CDEC FINAL RECOMMENDATION

ICATIBANT
(Firazyr — Shire Human Genetics Therapies [Canada] Inc.)
Indication: Hereditary Angioedema (Acute Attacks)

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that icatibant be listed for the treatment of acute attacks of hereditary angioedema (HAE) in adults with C1-esterase inhibitor deficiency, if the following clinical criteria and conditions are met:

Clinical Criteria:
- For the treatment of acute non-laryngeal attacks of at least moderate severity, or
- For the treatment of acute laryngeal attacks.

Conditions
- Limited to a single dose for self-administration.
- Prescribed by physicians with experience in the treatment of HAE.
- Reduced price.

Reasons for the Recommendation:

1. One randomized controlled trial (RCT) (FAST-3; N = 98) demonstrated that icatibant was superior to placebo for the treatment of non-laryngeal acute HAE attacks for time to onset of symptom relief, time to onset of primary symptom relief, time to initial symptom improvement, and time to almost complete symptom relief.
2. There was insufficient evidence from the two included RCTs (FAST-1 and FAST-3) to evaluate the comparative efficacy of icatibant for the treatment of laryngeal acute HAE attacks; however, patient group input and clinical expertise indicated that there is an unmet need for the treatment of these life-threatening events.
3. At the submitted price ($[redacted] per 30 mg syringe) and when only drug costs per acute HAE attack are considered, treatment with icatibant is more costly than treatment with Berinert (a plasma-derived C1-esterase inhibitor) for a patient weighing > 50 kg and ≤ 75 kg (3 vials for $2,169) and less costly than treatment with Berinert for a patient weighing > 75 kg and ≤ 100 kg (4 vials for $2,892).

Of Note:
CDEC noted that icatibant is not indicated for use as a prophylaxis against HAE attacks.

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Background:
Icatibant is indicated for the treatment of acute attacks of HAE in adults with C1-esterase inhibitor deficiency. It is available as 3 mL (10 mg/mL) single dose, single use, pre-filled syringes. Icatibant is administered by slow subcutaneous injection in the abdominal area at a recommended dose of 30 mg, with additional doses being administered at intervals of at least 6 hours if response is inadequate or if symptoms recur, with no more than 3 doses administered within a 24-hour period.

Summary of CDEC Considerations
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of icatibant, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to individuals living with HAE.

Patient Input Information
The following is a summary of key information provided by one patient group, consisting of patients and caregivers, which responded to the CDR call for patient input:

- Acute attacks of HAE are unpredictable with varied frequency and severity, which then have an impact on many facets of day-to-day living and diminish the quality of life of patients and their caregivers.
- Berinert is a commonly used treatment that has allowed some patients to resume a near-normal life. However, the intravenous administration and the need for reconstitution were cited as disadvantages of Berinert that could potentially delay its administration. Other treatments such as danazol have been associated with negative side effects.
- Patient groups noted that the subcutaneous administration of icatibant provides a greater sense of control for patients with HAE and allows them to travel with more ease and confidence.

Clinical Trials
The CDR systematic review included two double-blind, placebo-controlled RCTs. FAST-3 (N = 98) and FAST-1 (N = 64) evaluated the efficacy and safety of a single dose of icatibant 30 mg compared with placebo in patients with type I or type II HAE who experienced an acute attack in the cutaneous, abdominal, or laryngeal areas. Efficacy assessments were performed up to 120 hours after the onset of symptoms, and safety assessments were performed up to 14 days after the onset of symptoms unless a new attack occurred within those 14 days. Patients presenting with laryngeal symptoms were administered open-label icatibant in FAST-1 and initially in FAST-3, until a protocol amendment allowed for the randomization of patients presenting with mild to moderate laryngeal symptoms. Of the patients with a laryngeal attack who were randomized in FAST-3, three were randomized to the icatibant group and two were randomized to the placebo group. However, the two patients in the placebo group also received icatibant during their attack, precluding any meaningful comparison. Subsequent attacks were treated with open-label icatibant 30 mg with a maximum of three doses, administered at least six hours apart, in an open-label extension phase.

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

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- Time to onset of symptom relief (TOSR) — defined as the time from study drug administration to the earliest of three consecutive non-missing measurements of documented symptom relief. In FAST-3, symptom relief was defined as a ≥ 50% reduction in the pre-treatment composite visual analogue scale (VAS) score.
- Time to onset of primary symptom relief (TOSR-P) — defined as the time from study drug administration to the earliest of three consecutive non-missing measurements of documented symptom relief in the primary symptom (i.e., skin swelling or skin pain for cutaneous attacks and abdominal pain for abdominal attacks).
  - Symptom relief was defined as any value to the right and below a line with the equation Y = 6/7X – 16 (X = pre-treatment VAS; Y = post-treatment VAS), with X ≥ 30 mm.
- Time to almost complete symptom relief (TACSR) — defined as the time from study drug administration to the time of the first of three consecutive measures at which all VAS scores were < 10 mm.
- Time to initial symptom improvement (TISI) — defined as the time from study drug administration to the time at which the patient or investigator first perceived initial improvement of symptoms.
- Use of rescue medication — defined as any medication which, in the opinion of the investigator, was immediately necessary to alleviate acute symptoms resulting from the current HAE attack.
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

TOSR was the primary end point of FAST-3 and TOSR-P was the primary end point of FAST-1.

