Pfizer	CE-224535/P2X7 Receptor Antagonist
Mechanism of Action	Purinergic receptor 2 (P2X7) antagonist. IUPHAR link for target: http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=484 NCBI Gene data: http://www.ncbi.nlm.nih.gov/gene/5027 P2X7 is a member of a large family of ligand-gated ion channels, the purinergic receptors family.
Overview	CE-224535 is a potent (IC_{50} = 2–13 nM), highly selective (at least 500-fold over related $P2X_1$ and $P2Y_1$ receptors), orally bioavailable, non-competitive antagonist of the human P2X7 receptor. Polymorphic variants of the human P2X7 receptor have been reported (Thunberg, 2002; Li, 2002), with 7 nonsynonymous single-nucleotide polymorphisms confirmed. Two polymorphisms are reported to alter function of the P2X7 receptor (Sluyter, 2004; Wiley, 2003).
Safety/Tolerability	CE-224535 is safe and well tolerated after administration of up to 1600 mg as a single dose or 600 mg every 12 hours for 14 days in healthy subjects and 500 mg every 12 hours for 2 weeks in subjects with osteoarthritis of the knee and 12 weeks in rheumatoid arthritis patients with an inadequate response to methotrexate.
Additional Information	CE-224535 proof of mechanism was demonstrated after oral dosing by inhibiting IL-1β >90% in an *ex vivo* human whole blood LPS+ATP stimulation assay. This was consistent with the observed plasma concentrations of CE-224535 above the IC_{90} in human blood target concentration for this same time period. CE-224535 failed to demonstrate efficacy in a 2-week study of knee pain in osteoarthritis or a 12-week study in patients with rheumatoid arthritis.
Suitable for and Exclusions	Nonclinical toxicology data support clinical studies up to 13 weeks in duration. There is no toxicology support for clinical studies in pediatrics. Women of child-bearing potential should be excluded. Excluded Indications: Rheumatoid arthritis, osteoarthritis
Clinical Trials	http://www.clinicaltrials.gov/search?term=%22CE-224535%22
Additional Characteristics: CNS Penetrance/Pediatric Diseases	The selectivity of CE-224535 for the human P2X7 receptor precludes its evaluation in rodent disease models. Pre-clinical pharmacokinetic studies with CE-224535 indicate limited CNS penetration. CE-224535 is not suitable for use in pediatric studies. Embryo-fetal toxicity studies have not been conducted that would support inclusion of women of child-bearing potential.
Publications	http://www.ncbi.nlm.nih.gov/pubmed/?term=CE-224%2C535