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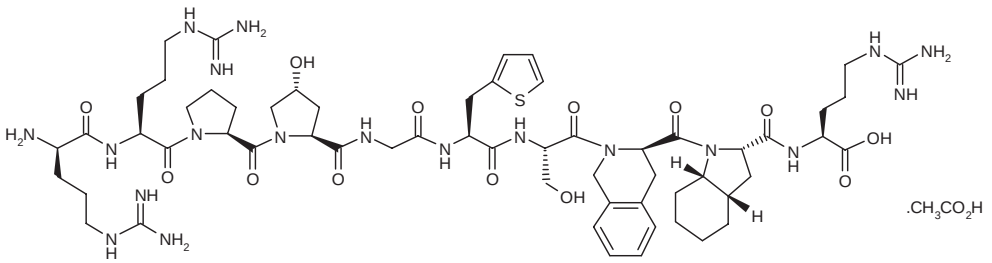
Icatibant Acetate

Rec INN; USAN

Treatment of Hereditary Angioedema
Agent for Liver Cirrhosis
Antiasthmatic Drug
Treatment of Osteoarthritis Pain
Bradykinin B_2 Antagonist

Hoe-140
JE-049

D-Arginyl-L-arginyl-L-prolyl-L-[(4*R*)-4-hydroxyprolyl]-glycyl-L-[3-(2-thienyl)alanyl]-L-seryl-D-(1,2,3,4-tetrahydroisoquinolin-3-ylcarbonyl)-L-[(3a*S*,7a*S*)-octahydroindol-2-ylcarbonyl]-L-arginine acetate



$C_{59}H_{89}N_{19}O_{13}S$

Mol wt: 1304.5242

CAS: 138614-30-9

CAS: 130308-48-4 (as free base)

EN: 166737

Abstract

The endogenous kinin bradykinin (BK) is known to exert both pathophysiological and beneficial physiological effects, the majority of which are transduced through activation of the ubiquitously distributed G-protein-coupled 7-transmembrane BK B_2 receptor subtype. The B_2 receptor mediates BK-stimulated hypotension, vasodilatation, increased vascular permeability and inflammatory pain. Antagonism of this receptor could result in antiinflammatory, antiallergic and antihyperalgesic actions and may represent an attractive approach for the treatment of many disorders involving B_2 receptor activation. Icatibant (Hoe-140, JE-049) is a B_2 antagonist that shows particular promise. It is a second-generation 10-residue peptide antagonist that displays affinity for the B_2 receptor comparable to that of BK itself. Icatibant has exhibited potent antiinflammatory, antiallergic and antihyperalgesic activity *in vitro* and *in vivo* in a number of pathological models and was chosen for further development. It has also shown significant activity clinically as a treatment for hereditary angioedema (HAE), cirrhosis, osteoarthritis pain and asthma, and is undergoing phase III development for HAE as the initial indication.

Synthesis

Icatibant is synthesized by solid-phase technology on Wang resin using conventional Fmoc procedures. Amino acids are coupled using DCC/HOBT and Fmoc-protecting groups are removed by means of piperidine. Cleavage of the peptide from the resin is done by means of TFA in the presence of phenol, thioanisole or ethanedithiol, and finally the peptide is purified by semipreparative high-performance liquid chromatography (HPLC) (1-3).

Background

The endogenous nonapeptide bradykinin (BK) and the decapeptide kallidin constitute the family of human kinins that are formed as part of the kallikrein-kinin system. Kinins exert both pathophysiological and beneficial physiological effects. The numerous effects of kinins are mediated through activation of two distinct, ubiquitously distributed G-protein-coupled 7-transmembrane BK receptor subtypes, B_1 and B_2. B_2 receptors are constitutively expressed and display high affinity for both BK and kallidin. Studies *in vitro* have shown that B_2 receptor-mediated physiological effects are rapidly reversible. This is due to the rapid desensitization and internalization via phosphorylation of Ser and Tyr residues in the *C*-terminal loop seen in this subtype during continuous stimulation.

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In contrast, B_1 receptors are inducible and have high affinity for des-Arg-BK and des-Arg-kallidin, the products of kinin peptidase-mediated metabolism (*i.e.*, carboxypeptidase kininase I cleavage of the *C*-terminal arginine from BK and kallidin). B_1 receptor expression is relatively low or undetectable under normal or resting physiological states. Expression of B_1 is upregulated as a response to inflammation and tissue injury, and the responses mediated by this receptor subtype are more sustained than those mediated by B_2 (4-11).