Efficacy

Non-laryngeal attacks

- In FAST-3, the median TOSR was statistically significantly shorter in the icatibant group compared with the placebo group (2.0 hours versus 19.8 hours, *P* < 0.001) with a hazard ratio (HR) of 3.17 (95% confidence interval [CI], 1.97 to 5.11).
- In FAST-3, the median TOSR-P was statistically significantly less in the icatibant group compared with the placebo group (1.5 hours versus 18.5 hours, *P* < 0.001; HR 2.76 [95% CI, 1.73 to 4.39]). In FAST-1, the median TOSR-P was 2.5 hours in the icatibant group and 4.6 hours in the placebo group (HR 1.09 [95% CI, 0.57 to 2.07]; *P* = 0.142).
- In FAST-3, the median TACSR was statistically significantly shorter in the icatibant group compared with the placebo group (8.0 hours versus 36.0 hours, *P* = 0.012). In FAST-1, the median TACSR was shorter in the icatibant group compared with the placebo group (8.5 hours versus 23.3 hours), but this difference was not statistically significant (*P* = 0.069).
- In FAST-3, the median TISI as assessed by the patient was statistically significantly shorter in the icatibant group compared with the placebo group (0.8 hours versus 3.5 hours, *P* < 0.001). The median TISI as assessed by the investigator was also statistically significantly shorter in the icatibant group compared with the placebo group (0.8 hours versus 3.4 hours, *P* < 0.001). In FAST-1, the median TISI as assessed by the patient was statistically significantly shorter in the icatibant group compared with the placebo group (0.8 hours versus 16.9 hours, *P* < 0.001). The median TISI as assessed by the investigator was 6.5 hours in the icatibant group and 14.0 hours in the placebo group (*P* = 0.240).
- In FAST-3, more patients required the use of rescue medication in the placebo group compared with the icatibant group (40.0% versus 7.0%) up to five days post-treatment. In FAST-1, more patients required the use of rescue medication in the placebo group

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compared with the icatibant group (51.7% versus 22.2%) during the double-blind phase.

Laryngeal attacks

In FAST-3, the two patients in the placebo group who experienced a laryngeal attack received icatibant. One patient developed laryngeal symptoms that investigators considered severe enough to warrant treatment with open-label icatibant. The other patient was treated with icatibant as a rescue medication 3.4 hours after receiving the original placebo treatment. Small sample numbers precluded a meaningful statistical comparison.

- The median TOSR was 2.5 hours in the icatibant group and 3.2 hours in the placebo group.
- The median TOSR-P was 2.5 hours in the icatibant group and 2.7 hours in the placebo group.

Subsequent attacks

- In FAST-3, the first 5 icatibant-treated attacks had similar median TOSR (range: 1.9 to 2.0 hours) and TOSR-P (range: 1.5 to 2.0 hours). In FAST-1, the first 10 icatibant-treated attacks had similar median TOSR-P (range: 1.2 to 2.0 hours).
- In FAST-3, 435 attacks were treated in the open-label extension: 19 (4.4%) required a second icatibant injection and one attack required a third injection. In FAST-1, 340 attacks were treated in the open-label extension: 36 (10.6%) required a second icatibant injection and 4 (1.2%) required a third icatibant injection.

Harms (Safety and Tolerability)

- The proportion of patients who experienced at least one adverse event was greater in the placebo group compared with the icatibant group in both FAST-3 (54.3% versus 41.3%) and FAST-1 (62.1% versus 40.7%). The most commonly reported adverse events included gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, and the worsening of a current HAE attack or occurrence of a new attack.
- No serious adverse events were reported within the icatibant groups of both FAST-1 and FAST-3. In FAST-3, five patients (10.9%) reported a serious adverse event in the placebo group.
- In FAST-3, one patient in the placebo group discontinued from the study due to an adverse event. In FAST-1, no patients discontinued from the study due to an adverse event.
- In FAST-3, 100% of patients experienced an injection-site reaction in the icatibant group compared with 58.7% of patients in the placebo group. In FAST-1, 96.3% of patients in the icatibant group experienced an injection-site reaction compared with 27.6% of patients in the placebo group. Symptoms at the injection-site included erythema, swelling, burning, itching, warm sensation, and skin pain.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing icatibant with Berinert, which is available through the Canadian Blood Services (CBS) program. The assumption of similar efficacy was based on the results of a manufacturer-funded indirect treatment comparison (ITC). The analysis was conducted from the Canadian public-payer perspective. Unit cost for Berinert was estimated from the CBS Annual Report. The time horizon for the analysis was the duration of one attack of HAE, estimated at 96 hours, which was expected to encompass the onset of symptom relief (primary end point of the majority of relevant trials). In the manufacturer's base case, it was assumed that one subcutaneous injection of icatibant

