GlaxoSmithKline	SB223412 (talnetant)
Mechanism of Action	Tachykinin receptor/neurokinin 3 receptor antagonist http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=362 http://www.ncbi.nlm.nih.gov/gene/6870
Overview	SB223412 is a potent, competitive, orally-bioavailable and selective neurokinin-3 (NK-3) receptor antagonist. Potent, competitive antagonist for human NK-3 receptors (CHO hNK-3 cell membrane binding, K_i= 1.0 nM; Ca^{2+} mobilization studies in CHO hNK-3 cells, K_B = 3 nM). Selectivity studies versus the other neurokinin receptors (hNK-2-CHO and hNK-1-CHO) revealed that SB223412 is about 100-fold selective for the hNK-3 versus hNK-2 receptor, with no affinity for the hNK-1 at concentrations up to 100 µM. SB223412 antagonized senktide-induced contraction of rabbit isolated iris sphincter muscle (K_B = 1.6 nM), and inhibited NK-3 receptor-induced membrane depolarization in guinea-pig bronchial parasympathetic ganglia and substantia nigra pars compacta in guinea pig. SB223412 inhibited senktide-induced miosis in rabbits when given iv (ED_{50} = 0.44mg/kg) and by 53% when given orally (25 mg/kg, PO). Oral administration of SB223412 produced a dose-related inhibition of senktide-induced behavioral effects in mice and guinea pigs, thought to be centrally-mediated, which suggests that SB223412 crosses the blood-brain barrier to a significant extent. The brain to blood ratio was 4:1 after intravenous infusion in the rat and monkey and following intravenous, oral and intraperitoneal administration in the guinea pig. Despite the "low" ratio, sufficient levels of drug in brain may be achieved.
Safety/Tolerability	Single oral doses up to 1000 mg/kg in dogs or up to 2000 mg/kg in mice and rats did not produce any signs of toxicity. Single oral doses of up to 2000 mg/kg caused emesis in monkeys. In the 28 day oral study in dog, testicular degeneration and prostatic atrophy were observed, appearing to result from the inhibition of testosterone synthesis. These changes reversed after treatment withdrawal and were not observed in the rat, mouse, or the monkey. Studies indicating that the genotoxic and potential carcinogenic risk of SB223412 to humans is low is supported by the absence of drug-related carcinogenic effects in the 24 month carcinogenicity studies in mice and rats. There were no additional significant safety pharmacology findings of concern for clinical use. Reproductive toxicity studies revealed no evidence of potential for effects on female fertility. SB223412 was generally well tolerated by healthy volunteers and patients in clinical studies for various indications. The most common adverse effects were headache, fatigue, and nausea. Studies in humans confirmed that SB223412 has an effect on testosterone, with a trend towards normalization following SB223412 discontinuation. There was no evidence of a SB223412 effect on female sex hormones including estradiol, FSH, or prolactin.
Additional Information	A total of 1040 subjects in Phase I studies (0.1 mg to 1000 mg as single doses; up to 800 mg twice daily on repeat doses). Over 1500 subjects in Phase II studies including patients with schizophrenia, irritable bowel syndrome, overactive bladder, COPD, and citric acid-induced cough. Despite extensive clinical evaluation in a number of disease areas, a clear therapeutic use has not yet been identified. The solubility of SB223412 results in less than proportional bioavailability with increasing dose.
Suitable for and Exclusions	Safety studies support clinical trials > 6 months in duration, including women of child bearing potential. SB223412 should not be administered to pregnant or nursing mothers or women of childbearing potential not observing adequate contraceptive precautions. Novel applications with a clear path to a clinical proof of concept are of interest.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=SB223412+or+talnetant
Publications	http://www.ncbi.nlm.nih.gov/pubmed?term=SB223412%20or%20talnetant