Kinins exert potent proinflammatory effects and the B_2 receptor is thought to be involved in induction of the majority of these effects, which include hypotension, vasodilatation, increased vascular permeability and inflammatory pain. Numerous actions are attributed to BK and it is associated with both pathophysiological and beneficial states. These effects are in part the result of BK-stimulated plasma extravasation, activation of mast cells, fibroblasts and macrophages, stimulation of sensory neurons and release of nitric oxide (NO), prostaglandins, leukotrienes and cytokines. In theory, antagonism of the B_2 receptor would have antiinflammatory, antiallergic and antihyperalgesic effects and is therefore an attractive approach to the treatment of many disorders involving B_2 receptor activation. These disorders include, among others, angioedema, cirrhosis, hepatorenal syndrome, asthma, rhinitis, brain edema, arthritis, sepsis, colitis, pancreatitis, tissue injury, infection, Alzheimer's disease and lung cancer (4, 5, 12-24).

There are currently two B_2 receptor antagonists under active development: anatibant mesilate and icatibant (Hoe-140, JE-049), the latter showing particular promise. It is a second-generation 10-residue peptide antagonist that displays an affinity for the BK B_2 receptor comparable to BK itself. Icatibant has displayed potent activity *in vitro* in a number of pathological models and was chosen for further development as a treatment for hereditary angioedema (HAE), cirrhosis, asthma, burn-induced edema and osteoarthritis.

Preclinical Pharmacology

Radioligand binding studies performed *in vitro* using [^{3}H]-BK (1.2 nM) and cultured human epidermoid carcinoma A-431 cells expressing B_2 receptors revealed a K_i for icatibant of 2.2 ± 0.7 nM. Icatibant was shown in further experiments using vascular smooth muscle cells isolated from rat aorta to inhibit mitogen-activated protein kinase (MAPK) phosphorylation, the major cell-signaling event induced by BK in this cell type. Treatment with the agent (0.1 nM-10 μM) concentration-dependently inhibited BK (10 nM)-mediated phosphorylation of p42, p44 and p38 MAPK (3).

The BK-antagonist activity of icatibant was demonstrated in various studies and species using several *in vitro* assays. IC_{50} and K_i values of 1.07 and 0.798 nM, respectively, were obtained for icatibant in receptor binding assays using membrane preparations from guinea pig ileum and [^{3}H]-BK. Icatibant concentration-dependently inhibited BK-induced contractions of isolated guinea pig ileum segments (IC_{50} = 11 nM; pA_2 = 8.42), rat uterus strips (IC_{50} = 4.9 nM) and isolated guinea pig pulmonary artery (IC_{50} = 5.4 nM). The agent had no effect on des-Arg-BK-mediated concentrations in rabbit aorta. Icatibant also inhibited BK-induced endothelium-derived relaxing factor (EDRF) release (IC_{50} = 10 nM) and BK-induced increases in cytosolic free calcium (IC_{50} = 1 nM) in cultured porcine aortic endothelial cells, and at a concentration of 100 nM, it completely blocked BK-induced prostacyclin (PGI_2) release from cultured bovine aortic endothelial cells. Icatibant potently but noncompetitively inhibited BK-induced contractions of rabbit jugular vein, with no agonist effects observed (estimated pA_2 = 9.04). In contrast, it was ineffective in the BK B_1 receptor-containing rabbit aorta preparation. Both BK and icatibant induced contractions of sheep femoral artery without endothelium in a similar manner (log EC_{50} = –8.05 ± 0.12 and –7.73 ± 0.10, respectively); these effects were inhibited by the B_2 antagonist NPC-567, but not by a B_1 antagonist, indicating that the effects occur via B_2 receptors. However, in assays using sheep femoral artery with endothelium, icatibant inhibited (pA_2 = 8.38 ± 0.12) the biphasic response (*i.e.*, endothelium-dependent relaxation and contraction) to BK. Icatibant had no agonist effects on the endothelial receptor (25, 26).

The potent and long-lasting B_2-antagonist effects of icatibant were demonstrated in a study examining its effects on BK-induced contractions of isolated human bronchus, pulmonary artery and umbilical artery and vein. Icatibant was a noncompetitive antagonist in human bronchial tissue (pK_B = 8.19 ± 0.30) and a competitive antagonist in human pulmonary artery, umbilical artery and vein (pA_2 = 7.97 ± 0.12, 8.16 ± 0.16 and 8.00 ± 0.11, respectively). The effects of icatibant were selective, since the agent did not alter 5-HT- or histamine-induced contractile responses of umbilical vein. Its actions on both bronchial airways and umbilical veins were reversible but of a long duration, with activity lasting 1 h after washout. Icatibant did not exhibit agonist activity in any of the human tissue studies when tested at concentrations up to 3 μM (27).

