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Implementation Advice for Icatibant

> Indication: For the treatment of acute attacks of hereditary angioedema with normal C1-inhibitor

Introduction

Disease Background

Hereditary angioedema (HAE) is a rare disease characterized by unpredictable attacks of painful swelling typically affecting the extremities, skin, upper respiratory tract, oropharynx, and gastrointestinal tract.[1] Attacks of HAE are unpredictable and potentially life-threatening when they affect the airway; mortality due to laryngeal angioedema is well recognized.[1] HAE is categorized into 3 different types: HAE with deficient C1-inhibitor levels (HAE type I), HAE with dysfunctional C1-inhibitor (HAE type II), and HAE with normal C1-inhibitor function (HAE nC1-INH), sometimes referred to as HAE type III. HAE type I is the most prevalent, representing approximately 85% of cases, and results from low antigenic and functional levels of C1-INH. HAE type II accounts for approximately 15% of cases and is associated with a normal C1-inhibitor protein concentration but impaired C1-inhibitor function.[1] HAE types I and II are well-characterized forms of bradykinin-mediated angioedema; the swelling in HAE types I and II is linked to impaired regulation of bradykinin, a powerful vasodilator that increases capillary permeability, constricts smooth muscle, and stimulates pain receptors. HAE with normal C1-INH is much less prevalent than HAE type I and II, and while it presents similarly to HAE type I and II, its pathogenesis has not been clearly defined. HAE nC1-INH is more difficult to identify than HAE type I and II because of the lack of accessible and genetic testing. The presence of HAE nC1-INH was first reported in Canada and Germany by Binkley and Bork respectively in 2000.[2,3] As of 2018, there were more than 200 identified families with the disease worldwide; however, the true prevalence of HAE nC1-INH remains unknown.[1]

Current Management

Angioedema of all causes is often chronic, may be life-threatening due to airway swelling, is often difficult to treat, and may lack clear etiology. With no approved treatments for HAE nC1-INH, the treatment strategy is often a “trial of therapy,” and responses may be incomplete. Effective management of HAE is targeted at either preventing or treating attacks. Long-term prophylaxis refers to ongoing treatment of HAE aimed at minimizing the overall number, frequency, and/or severity of attacks. Acute treatment of HAE attacks (also referred to as “on-demand therapy”) aims to minimize the severity and duration of HAE attacks, including potentially fatal upper airway edema.[1]

The clinical experts consulted indicated that treating angioedema attacks early using safe, effective, easy-to-administer, readily available medication; improving quality of life; and in life-threatening cases (e.g., laryngeal attacks), saving life with prompt treatment of acute attacks are the most important goals of acute treatment for patients with HAE. Icatibant (SC), a selective bradykinin B2 receptor antagonist, is approved by Health Canada for HAE types I and II and is not approved for the treatment of other types of bradykinin-mediated angioedema. Berinert (IV), a C1 esterase inhibitor, is a purified concentrate of C1 esterase inhibitor derived from human plasma (supplied by Canadian Blood Services) and may be used to treat acute attacks of HAE. The International/Canadian Hereditary Angioedema Guideline recommends plasma-derived C1-INH (e.g., Berinert) and icatibant as effective therapies for acute treatment of attacks in patients with HAE nC1-INH.[1] The clinical experts noted that icatibant (SC) and Berinert (IV) are considered first-line treatments for acute HAE attacks and should both be available, particularly in emergency situations. Icatibant is a bradykinin

antagonist and, therefore, works by a different mechanism than Berinert to treat an acute angioedema attack and, since it is a subcutaneous autoinjector, it may be easier to self-administer. Use of an autoinjector will allow patients to treat an angioedema attack early and more easily, thereby reducing disease and treatment burden and improving quality of life.

Input

This section is the summary of the input provided by patient and clinician groups as well as industry. The full input is available in a separate document.

Patient Group Input

HAE Canada provided input, which included results of a survey conducted in April 2024 and a national survey conducted in 2020, as well as patient commentary specific to the use of icatibant.

