CX-397:
A Novel Antithrombotic Recombinant Hirudin Analog

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ABSTRACT

CX-397 is a recombinant hirudin analog that has the hybrid sequence of rHV1 and rHV3 (i.e., N- and C-terminal halves of rHV1 and rHV3, respectively). CX-397 inhibits the enzymatic activity of thrombin more strongly than its parent hirudins, rHV1 and rHV3. CX-397 does not inhibit serine proteases other than thrombin, and it prevents platelet aggregation induced by thrombin but not that by collagen or ADP, indicating it has a very high specificity for thrombin. CX-397 was effective in all thrombosis models examined, including stasis and thrombin-induced venous thrombosis model in rats, glass surface-activated arterio-venous shunt thrombosis model in rats, ferric chloride-induced arterial thrombosis model in rats, electrolytically-induced arterial thrombosis model in dogs, photochemically-induced arterial thrombosis model in rats, DIC model in rats, and thrombin-induced pulmonary thromboembolism model in mice. In these models, data on the effectiveness and the hemorrhagic risks of CX-397 and the other antithrombotic drugs (i.e., rHV1, argatroban, heparin) indicate that CX-397 is more beneficial than, or at least has benefits comparable to those of directly or indirectly acting thrombin inhibitors. Future clinical studies may elucidate whether CX-397 is truly more beneficial than the other antithrombotic drugs. CX-397 obeys linear pharmacokinetics, both in experimental animals and humans, and is eliminated mainly in the urine without accumulation. No serious toxicity was observed in either animal or phase I clinical studies. A phase II clinical trial is now in progress in Japan.