Icatibant also exhibited potent BK-antagonist activity *in vivo*. Two studies using murine models of antigen-induced lung inflammation reported differential modulatory activity for icatibant. Treatment of ovalbumin-sensitized C57B1/6 mice with icatibant (100 μg/kg i.p.) 30 min before ovalbumin challenge significantly increased bronchoalveolar lavage fluid (BALF) eosinophils (182%), neutrophils (98%), $CD4^+$ and $CD8^+$ lymphocytes (192% and 236%, respectively), $B220^+$ (840%), $T\gamma\delta^+$ (194%) and $NK1.1^+$ (246%) cells, but had no effect on hyperreactivity or mucus secretion. In contrast, in another study, treatment of ovalbumin-sensitized Balb/c mice with icatibant (1 μg/kg i.v.) 5 min prior to ovalbumin challenge significantly decreased the number of eosinophil (72%) and mononuclear cells (26%) in BALF as compared to controls. Moreover, treatment with icatibant (100 μg/kg i.v. 5 min before challenge) completely blocked the airways

hyperreactivity to carbachol. Icatibant was also shown to inhibit the effects of a B_2-selective agonist in this model (28, 29).

The antagonist effects of icatibant (100 nmol/kg i.v.) on BK (15 nmol/kg i.v. or 1 mM inhaled in 45 breaths)-induced bronchoconstriction and airways microvascular leakage were investigated in anesthetized guinea pigs. Icatibant treatment almost completely abolished i.v. and inhaled BK-induced increases in lung resistance and i.v. BK-induced airways microvascular leakage, but had no effect on inhaled BK-induced tracheal microvascular leakage or on platelet-activating factor (PAF; 3 mM inhaled in 30 breaths)-induced increases in lung resistance and airways microvascular leakage (30).

Icatibant pretreatment (0.1-10 mg/kg s.c. 30 min before ovalbumin challenge) was also shown to significantly and dose-dependently inhibit airways microvascular leakage in ovalbumin-sensitized guinea pigs during the late allergic response (31).

In other studies, icatibant potently and dose-dependently inhibited BK-induced hypotensive responses in the rat. This inhibitory effect was sustained, as 60% inhibition was observed even at 4 h postdosing with 20 nmol/kg s.c. Icatibant also produced long-lasting inhibition of guinea pig bronchoconstriction and markedly inhibited carrageenan-induced inflammatory edema of the rat paw at i.v. doses of 0.1 and 1 mg/kg. When given for 9 days, icatibant (1.5 mg/kg i.p.) significantly inhibited knee joint swelling in a rat model of chronic adjuvant arthritis of the knee; significant decreases in tissue kallikrein levels and increases in synovial tissue plasma kallikrein levels were also seen with icatibant in this model (32, 33).

The inhibitory effects of icatibant on BK-induced vasodilator responses were demonstrated in the mesenteric vascular bed of anesthetized cats *in vivo*. Icatibant significantly attenuated BK-induced decreases in perfusion pressure, with inhibitory effects sustained for more than 3 h. Icatibant had little effect on baseline systemic arterial pressure or mesenteric arterial perfusion pressure and had no influence on acetylcholine- and SNAP-induced vasodilator responses or on norepinephrine-, angiotensin II- or thromboxane mimetic (U-46619)-induced vasoconstrictor responses (34).

Icatibant (0.3 mg/kg s.c. at time 0 and 6 h) effectively normalized avid Na^+ retention in rats with CCl_4-induced liver cirrhosis. Treatment with the agent also reduced hyperactivity of the renin-aldosterone-angiotensin system, but had no effects on CCl_4-induced mild hypotension (21).

Pharmacokinetics and Metabolism

A randomized study involving 24 healthy subjects examined the pharmacokinetics, safety and local tolerability of an s.c. formulation of icatibant as compared to an i.v. infusion. Results indicated good bioavailability (90%) and low variability for s.c. icatibant. C_{max} was achieved at about 30 min after s.c. doses (35).

