Nonpeptide Factor Xa Inhibitors: DPC423, A Highly Potent and Orally Bioavailable Pyrazole Antithrombotic Agent

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ABSTRACT

DPC423, 1-[3-(aminomethyl)phenyl]-N-[3-fluoro-2’-(methylsulfonyl)[1,1’-biphenyl]-4-yl]-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide, is a synthetic, orally bioavailable, competitive, and selective inhibitor of human coagulation factor Xa ($K_i$ [nM]: factor Xa, 0.15; trypsin, 60; thrombin, 6000; plasma kallikrein, 61; activated protein C, 1800; factor IXa, 2200; factor VIIa, >15,000; chymotrypsin, >17,000; urokinase, >19,000; plasmin, >35,000; tissue plasminogen activator, >45,000; complement factor I, 44,000 [$IC_{50}$]). In vitro, DPC423 produced anticoagulant effects in human plasma in which it doubled prothrombin time, activated partial thromboplastin time, and Heptest clotting time at 3.1 ± 0.4, 3.1 ± 0.4, and 1.1 ± 0.5 $\mu$M, respectively. In dogs, DPC423 had a good pharmacokinetic profile with an oral bioavailability of 57%, a plasma clearance of 0.24 L/kg/h, and a plasma half-life of 7.5 h. In rabbit and rat models of arteriovenous shunt thrombosis, DPC423 was an effective antithrombotic agent with an $IC_{50}$ of 150 and 470 nM, respectively. The antithrombotic effect of DPC423 is likely to be related to the inhibition of factor Xa but not to the inhibition of thrombin or due to direct inhibition of platelet aggregation. Therefore, based on potency, selectivity, efficacy, and oral bioavailability, DPC423 was selected for clinical development as an oral anticoagulant for the potential treatment of thrombotic disorders. Preliminary human data suggest that DPC423 is orally bioavailable in humans and has a long plasma half-life.