The input noted that patients with HAE nC1-INH experience the same burden of disease as those with type I or II HAE, with the impacts of the disease going well beyond its immediate debilitating and life-threatening manifestations. Many of the surveyed patients reported having regular fear of unpredictable attacks and experiencing generalized anxiety and stress along with many other emotional and cognitive impacts. HAE also interferes with patients' daily activities and has a substantial negative impact on many patients' ability to work, travel, and engage in daily activities. The input noted that patients with HAE nC1-INH have an urgent need for on-demand treatments that can better control their attacks, enhance their quality of life, and reduce the financial burden and impacts on an already stressed health care system. With respect to the currently available treatments for patients with HAE nC1-INH, concerning Berinert IV, patients reported that during an attack, they may not be able to perform all the necessary steps or have the required precision to administer IV treatment and that a treatment that is easy to administer is a critical unmet need. Patients also reported needing a faster-acting treatment during the onset of an attack, particularly when attacks are life-threating laryngeal attacks. Icatibant is the only approved alternative treatment to plasma-derived C1-INH for acute attacks available for patients with HAE in Canada that meet these criteria. Treatment choice is essential because of the varied response to and efficacy of treatments among patients. The input suggested that access to, and reimbursement for, icatibant for patients with HAE nC1-INH can be cost-effective. These patients reported that effective rescue treatments frequently obviate the need for emergency department visits, which reduces the burden on the patient, their families, and the health care system. Patients who have access to icatibant have reported that the treatment is life-saving.

Clinician Group Input

The Canadian Hereditary Angioedema Network (CHAEN) provided input. This clinician group cited the International/Canadian Hereditary Angioedema Guideline recommendations for the treatment of acute attacks in patients with HAE nC1-INH and indicated that the use of icatibant for the treatment of acute attacks can be generalized to all patients with HAE nC1-INH. They noted that patients with HAE nC1-INH have an urgent need for treatments that better control acute attacks and that all patients should be equipped

to treat angioedema attacks. Recognizing the burden to patients associated with all types of HAE, including the ever-present risk of experiencing a life-threatening laryngeal attack, reducing the treatment burden of HAE acute treatment is an important consideration. As such, some patients may prefer a safe and effective subcutaneously administered treatment instead of the current intravenously administered treatment. The clinician group indicated that because icatibant is administered subcutaneously, it may be associated with a lower treatment burden compared to injectable prophylactics such as plasma-derived C1 inhibitors for some patients and may also provide patients with a faster-acting treatment, which is particularly important during life-threating laryngeal attacks. In addition, patients who can use icatibant would not need to use blood products.

Industry Input

Takeda, the manufacturer of icatibant, submitted input, which included background on HAE nC1-INH and unmet needs. The input cited the 2019 International/Canadian Hereditary Angioedema Guideline, led by CHAEN, which provides a strong recommendation for the treatment of HAE nC1-INH with icatibant as an effective therapy for the acute treatment of attacks in patients with HAE nC1-INH. The input also included a summary of the studies on icatibant in the treatment of patients with HAE nC1-INH and the expected costs of icatibant and comparators including Berinert.

Clinical Evidence

A systematic literature search was used to identify evidence regarding the efficacy and safety of icatibant for treating acute episodes of HAE nC1-INH. Five studies were identified. There were no clinical trials. Four studies were retrospective observational studies/case series; 1 study was a noncomparative prospective study. The evidence is largely descriptive and does not include a between-group statistical comparison of the efficacy of icatibant. There were no studies comparing icatibant to Berinert for treating acute attacks in patients with HAE nC1-INH. Following is a summary of the identified evidence.

The Icatibant Outcome Survey Registry Study — Icatibant Use in Brazil (Grumach et al., 2022)[4]

This was a retrospective observational study reporting data from the Icatibant Outcome Survey (IOS) registry, which is open to all patients with HAE who have received at least 1 dose of icatibant. The study reported data on a total of 42 patients from Brazil (HAE type I or II, n = 26; HAE nC1-INH, n = 16) enrolled in the IOS registry. A total of 165 icatibant-treated attacks were reported in 18 patients with HAE type I or II, and 63 icatibant-treated attacks were reported in 10 patients with HAE nC1-INH. One dose of icatibant was used for most attacks (95.7% in patients with HAE type I or II; 96.7% in those with HAE nC1-INH). Treatment outcome data were available for up to 142 attacks in 17 patients with HAE type I or II, and for up to 52 attacks in 8 patients with HAE nC1-INH. The mean (SD) time from attack onset to resolution was shorter for patients with HAE nC1-INH compared to patients with HAE type I or II (9.8 [18.7] hours versus 19.6 [24.0] hours; P = 0.0174).