Safety

Administration of icatibant (0.01 and 0.1 mg/kg i.v.) was well tolerated in conscious dogs; adverse events such as decreases in blood pressure, pain, restlessness and hypersalivation were seen at a dose of 1 mg/kg i.v. and were attributed to residual agonist effects of the agent (32). Icatibant had no effect on renal function in a 2-part study conducted in 14 healthy males. Part I was an ascending-dose, double-blind, placebo-controlled phase in which single 4-h icatibant infusions (0.005-0.8 mg/kg) were evaluated, while part II was crossover, double-blind and placebo-controlled in design and examined renal function on the third day of a 72-h placebo or icatibant infusion. Treatment with the agent was very well tolerated and had no effect on glomerular filtration rate (sinistrin clearance), renal blood flow (*para*-aminohippurate [PAH] clearance) or proximal renal tubular function (lithium and urate clearance). In addition, treatment did not alter Na^+, K^+ or Cl^- excretion, microalbuminuria, urinary volume, hematocrit, supine and orthostatic blood pressure, heart rate, body weight or hormone concentrations (36). The results from this and several of the following studies are summarized in Table I.

Clinical Studies

The safety, pharmacokinetics and pharmacodynamics of i.v. icatibant were examined in 18 healthy males in a 2-part study. The first part of the study was an ascending-dose, double-blind and placebo-controlled phase comparing single 1- and 4-h icatibant infusions (0.005-3.2 mg/kg), while the second part followed a double-blind, crossover design and compared 24- and 1-h infusions (0.5 mg/kg every 8 h). Dose-dependent suppression of BK responses (*i.e.*, 10-15-mmHg blood pressure drop with reflex tachycardia induced by repeated BK i.v. bolus challenges) was observed; icatibant blockade correlated with plasma concentrations and was not associated with hysteresis. A 4-fold increase in BK dose overcame the icatibant block, suggesting competitive inhibition. Icatibant exhibited linear kinetics over the dose range and was distributed and eliminated ($t_{1/2}$ = 1.8 h) rapidly. Doses up to 1.6 mg/kg were well tolerated. However, transient head/trunk flushing, itching and 1 case of orthostatic hypotension were reported with a dose of 3.2 mg/kg (37).

Results from a randomized, double-blind, placebo-controlled, proof-of-concept trial in 8 patients with liver cirrhosis (Child Pugh score of 5-8) and 8 healthy subjects all placed on a standardized diet showed that treatment with icatibant (0.15 mg/kg/day as a constant 3-day infusion) increased electrolyte and water excretion after an Na^+ challenge (2 l NaCl 0.9% i.v. on day 2). Treatment was well tolerated in both patients and healthy subjects. Icatibant did not alter renal function (sinistrin clearance) or cause orthostatic hypotension, reflex tachycardia or Q-T_c prolongation. At 6-12 h following the Na^+ load, treatment with icatibant in patients resulted in significant increases in Na^+ excretion (+6.9 mmol/h), K^+ excretion

(+1.24 mmol/h), urine osmolarity (+18.54 mmol/h) and urine flow (+41.4 ml/h) as compared to placebo; the delayed response to Na^+ load typical of this patient population was unaltered by treatment. In addition, on day 3, body weight was significantly lower (–0.53 kg) in icatibant-treated patients. In contrast, the response to Na^+ load was prompt and similar for both icatibant- and placebo-treated healthy subjects (38).

A multicenter, randomized, double-blind, placebo-controlled, parallel trial in 113 patients with symptomatic osteoarthritis of the knee examined the safety and efficacy of icatibant in relieving pain. Patients were randomized after removal of excessive synovial fluid to a single intra-articular dose of icatibant (90 μg diluted in 1 ml saline) or placebo and were followed for 6 weeks postdosing. Intra-articular administration of the agent was well tolerated. A total of 8 icatibant-treated patients (14.5%) and 6 patients on placebo experienced adverse events. As compared to placebo, responder rates for mean pain reduction of at least 21 visual analog scale (VAS) units in pain at rest and pain during activity were consistently higher during the first week in the group receiving icatibant. While both groups experienced a reduction in patient's global assessment, a greater reduction was observed in the group receiving icatibant. Rescue medication consumption was also reduced in the icatibant group. However, reductions in WOMAC indices were similar for both treatment and placebo groups (39).

