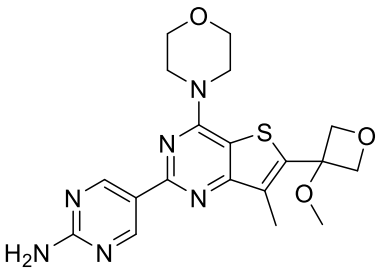
Product data sheet

MedKoo Cat#: 406637 Name: GNE-317 CAS#: 1394076-92-6 Chemical Formula: $C_{19}H_{22}N_6O_3S$ Exact Mass: 414.1474 Molecular Weight: 414.48	
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:

GNE-317 is a potent and selective PI3K inhibitor with potential anticncer activity. GNE-317 targets the PI3K pathway and can cross the BloodÂ–Brain Barrier. GNE-317 was identified as having physicochemical properties predictive of low efflux by P-gp and BCRP. Studies in transfected MDCK cells showed that GNE-317 was not a substrate of either transporter. GNE-317 markedly inhibited the PI3K pathway in mouse brain, causing 40% to 90% suppression of the pAkt and pS6 signals up to 6-hour postdose.

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	20.0	48.3

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	**1 mg**	**5 mg**	**10 mg**
1 mM	2.41 mL	12.06 mL	24.13 mL
5 mM	0.48 mL	2.41 mL	4.83 mL
10 mM	0.24 mL	1.21 mL	2.41 mL
50 mM	0.05 mL	0.24 mL	0.48 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. Salphati L, Heffron TP, Alicke B, Nishimura M, Barck K, Carano RA, Cheong J, Edgar KA, Greve J, Kharbanda S, Koeppen H, Lau S, Lee LB, Pang J, Plise EG, Pokorny JL, Reslan HB, Sarkaria JN, Wallin JJ, Zhang X, Gould SE, Olivero AG, Phillips HS. Targeting the PI3K pathway in the brain--efficacy of a PI3K inhibitor optimized to cross the blood-brain barrier. Clin Cancer Res. 2012 Nov 15;18(22):6239-48. doi: 10.1158/1078-0432.CCR-12-0720. Epub 2012 Sep 19. PMID: 22992516.

2. Salphati L, Shahidi-Latham S, Quiason C, Barck K, Nishimura M, Alicke B, Pang J, Carano RA, Olivero AG, Phillips HS. Distribution of the phosphatidylinositol 3-kinase inhibitors Pictilisib (GDC-0941) and GNE-317 in U87 and GS2 intracranial glioblastoma models-assessment by matrix-assisted laser desorption ionization imaging. Drug Metab Dispos. 2014 Jul;42(7):1110-6. doi: 10.1124/dmd.114.057513. Epub 2014 Apr 22. PMID: 24754926.

In vivo study

1. Salphati L, Heffron TP, Alicke B, Nishimura M, Barck K, Carano RA, Cheong J, Edgar KA, Greve J, Kharbanda S, Koeppen H, Lau S, Lee LB, Pang J, Plise EG, Pokorny JL, Reslan HB, Sarkaria JN, Wallin JJ, Zhang X, Gould SE, Olivero AG, Phillips HS. Targeting the PI3K pathway in the brain--efficacy of a PI3K inhibitor optimized to cross the blood-brain barrier. Clin Cancer Res. 2012 Nov 15;18(22):6239-48. doi: 10.1158/1078-0432.CCR-12-0720. Epub 2012 Sep 19. PMID: 22992516.

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2. Salphati L, Shahidi-Latham S, Quiason C, Barck K, Nishimura M, Alicke B, Pang J, Carano RA, Olivero AG, Phillips HS. Distribution of the phosphatidylinositol 3-kinase inhibitors Pictilisib (GDC-0941) and GNE-317 in U87 and GS2 intracranial glioblastoma models-assessment by matrix-assisted laser desorption ionization imaging. Drug Metab Dispos. 2014 Jul;42(7):1110-6. doi: 10.1124/dmd.114.057513. Epub 2014 Apr 22. PMID: 24754926.

7. Bioactivity

Biological target:

GNE-317 is a potent, brain-penetrant PI3K inhibitor.

In vitro activity

The bidirectional transport of GNE-317 was assessed in transfected cell lines overexpressing human or mouse P-gp or BCRP. The apparent permeability (Papp) was high and comparable to that determined for metoprolol, the high Papp marker used in the same experiments (data not shown). The ERs (Papp, B-A/Papp, A-B) were not markedly different from 1 in the MDCK or LLC-PK1 transfected cells (Table 1), indicating that GNE-317 was not impacted by the overexpression of the human or mouse P-gp and BCRP, and suggesting that this compound was a poor substrate of these transporters.

Reference: Clin Cancer Res. 2012 Nov 15;18(22):6239-48.
http://clincancerres.aacrjournals.org/cgi/pmidlookup?view=long&pmid=22992516

In vivo activity

The efficacy of GNE-317 was tested in 3 intracranial tumor models, the U87, the neurosphere GS2 and the GBM10 models. GNE-317 was administered PO at 40 mg/kg daily for 3 and 6 weeks to U87 and GS2 tumor-bearing mice, respectively, and for more than 12 weeks to GBM10 tumor-bearing mice. The effect of the treatment on the U87 and GS2 tumor volumes was assessed at the end of the dosing period. A U87 tumor image obtained by micro-CT is presented in Fig. 2C. GNE-317 reduced the U87 tumor volumes by more than 90%, when compared with the vehicle control (Fig. 2D). Bioluminescence measured before and at the end of treatment (Supplementary Table 1) displayed halted tumor growth with GNE-317, which was consistent with in vitro findings that showed cytostasis (Supplementary Fig. 2) but no cell death. Similarly, the GS2 tumors measured by MRI (Fig. 2A) in the treated mice were more than 50% smaller than those in the control group (Fig. 2B). GDC-0941, a PI3K inhibitor that does not cross the BBB (16), was also tested in these 2 models. In contrast to GNE-317, GDC-0941 showed no activity in the GS2 model (Fig. 2A and B), whereas it was able to reduce the U87 tumor volumes by 66% (Fig. 2C and D). To assess whether the absence of efficacy of GDC-0941 was related to its lack of mTOR inhibition, the dual PI3K/mTOR inhibitor GDC-0980 (17, 18) was also tested in the GS2 model. GDC-0980 is a substrate of P-gp and bcrp1 (19). Similarly to GDC-0941, GDC-0980 showed no activity against the GS2 model (Fig. 2A and B). Plasma and brain concentrations and brain-to-plasma ratios determined at the end of the study in the GS2 tumor-bearing mice are presented in Supplementary Table 2. For the 3 compounds, the brain concentrations and brain-to-plasma ratios were comparable in the normal part of the brain and in the tumored brain. In the GBM10 model, GNE-317 was able to extend the survival of mice from a median of 55.5 to 75 days ($P < 0.05$, log rank test; Fig. 2E) when administered at 30 mg/kg (40 mg/kg the first 2 weeks).

Reference: Clin Cancer Res. 2012 Nov 15;18(22):6239-48.
http://clincancerres.aacrjournals.org/cgi/pmidlookup?view=long&pmid=22992516