

GlaxoSmithKline	GW274150
<b>Mechanism of Action</b>	Inducible nitric oxide synthase (iNOS) inhibitor <a href="http://www.ncbi.nlm.nih.gov/gene/4843">http://www.ncbi.nlm.nih.gov/gene/4843</a>
<b>Overview</b>	<p>GW274150 is a selective and orally-bioavailable inhibitor of human iNOS and Selective for iNOS (IC<sub>50</sub> = 2.19 μM) vs. eNOS (IC<sub>50</sub> = 544 μM) or nNOS (IC<sub>50</sub> = 177 μM). The inhibition of iNOS by GW274150 was not readily reversible, whereas its weak inhibition of nNOS and eNOS was reversible.</p> <p>Following a single intravenous dose of 14C-GW274150 at 4.7 mg/kg, drug-related material in rat brain homogenates at 30 minutes post-dose was found to be less than 0.2% of dose.</p> <p>In guinea pig, oral GW274150 suppressed allergic asthma (ED<sub>50</sub> ~ 10mg/kg). In mouse, GW274150 (60mg/kg) inhibited antigen induced airway hyper-responsiveness and total inflammatory cell infiltration, and inhibited ozone-induced neutrophilia in the lung. Oral GW274150 (60 mg/kg) showed positive results in models of arthritis in the mouse but was ineffective in the rat.</p>
<b>Safety/Tolerability</b>	<p>In definitive toxicity studies of up to 13 weeks duration, GW274150 activity leads to secondary effects seen in the liver, kidneys and pancreas, likely associated with constriction of bile and pancreatic ducts at the Sphincter of Oddi due to nNOS activity at supra-pharmacological doses. Dose-related erosion of GI tract (principally small intestine), extending to breakthrough into the peritoneal cavity, was seen in carcinogenicity study in rats. No similar effects seen in mice. GW274150 showed no genotoxic or clastogenic activity in a standard battery of in vitro and in vivo tests. There were no additional significant safety pharmacology or reproductive toxicology findings of concern for clinical use.</p> <p>No adverse effects were noted in rat and rabbit reproduction studies designed to support the use in women of child-bearing potential.</p> <p>GW274150 was generally well tolerated by healthy volunteers and patients in clinical studies for various indications. Review of the safety data from clinical studies shows acceptable safety, and tolerability of GW274150 up to a single dose of 180mg and for repeated doses of 120 mg daily given for up to 12 weeks.</p>
<b>Additional Information</b>	Total exposure to GW274150 is 484 subjects dosed in a mixture of single and repeat dose studies in healthy volunteers and patients. In single doses up to 180 mg and repeat doses up to 120 mg once-daily for 12 weeks. Despite extensive clinical evaluation in a number of disease areas, a clear therapeutic use has not yet been identified.
<b>Suitable for and Exclusions</b>	The GI effects in rats currently preclude use of GW274150 in the clinic beyond 13 weeks. Novel applications with a clear path to a clinical proof of concept are of interest.
<b>Clinical Trials</b>	<a href="http://clinicaltrials.gov/ct2/results?term=GW274150">http://clinicaltrials.gov/ct2/results?term=GW274150</a>
<b>Publications</b>	<a href="http://www.ncbi.nlm.nih.gov/pubmed?term=GW274150">http://www.ncbi.nlm.nih.gov/pubmed?term=GW274150</a>