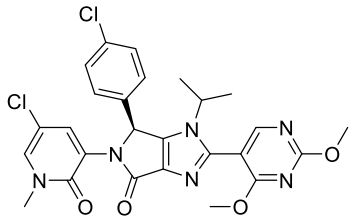
Product data sheet

MedKoo Cat#: 206159 Name: Siremadlin CAS#: 1448867-41-1 Chemical Formula: $C_{26}H_{24}Cl_2N_6O_4$ Exact Mass: 554.1236 Molecular Weight: 555.42	
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:
Siremadlin, also known as HDM201, is an orally bioavailable human double minute 2 homolog (HDM2) inhibitor with potential antineoplastic activity. HDM2 inhibitor HDM201 inhibits the binding of the HDM2 protein to the transcriptional activation domain of the tumor suppressor protein p53. HDM2, a zinc finger protein and negative regulator of the p53 pathway, is often overexpressed in cancer cells and has been implicated in cancer cell proliferation and survival.

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	20	36.01
DMSO	10	18.00
Ethanol	15	27.01

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	1.80 mL	9.00 mL	18.00 mL
5 mM	0.36 mL	1.80 mL	3.60 mL
10 mM	0.18 mL	0.90 mL	1.80 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. Witkowski J, Polak S, Pawelec D, Rogulski Z. In Vitro/In Vivo Translation of Synergistic Combination of MDM2 and MEK Inhibitors in Melanoma Using PBPK/PD Modelling: Part III. Int J Mol Sci. 2023 Jan 23;24(3):2239. doi: 10.3390/ijms24032239. PMID: 36768563; PMCID: PMC9917191.
2. Wang HQ, Mulford IJ, Sharp F, Liang J, Kurtulus S, Trabucco G, Quinn DS, Longmire TA, Patel N, Patil R, Shirley MD, Chen Y, Wang H, Ruddy DA, Fabre C, Williams JA, Hammerman PS, Mataraza J, Platzer B, Halilovic E. Inhibition of MDM2 Promotes Antitumor Responses in p53 Wild-Type Cancer Cells through Their Interaction with the Immune and Stromal Microenvironment. Cancer Res. 2021 Jun 1;81(11):3079-3091. doi: 10.1158/0008-5472.CAN-20-0189. Epub 2021 Jan 27. PMID: 33504557.

In vivo study

1. Stein EM, DeAngelo DJ, Chromik J, Chatterjee M, Bauer S, Lin CC, Suarez C, de Vos F, Steeghs N, Cassier PA, Tai D, Kiladjian JJ, Yamamoto N, Mous R, Esteve J, Minami H, Ferretti S, Guerreiro N, Meille C, Radhakrishnan R, Pereira B, Mariconti L, Halilovic E, Fabre C, Carpio C. Results from a First-in-Human Phase I Study of Siremadlin (HDM201) in Patients

with Advanced Wild-Type TP53 Solid Tumors and Acute Leukemia. Clin Cancer Res. 2022 Mar 1;28(5):870-881. doi: 10.1158/1078-0432.CCR-21-1295. PMID: 34862243; PMCID: PMC9377734.

2. Jeay S, Ferretti S, Holzer P, Fuchs J, Chapeau EA, Wartmann M, Sterker D, Romanet V, Murakami M, Kerr G, Durand EY, Gaulis S, Cortes-Cros M, Ruetz S, Stachyra TM, Kallen J, Furet P, Würthner J, Guerreiro N, Halilovic E, Jullion A, Kauffmann A, Kuriakose E, Wiesmann M, Jensen MR, Hofmann F, Sellers WR. Dose and Schedule Determine Distinct Molecular Mechanisms Underlying the Efficacy of the p53-MDM2 Inhibitor HDM201. Cancer Res. 2018 Nov 1;78(21):6257-6267. doi: 10.1158/0008-5472.CAN-18-0338. Epub 2018 Aug 22. PMID: 30135191.

7. Bioactivity

Biological target:

Siremadlin is an inhibitor of the protein-protein interaction between the E3 ubiquitin ligase MDM2 and p53 (IC50 = 0.21 nM). It selectively inhibits the MDM2-p53 protein-protein interaction over MDM4-p53, YAP1-TEAD4, PCSK9-LDLR, and Bcl-2-Bak interactions in time-resolved FRET (TR-FRET) assays (IC50s = 3.3, >150, >50, and >50 µM, respectively). Siremadlin inhibits the growth of SJSA-1 osteosarcoma cells (GI50 = 38 nM).

In vitro activity

Inhibition of MDM2 by siremadlin promotes the antitumor responsed in p53 wild-type cancer cells. In response to HDM201 treatment, the percentage of dendritic cells increased, including the CD103+ antigen cross-presenting subset. Furthermore, HDM201 increased the percentage of Tbet+Eomes+ CD8+ T cells and the CD8+/Treg ratio within the tumor.

Reference: Cancer Res. 2021 Jun 1;81(11):3079-3091. https://pubmed.ncbi.nlm.nih.gov/33504557/

In vivo activity

Siremadlin demonstrates therapeutic efficacy in p53 wild-type cancers. High-dose regimen rapidly induces PUMA, apoptosis, and downregulates Bcl-xL in vivo. Clinical trials suggest reproducibility of pulse dosing's molecular mechanism in patients, supporting the comparison of daily and intermittent regimens for p53-MDM2 inhibitors, such as siremadlin.

Reference: Cancer Res. 2018 Nov 1;78(21):6257-6267. https://pubmed.ncbi.nlm.nih.gov/30135191/

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.