| AstraZeneca | AZD7325 |
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| **Mechanism of Action** | Gamma-aminobutyric acid receptor A alpha 2 & 3 ($GABA_{A\alpha2,3}$) positive modulator<br>http://www.ncbi.nlm.nih.gov/gene/2555; http://www.ncbi.nlm.nih.gov/gene/2556 |
| **Overview** | AZD7325 is a high-affinity, selective modulator of the $GABA_A$ receptor system, with differential binding and modulatory properties dependent on the particular $GABA_A$ subtype. Binding affinity is high at $GABA_{A\alpha1}$, $_{\alpha2}$ and $_{\alpha3}$ ($K_i$ of 0.5, 0.3 and 1.3 nM, respectively), but not $GABA_{A\alpha5}$ (230 nM). Using whole-cell electrophysiology after specific expression of a $GABA_A$ subunit in Xenopus oocytes, AZD7325 did not display intrinsic agonist activity at any subtype, but potentiated the response of diazepam at Aα2 and Aα3 (43 and 45%, respectively, at 100 nM), but not Aα1 or Aα5. In contrast, AZD7325 acted as a full antagonist of zolpidem at Aα1 consistent with a lack of sedative liabilities *in vivo.* Selectivity was >100-fold in a panel of 160 other receptors, ion channels and enzymes, with the closest secondary pharmacology target being melatonin MT1 receptor antagonism ($IC_{50}$ of 126 nM). AZD7325 also potentiated native GABA responses in neurons prepared from the rat prefrontal cortex, occupied brain binding sites in non-human primates as assessed by PET (approximately 50% receptor occupancy at plasma levels of near the $K_i$), and demonstrated efficacy in a number of rat anxiety models. |
| **Safety/Tolerability** | AZD7325 has been administered orally to healthy volunteers at single doses of up to 100 mg and repeated doses up to 50 mg per day for 7 days. In patients, AZD7325 has been administered up to 15 mg twice daily (BID) for 28 days. Adverse events were CNS in nature, and included dizziness, feeling of relaxation, euphoric mood, somnolence and headache. These were transient, mild and related to peak plasma concentrations. The most frequent adverse events were dizziness, headache and somnolence, although one grand mal convulsion was also reported and considered to be treatment related.<br><br>Preclinical toxicity studies of up to 3-month duration have been performed. These have identified pharmacologically mediated changes in behavior and, additionally, changes to heart rate; increases in cholesterol, AST and ALT; and also changes in hematology parameters. No compound-related histopathological changes were found. |
| **Additional Information** | Receptor occupancy was measured by PET imaging in healthy volunteers; maximal occupancy was achieved at doses of 10, 20 and 30 mg.<br><br>Two Phase 2a general anxiety disorder studies have been conducted. In the first, AZD7325 was dosed at either 2 or 5 mg BID or 10 mg every day (QD) for 28 days, achieving compound plasma exposures of ~4 times the $K_i$. In the second, it was dosed at either 5 or 15 mg BID for 28 days and compared with lorazepam. While the primary objective of greater efficacy vs. placebo and/or lorazepam, as assessed by the Hamilton Anxiety scale, was not met at any of the doses tested, the placebo response rate was considered to be high and reduction in other anxiety endpoints at 10 mg and depression MADRS score were noted. |
| **Suitable for and Exclusions** | Preclinical reproductive toxicology data are available and have not identified any specific risks. Women of child-bearing potential using highly effective contraception can be included.<br><br>Subjects with past or present symptoms of alcohol or drug abuse/dependence and/or subjects suspected of abusing alcohol or illicit or prescription medications should probably be excluded. |
| **Clinical Trials** | http://www.clinicaltrials.gov/ct2/results?term=AZD7325&Search=Search |

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| **Additional Characteristics: CNS Penetrance/Pediatric Diseases** | AZD7325 is a CNS penetrant (see above) and, thus, potentially is suitable for appropriate CNS indications.<br><br>Pediatric disease proposals will be considered (≤ 3 months dosing duration based on prior clinical exposures). However, due to the lack of juvenile toxicology data or prior experience in pediatric subjects, use will depend on risk/benefit, dosing duration and regimen, and age of the pediatric population. |
| **Publications** | http://www.ncbi.nlm.nih.gov/pubmed?term=AZD7325 |