

Product data sheet



MedKoo Cat#: 203165 Name: Belnacasan (VX765) CAS#: 273404-37-8 Chemical Formula: C ₂₄ H ₃₃ C ₁ N ₄ O ₆ Exact Mass: 508.20886 Molecular Weight: 508.99	
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:

Belnacasan, also known as VX-765, is designed to inhibit Caspase, which is an enzyme that controls the generation of two cytokines, IL-1b and IL-18. VX-765 has been shown to inhibit acute seizures in preclinical models. In addition, VX-765 has shown activity in preclinical models of chronic epilepsy. VX-765 had been dosed in over 100 patients in phase-I and phase-IIa clinical trials relating to other diseases, including a 28-day phase-IIa clinical trial in patients with psoriasis. It has completed the treatment phase of a phase-IIa clinical trial of VX-765 that enrolled approximately 75 patients with treatment-resistant epilepsy. The double-blind, randomized, placebo-controlled clinical trial was designed to evaluate the safety, tolerability and clinical activity of VX-765.

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	57.73	113.41
DMF	30.0	58.94
Ethanol	60.3	118.47
Ethanol:PBS (pH 7.2) (1:9)	0.1	0.2
Water	1.0	1.96

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	1.96 mL	9.82 mL	19.65 mL
5 mM	0.39 mL	1.96 mL	3.93 mL
10 mM	0.20 mL	0.98 mL	1.96 mL
50 mM	0.04 mL	0.20 mL	0.39 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. Israelov H, Ravid O, Atrakchi D, Rand D, Elhaik S, Bresler Y, Twitto-Greenberg R, Omesi L, Liraz-Zaltsman S, Gosselet F, Schnaider Beeri M, Cooper I. Caspase-1 has a critical role in blood-brain barrier injury and its inhibition contributes to multifaceted repair. *J Neuroinflammation*. 2020 Sep 9;17(1):267. doi: 10.1186/s12974-020-01927-w. PMID: 32907600; PMCID: PMC7488082.
2. Stack JH, Beaumont K, Larsen PD, Straley KS, Henkel GW, Randle JC, Hoffman HM. IL-converting enzyme/caspase-1 inhibitor VX-765 blocks the hypersensitive response to an inflammatory stimulus in monocytes from familial cold autoinflammatory syndrome patients. *J Immunol*. 2005 Aug 15;175(4):2630-4. doi: 10.4049/jimmunol.175.4.2630. PMID: 16081838.

In vivo study

Product data sheet



1. Chen J, Chen YQ, Shi YJ, Ding SQ, Shen L, Wang R, Wang QY, Zha C, Ding H, Hu JG, Lü HZ. VX-765 reduces neuroinflammation after spinal cord injury in mice. *Neural Regen Res.* 2021 Sep;16(9):1836-1847. doi: 10.4103/1673-5374.306096. PMID: 33510091.
2. Flores J, Noël A, Foveau B, Beauchet O, LeBlanc AC. Pre-symptomatic Caspase-1 inhibitor delays cognitive decline in a mouse model of Alzheimer disease and aging. *Nat Commun.* 2020 Sep 11;11(1):4571. doi: 10.1038/s41467-020-18405-9. Erratum in: *Nat Commun.* 2021 Apr 9;12(1):2271. PMID: 32917871; PMCID: PMC7486940.

7. Bioactivity

Biological target:

Belnacasan (VX-765) is the prodrug of VRT-043198, which is an inhibitor of IL-converting enzyme (ICE)/caspase-1 with Kis of 0.8 nM and less than 0.6 nM for caspase-1 and caspase-4, respectively.

In vitro activity

Next, VX-765 was utilized to assess caspase-1 role in PX (paraoxon)-induced inflammatory response in the BBB. First, VX-765 inhibited the adhesion of PBMCs to BLECs monolayers (Fig. 4a). Second, VX-765 reversed the transmigration of PBMCs (peripheral blood mononuclear cells) across the BBB model back to control levels (Fig. 4b), and third, VX-765 attenuated the PX-induced increase in expression of the adhesion molecules ICAM-1 and E-selectin (Fig. 4c, d, and e). The images shown in Fig. 4c represent the increase in ICAM-1 staining, and an increased localization of E-selectin in cell-cell junctions (arrows), and demonstrate that these effects are attenuated with the inhibition of caspase-1. These multifaceted effects demonstrate that caspase-1 has a key role in triggering the immune response in BLECs following PX exposure.

Reference: *J Neuroinflammation.* 2020; 17: 267. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7488082/>

In vivo activity

Activated Casp1 cleaves the inflammatory cytokines IL-1 β and IL-18 into their active states, leading to IL-1 β -mediated inflammation through microglial activation and astrogliosis. IL-1 β and IL-18 were assessed to determine whether Casp1 is directly implicated in inflammation in the J20 brain. There were no differences in hippocampal IL-1 β and IL-18 mRNA levels between groups across any WO period, except for increased IL-1 β mRNA in the J20 hippocampus that was normalized with VX-765 treatment at 16-week WO (Fig. 5a and Supplementary Fig. 6a). Pro-, active (Δ) and total (pro + active) IL-1 β protein levels were measured by western blot in the hippocampus and cortex at 4- and 20-week WO (Fig. 5b). While hippocampal pro IL-1 β levels remained unchanged (Fig. 5c, f), active and total IL-1 β levels seemed higher in vehicle-treated J20 versus WT mice at both 4- and 20-week WO (Fig. 5d, e, g, h). This trend of increased active and total hippocampal IL-1 β levels was not observed with VX-765 treatment. Active IL-1 β levels were significantly higher in vehicle-treated J20 cortex but were normalized with VX-765 treatment at 20-week WO (Fig. 5g).

Reference: *Nat Commun.* 2020; 11: 4571. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7486940/>

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.