A total of 83 events in 42 patients were reported, most of which were rated as mild (66.3%) or moderate (13.3%) in severity; none were reported to be life-threatening or fatal. The most commonly occurring icatibant-related adverse event was injection site erythema, affecting 34.6% of patients with HAE type I or II and 18.8% of patients with HAE nC1-INH.

The IOS Registry Study — Icatibant Use in France (Bouillet et al., 2017)[5]

This was a retrospective observational study reporting data from the IOS registry reporting data from France. Twenty-two patients with HAE nC1-INH were compared to patients with C1-INH-deficient HAE (153 patients with HAE type I and 7 patients with HAE type II). The study reported that icatibant was effective in both groups, though the median time to resolution of attack was significantly longer in the HAE nC1-INH group (20.0 hours, 37 attacks) versus the HAE type I group (14.0 hours, 67 attacks). Icatibant was self-administered for 96.1% of attacks in patients with HAE-nC1 INH and 75.8% in patients with HAE type I. Eleven patients reported 44 adverse events. The study reported no serious adverse side effects related to icatibant.

Manitoba Cohort of Patients With HAE nC1-INH (McKibbin et al., 2019)[6]

This was a retrospective review of patients with angioedema who were dispensed icatibant while being treated at Winnipeg Regional Health Authority hospitals. The review reported on the treatment of 6 patients with a confirmed HAE-nC1INH diagnosis from a retrospective chart review of 418 patients diagnosed with angioedema. Four of the 6 patients used icatibant to treat acute angioedema attacks, and all 4 patients demonstrated a response. Three of the 4 patients used icatibant and demonstrated a response after all other available therapies had failed. Two patients experienced life-threatening symptoms that were only resolved with the use of icatibant.

A Study of Patients With HAE With the c.988A > G (p.Lys330Glu) Variant in the Plasminogen Gene in Germany (Bork et al., 2020)[7]

This was an observational retrospective study of 111 patients with nC1-INH HAE and the c.988A > G (p.Lys330Glu; p.K330E) variant in the plasminogen gene (HAE-PLG). Thirteen patients were treated with icatibant for 201 acute swelling attacks of the face, abdomen, and tongue. The mean duration of the treated attacks (mean 4.3 hours; SD = 2.6 hours) was shorter than that of the previous 149 untreated attacks (mean 44.7 hours; SD = 28.6 hours, $P < 0.0001$). Twelve patients were treated with plasma-derived C1-INH for 74 acute swelling attacks. The duration of the treated attacks (mean 31.5 hours; SD 18.6 hours) was shorter than that of the previous 129 untreated attacks in the same patients (mean 48.2 hours; SD 32.5 hours, $P < 0.0001$). Icatibant shortened the duration of swelling attacks by 88%.

Safety and Efficacy of Icatibant Self-Administration for Acute HAE in France (Boccon-Gibod et al., 2012)[8]

This was a prospective noncomparative study of adult patients with HAE (types I, II, or III) in France who had previously received health care professional–administered icatibant for at least 1 acute attack and were trained to self-administer icatibant. Fifteen patients self-administered icatibant for 55 acute attacks. Icatibant

was reported to be generally effective. The first symptom improvement occurred within 5 minutes to 2 hours (HAE type I; n = 17) and 8 minutes to 1 hour (HAE type III; n = 9) for abdominal attacks, and within 5 minutes to 30 minutes (HAE type I; n = 4) and 10 minutes to 12 hours (HAE type III; n = 6) for laryngeal attacks. Complete symptom resolution occurred within 15 minutes to 19 hours (HAE type I; n = 8) and 15 minutes to 48 hours (HAE type III; n = 9) for abdominal attacks, and within 5 hours to 48 hours (HAE type I; n = 3) and 8 hours to 48 hours (HAE type III; n = 5) for laryngeal attacks. None of the patients required emergency hospitalization. The majority of patients (89.4%) reported that carrying syringes of icatibant with them gave them greater confidence in their ability to manage their condition.

