

AstraZeneca	AZD6765/Lanicemine
Mechanism of Action	N-methyl-D-aspartate (NMDA) receptor, low-trapping, open-channel blocker http://www.ncbi.nlm.nih.gov/gene/2903 ; http://www.ncbi.nlm.nih.gov/gene/2904
Overview	<p>AZD6765 binds within the NMDA channel pore (K_i 0.5–3 μM) and functionally blocks the flow of charged ions through recombinant human NR2A and NR2B receptor complexes (IC_{50} 4 to 40 μM), as reported throughout various literature references. Different from classic NMDA channel blockers (ketamine and MK801), AZD6765 is rapidly reversible (fast off-rate, 2.8 seconds, and low-trapping, 52–59%), which is believed to underlie an improved safety/efficacy profile. Elevations in cortical gamma wave EEG across multiple species (mouse, rat and non-human primates), characteristic of non-selective NMDA channel blockage, occur at plasma exposures that overlap with efficacy (1 to 5 μM) and represent a useful biomarker for demonstrating central target engagement in the clinical setting.</p> <p>Relative to projected therapeutic concentrations, AZD6765 has >10-fold margins to elevations in locomotor activity and other behavioral abnormalities (head weaving, retropulsion and ataxia) typically associated with the psychotomimetic liabilities of the NMDA class. At targeted plasma concentrations (1 to 5 μM), AZD6765 produces changes in behavioral performance consistent with mild and transient reductions in attention/vigilance. However, at targeted concentrations, there is no evidence for learning and/or memory deficits following either acute or sub-chronic dosing.</p>
Safety/Tolerability	<p>Overall in more than 15 clinical studies comprising over 700 subjects, AZD6765 has been given to healthy volunteers; subjects with renal impairment; or patients with stroke, sleep apnea or major depressive disorder in single i.v. infusions (1 to 350 mg) or multiple i.v. infusions (loading doses between 120 and approximately 460 mg plus maintenance doses of up to 120 mg every 8 hours for 3 days; 100 or 150 mg, 3 times weekly for 3 weeks). The most common adverse effects observed have been CNS-type, including dizziness, orthostatic hypotension and transient increases in blood pressure.</p> <p>Preclinical 3-, 6- and 9-month intermittent i.v. infusion studies have been performed to support over 45 infusions in humans. NMDA-class associated neurotoxicity findings have been observed in rats at supra-therapeutic doses.</p>
Additional Information	<p>Following i.v. infusion (up to 1 h), AZD6765 reaches maximum plasma concentration (C_{max}) at the end of the infusion and clears slowly from the body with a total clearance of approximately 0.13 L/h/kg and a half-life of about 13 h. Since renal CL is one of the major routes of elimination (accounting for approximately $\frac{1}{4}$ of total CL), mild to moderate renal impairment had some effects on the PK of AZD6765.</p> <p>Quantitative EEG and functional MRI (fMRI) have been used to guide dose for subsequent efficacy studies.</p>
Suitable for and Exclusions	<p>The reproductive toxicology package indicates a risk of fetal toxicity. The inclusion of women of child-bearing potential would need to be assessed for any proposal based on the risk-benefit and the use of appropriate highly effective contraception.</p> <p>Suitable for study in indications, sub-populations and/or endpoints that are manifestly distinct from those previously studied for this compound or mechanism of action.</p>
Clinical Trials	http://www.clinicaltrials.gov/ct2/results?term=AZD6765&Search=Search
Additional Characteristics: CNS Penetration/Pediatric Diseases	AZD6765 is a CNS penetrant (see above) and, thus, is suitable for appropriate CNS indications. Studies in pediatric populations for which there is no adult population will be considered. Studies for diseases/conditions that have a pediatric and adult population will also be considered if studies in a pediatric population are scientifically justified. To date, no juvenile pre-clinical toxicology studies have been conducted with AZD6765.
Publications	http://www.nature.com/mp/journal/vaop/ncurrent/pdf/mp2013130a.pdf ; http://www.ncbi.nlm.nih.gov/pubmed/23206319