The efficacy and tolerability of nebulized icatibant (900 or 3000 μg t.i.d. for 4 weeks followed by a 2-week placebo run-out period) were examined in an early multicenter, randomized, double-blind, placebo-controlled, parallel-group phase II pilot study conducted in 264 adult patients with chronic asthma. Approximately 84-87 patients were evaluable for efficacy in each group. The agent was very well tolerated and treatment resulted in a dose-dependent improvement in investigator-measured objective pulmonary function tests (PFTs), including forced expiratory volume (FEV_1), peak expiratory flow (PEFR), forced vital capacity (FVC) and mid-expiratory flow rate (FEF[25-75%]). A significant 10% improvement in all PFTs was observed after 4 weeks in the higher dose group as compared to placebo. With the lower dose, significant improvements with icatibant treatment were only seen in FEV_1 and FEF(25-75%). Improvements in PFTs were first observed between weeks 1 and 2, increased until the end of treatment and gradually decreased during the placebo run-out phase, suggesting an antiinflammatory effect of the agent. No significant improvement in global symptom scores or in the need for rescue mediation was observed with treatment (40).

The efficacy of icatibant in alleviating symptoms of acute cutaneous, abdominal or combined attacks of HAE was demonstrated in an open-label, proof-of-concept trial evaluating doses of 0.4 mg/kg i.v. over 30 min or 2 h, 0.8 mg/kg i.v. over 30 min and 30 or 45 mg s.c. during 20

Table I: Clinical studies of icatibant (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized Double-blind	Icatibant, 0.005-0.8 mg/kg i.v. infusion over 4 h Icatibant i.v. infusion over 72 h Placebo	14	Icatibant was safe and induced no adverse effects on glomerular filtration rate, renal blood flow or proximal renal tubular function in healthy male volunteers	36
Healthy volunteers	Randomized Double-blind	Icatibant, 0.005-3.2 mg/kg i.v. infusion over 1 h Icatibant, 0.005-3.2 mg/kg i.v. infusion over 4 h Icatibant, 0.15 mg/kg i.v. infusion over 24 h Icatibant, 0.5 mg/kg i.v. infusion over 1 h 1x/8 h x 3	18	Icatibant at doses up to 1.6 mg/kg was well tolerated and effectively blocked bradykinin activity in healthy male volunteers	37
Cirrhosis, Healthy volunteers	Randomized Double-blind	Icatibant, 0.15 mg/kg/d i.v. infusion over 3 d Placebo	16	Icatibant was well tolerated and increased the natriuretic response to a 2-l load of NaCl 0.9% in patients with cirrhosis. The natriuretic response found in healthy volunteers was similar on icatibant and placebo	38
Osteoarthritis	Randomized Double-blind Multicenter	Icatibant, 90 μg i.art. (n=58) Placebo (n=55)	113	A single intra-articular dose of icatibant was well tolerated and effective in reducing pain scores in patients with osteoarthritis of the knee	39
Asthma	Randomized Double-blind Multicenter	Icatibant, 900 μg inhal. t.i.d. x 4 wks Icatibant, 3000 μg inhal. t.i.d. x 4 wks Placebo	300	Icatibant improved pulmonary function tests but not subjective variables in patients with chronic asthma	40
Angioedema, hereditary	Open	Icatibant, 0.4 mg/kg i.v. over 2 h (n=4) Icatibant, 0.4 mg/kg i.v. over 30 min (n=4) Icatibant, 0.8 mg/kg i.v. over 30 min (n=4) Icatibant, 30 mg s.c. (n=4) Icatibant, 45 mg s.c. (n=4)	15	Icatibant was well tolerated and showed efficacy in the treatment of acute attacks of hereditary angioedema	41

acute HAE attacks (10 cutaneous, 3 abdominal and 7 combined) in 15 hospitalized patients. Icatibant was well tolerated. The time to onset of symptom resolution was shortened (1.5, 1.4, 1.1, 0.5 and 0.6 h, respectively) with icatibant as compared to untreated attacks (24-48 h). In addition, duration of attacks was shorter as compared to previous attacks (41).

A multicenter, randomized, double-blind, placebo-controlled, parallel-assessment phase II/III study is recruiting patients diagnosed with HAE type I or II (approximately 56) to examine the safety and efficacy of an s.c. formulation of icatibant. The primary outcome is patient pain relief and secondary outcomes include safety and tolerability (42). In 2004, the FDA granted icatibant orphan drug status for the treatment of edema in severe burn patients, an indication for which the product is undergoing preclinical evaluation, and it received fast track designation for the treatment of HAE. Results from phase III clinical trials and regulatory submissions for marketing approval in the U.S. and Europe for HAE are expected in 2006. The drug is also expected to be developed for refractory ascites in liver cirrhosis and asthma (43).

Sources

Jerini AG (DE) (licensed from Sanofi-Aventis*); licensed to Kos Pharmaceuticals, Inc. for Canada and the U.S.

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* Sanofi-Aventis is conducting phase II studies with icatibant for the treatment of osteoarthritis pain.