kosciuczuk EM, Saleiro D, Kroczynska B, Beauchamp EM, Eckerdt F, Blyth GT, Abedin SM, Giles FJ, Altman JK, Platanias LC. Merestinib blocks Mnk kinase activity in acute myeloid leukemia progenitors and exhibits antileukemic effects in vitro and in vivo. Blood. 2016 Jul 21;128(3):410-4. doi: 10.1182/blood-2016-02-698704. Epub 2016 Jun 15. PMID: 27307295; PMCID: PMC4957163.

7. Bioactivity

Biological target:

Merestinib (LY2801653) is a potent, c-Met inhibitor (Ki=2 nM) with anti-tumor activities and activity against MST1R (IC50=11 nM), FLT3 (IC50=7 nM), AXL (IC50=2 nM), MERTK (IC50=10 nM), TEK (IC50=63 nM), ROS1, DDR1/2 (IC50=0.1/7 nM) and MKNK1/2 (IC50=7 nM.

In vitro activity

To examine if merestinib inhibits NTRK1 phosphorylation in vitro, KM-12 cells were treated for 2 hours ranging in concentration from 3.9 -1000 nM. Merestinib showed a dose dependent decrease in p-NTRK1 Y490 resulting in complete inhibition at 62.5 nM as determined by western blot (Figure1B). Merestinib showed dose dependent inhibition of phosphorylated MAPK 42/44 (ERK) in concordance with their respective p-NTRK downstream signaling (Figure1B). Merestinib is a potent direct inhibitor of MKNK1/2, the kinases responsible for phosphorylating eIF4E at S209 [16]. In KM-12 cells, merestinib reduced p-eIF4E levels with near-complete inhibition at 62.5 nM (Figure1B). It was further examined if merestinib, M1 and M2 metabolites suppress KM-12 cell proliferation in vitro. Within 72 hours, treatment with merestinib, M1, or M2 suppressed cell proliferation with an IC50 of 10 nM, 16 nM and 102 nM, respectively. Collectively, these data suggest that merestinib and the metabolites M1 and M2 block both anchorage dependent and independent cell growth in TPM3-NTRK1 bearing KM-12 cells.

Reference: Oncotarget. 2018 Mar 2; 9(17): 13796–13806. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5862616/

In vivo activity

Merestinib (dosed once daily at 12 mg/kg or 24 mg/kg) (dosed twice daily at 30 mg/kg) was evaluated in mouse tumor models with NIH-3T3 cells expressing wild-type TPM3-NTRK1, TPM3-NTRK1 with G595R or G667C mutation. Merestinib treatment resulted in tumor regression in tumors expressing wild-type TPM3-NTRK1 (Figure6A). Similar extent of tumor regression was observed in both doses of merestinib treated cohorts in animals bearing tumors with the G667C mutant within 4 days of treatment initiation (12 mg/kg once daily, regression = 46.8%, $p < 0.001$; 24 mg/kg once daily, regression = 51.3%, $p < 0.001$) and maintained through the study period. Tumors expressing mutant G595R TPM3-NTRK1 insensitive to merestinib (T/C=65.2%, p=0.147) treatment (Figure (Figure 6C). Together, these data indicate that merestinib is a potent inhibitor of NTRK and blocks tumor progression in vivo in preclinical studies.

Reference: Oncotarget. 2018 Mar 2; 9(17): 13796–13806. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5862616/