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would be required per attack. Berinert dosing was based on patient weight distribution in the FAST-1 and FAST-2 trials. When only drug costs were considered, the manufacturer suggested that icatibant is more expensive than Berinert by $[redacted] per HAE attack ($[redacted] versus $2,569). Due to its more convenient route of administration (subcutaneous for icatibant versus intravenous for Berinert), the manufacturer assumed that self-administration at home would occur more frequently with icatibant than Berinert, and that Berinert would only be administered in a hospital setting. Consequently, costs of training, administration, monitoring, and supportive care are assumed to be lower with icatibant than Berinert ($132 versus $515). The manufacturer reported that the average total cost of icatibant per HAE attack ($[redacted]) is less than that of Berinert ($3,084), resulting in expected cost savings of $[redacted] per HAE attack.

CDR identified the following key limitations with the manufacturer's pharmacoeconomic evaluation:

- The ITC was limited by significant heterogeneity between the included clinical trials, which generates uncertainty regarding the comparative effectiveness of icatibant and Berinert.
- The manufacturer did not consider weight variation in the determination of the number of vials of Berinert required per HAE attack.
- Although icatibant is likely to be associated with lower costs of training, administration, monitoring, and supportive care compared with Berinert, based on clinical expert feedback, the manufacturer may have underestimated the percentage of patients self-administrating Berinert.

Given the uncertainty with drug use and actual administration costs, the cost impact of icatibant could range from cost savings of $[redacted] per attack (in patients weighing > 75 kg and ≤ 100 kg) to an additional cost of $[redacted] per attack (in patients weighing > 50 kg and ≤ 75 kg), when compared with Berinert, assuming only one injection of icatibant is required.

When only drug costs are considered, if only one injection of icatibant ($[redacted] per 30 mg syringe) is required, the cost would be similar to Berinert ($2,169 per attack per patient weighing between > 50 and ≤ 75 kg or $2,892 per attack per patient weighing > 75 and ≤ 100 kg). Where more than one injection of icatibant is required ($[redacted] to $[redacted] per attack for two or three doses), it is more expensive than Berinert.

Other Discussion Points:

CDEC noted the following:

- For the majority of HAE attacks reported in the clinical trials, a single dose of icatibant was sufficient to alleviate symptoms (e.g., approximately 95% of the 435 attacks in FAST-3 were treated with a single dosage of icatibant). In addition, it was noted by the clinical expert that patients who fail to respond to a single dose of icatibant would likely benefit from receiving medical attention.
- The clinical expert consulted during the review advised that many patients with HAE are treated with low-dose danazol for prophylaxis against HAE attacks; however, it is not indicated for this clinical use in Canada.
- Icatibant is indicated for the treatment of acute attacks of HAE in adults with C1-esterase inhibitor deficiency; however, it is possible that it could be used as a prophylaxis against

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HAE attacks or used in children with HAE, both of which fall outside of the approved indication.
- FAST-1 and FAST-3 did not evaluate the self-administration of icatibant; however, a non-randomized, open-label study (*Evaluation of the Safety of Self-Administration with Icatibant*; N = 97) demonstrated a TOSR with self-administration that was similar to the TOSR reported in FAST-3.
- There were significant limitations with the design of FAST-1 that restricted the ability of CDEC to make inferences regarding the efficacy of icatibant from this RCT. Issues of particular importance included: the increased use of rescue medication among the placebo group compared with the icatibant group, the lack of statistical power for the primary end point, and the selection of a primary end point that may not be representative of all symptoms experienced during an attack (i.e., TOSR-P).
- Nearly all patients in the icatibant groups (96.3% and 100%) experienced injection-site reactions compared with a much lower proportion of patients in the placebo group (27.6% and 58.7%). This may have resulted in the awareness of treatment assignment for both patients and investigators.

Research Gaps:
- Evidence for the use of icatibant in the treatment of laryngeal acute HAE attacks is limited.
- There are no direct comparisons of icatibant against Berinert for the treatment of acute HAE attacks.
- There are no data evaluating the efficacy and safety of icatibant in children with HAE.

CDEC Members:

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November 19, 2014 Meeting

Regrets:

None

Conflicts of Interest:

None

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