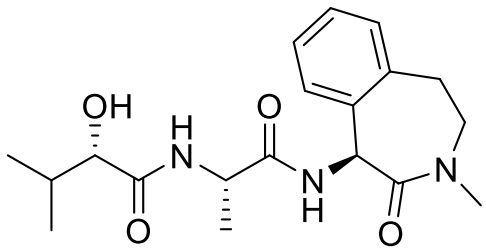
Product data sheet

MedKoo Cat#: 315251 Name: Semagacestat CAS#: 425386-60-3 Chemical Formula: $C_{19}H_{27}N_3O_4$ Exact Mass: 361.2002 Molecular Weight: 361.43	
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:
Semagacestat, also known as LY450139 or LY4501; is a γ-secretase inhibitor. It was a candidate drug for a causal therapy against Alzheimer's disease. It was originally developed by Eli Lilly and Ãlan, and clinical trials were conducted by Eli Lilly. Phase III trials included over 3000 patients, but in August 2010, a disappointing interim analysis, in which semagacestat performed less well than the placebo, led to investigators being instructed to tell subjects to stop taking the drug.

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
DMF	25	69.17
DMSO	25	69.17
Ethanol	1	2.77

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	2.77 mL	13.83 mL	27.67 mL
5 mM	0.55 mL	2.77 mL	5.53 mL
10 mM	0.28 mL	1.38 mL	2.77 mL
50 mM	0.06 mL	0.28 mL	0.55 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. Schellekens H, McNamara O, Dinan TG, McCarthy JV, McGlacken GP, Cryan JF. Semagacestat, a γ-secretase inhibitor, activates the growth hormone secretagogue (GHS-R1a) receptor. J Pharm Pharmacol. 2013 Apr;65(4):528-38. doi: 10.1111/jphp.12010. Epub 2012 Nov 27. PMID: 23488781.

In vivo study

1. Tagami S, Yanagida K, Kodama TS, Takami M, Mizuta N, Oyama H, Nishitomi K, Chiu YW, Okamoto T, Ikeuchi T, Sakaguchi G, Kudo T, Matsuura Y, Fukumori A, Takeda M, Ihara Y, Okochi M. Semagacestat Is a Pseudo-Inhibitor of γ-Secretase. Cell Rep. 2017 Oct 3;21(1):259-273. doi: 10.1016/j.celrep.2017.09.032. PMID: 28978478.
2. Rosenberg PB, Lanctôt KL, Herrmann N, Mintzer JE, Porsteinsson AP, Sun X, Raman R. Changes in Neuropsychiatric Inventory Associated with Semagacestat Treatment of Alzheimer's Disease. J Alzheimers Dis. 2016 Aug 10;54(1):373-81. doi: 10.3233/JAD-151113. PMID: 27567808.

7. Bioactivity

Product data sheet

Biological target:

Semagacestat is a potent inhibitor of γ-secretase that blocks the production of Aβ38, Aβ40, and Aβ42 with IC50 values of 12.0, 12.1, and 10.9 nM, respectively. It also blocks Notch signaling (IC50 = 14.1 nM).

In vitro activity

This study suggests a novel mechanism of action for semagacestat via modest GHS-R1a receptor activation. Semagacestat and its precursor were shown to activate the GHS-R1a receptor. Moreover, a synergistic GHS-R1a receptor activation was shown following a combined exposure to ghrelin and semagacestat. In addition, GHS-R1a receptor internalization was observed upon exposure to semagacestat and its precursor.

Reference: J Pharm Pharmacol. 2013 Apr;65(4):528-38. https://pubmed.ncbi.nlm.nih.gov/23488781/

In vivo activity

This study provides reasoning behind why the Eli Lilly clinical trial for semagacestat failed. The results of this study demonstrated that semagacestat is a pseudo-γ-secretase inhibitor (GSI) and not a true GSI, which would impact trial hypothesis, methods, and outcomes. Semagacestat increased intracellular byproduct peptides, produced along with Aβ through serial γ-cleavage of βAPP, as well as intracellular long Aβ species, in cell-based and in vivo studies of AD model mice.

Reference: Cell Rep. 2017 Oct 3;21(1):259-273. https://pubmed.ncbi.nlm.nih.gov/28978478/

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.