Implementation Advice

Consultation Process

The clinical expert panel comprised a panel chair and 5 specialists with expertise in the diagnosis and management of HAE. A consensus-based approach was used, and input was captured using a questionnaire and a panel meeting. Two clinical experts were unable to attend the panel meeting but provided their expertise before and following the meeting. The advice in this report is based on the experience and expertise of the implementation advice panel members.

Clinical Expert Panel Input

Table 1: Questions for Panel Discussion

Questions	Responses
Place in therapy	
Based on the available evidence and your clinical experience, do you consider the treatment approach for the management of acute attacks similar for patients with HAE types I and II and those with HAE nC1-INH? (That is, can these patients be treated similarly?)	All 5 panellists indicated that the approach to acute treatment is similar for patients with HAE with C1-INH deficiency and those with HAE with normal C1-INH. Icatibant and C1 inhibitor concentrate are considered first-line treatments for acute attacks both in patients with HAE with C1 inhibitor deficiency (types I and II) and in patients with HAE with normal C1 inhibitor (type III).
Would you consider the clinical evidence of the efficacy and safety of Berinert and icatibant comparable for treating acute attacks in patients with HAE (all types)? Additionally, how would you compare their efficacy and safety, specifically for patients with HAE nC1-INH?	The panellists indicated that the clinical evidence for the efficacy and safety of Berinert and icatibant for patients with HAE with normal C1-INH is limited and mostly anecdotal in nature due to the rarity of this disease. There are no RCTs (with icatibant or Berinert) in this population and no head-to-head studies comparing them. Several small observational studies and case reports have shown both efficacy and lack of efficacy for both Berinert and icatibant in patients with HAE nC1-INH. In case series in which patients have received both, some respond to icatibant but not to Berinert. It was noted that in patients with HAE with C1-INH deficiency, both Berinert and icatibant have strong data suggesting that

Questions	Responses
	they are effective and safe in treating acute attacks and that both are considered first-line treatment for acute attacks. One panellist further noted that, based on international consensus, the efficacy and safety of Berinert and icatibant is thought to be comparable for all HAE types.
Does icatibant offer nonclinical benefits or advantages over the currently available treatment option (i.e., Berinert) for patients, caregivers, or clinicians?	The panellists noted that icatibant offers several potential benefits. Most importantly, icatibant is a subcutaneous medication and is easier than IV treatment (Berinert) both for self-administration and caregiver administration, especially in children for which IV administration of Berinert is difficult for caregivers. Icatibant is also considered a more portable medication (e.g., more easily transported for patients that are frequent travellers) compared to Berinert, which offers patients a better quality of life. Ease of use can allow patients to self-inject at home, which can lower the burden of disease. It can reduce travel, increase patient autonomy, and empower patients in managing their condition. The speed of (self-) administration was also noted as critical, given that delay in obtaining IV access can be fatal. They highlighted that icatibant is not a blood product like Berinert, and supply is not dependent on global plasma availability. According to the panellists, it is more widely accessible, especially for rural patients who do not have convenient access to a blood bank. In addition, for patients who cannot or do not wish to receive a blood product (i.e., Berinert) due to religious (e.g., Jehovah's Witnesses) or other reasons, icatibant is the only treatment option for acute attacks. It was also noted that there is no risk of bloodborne infections with icatibant. Icatibant may also carry a lower risk of allergic reactions compared to blood-derived products, which can be particularly advantageous for patients with a history of allergies or adverse reactions to blood products.
Does the current available evidence for the use of icatibant in patients with HAE nC1-INH present any challenges for clinical decision-making (e.g., lack of evidence to provide guidance on optimal dose, duration of treatment, and so forth)?	The panellists acknowledged that the lack of evidence in this setting presents some challenges. Diagnosis is also complex, which translates into challenges for patients because treatments are hard to access without a diagnosis. With regard to the lack of evidence to guide optimal dosing and duration of treatment, it was noted that the dosing for icatibant is standardized and is the same as in patients with HAE with C1-INH deficiency (standard dose of 30 mg for adults). Frequency of treatment is also standardized and would be the same as in patients with HAE with C1 inhibitor deficiency (q.6.h. dosing with a maximum dose of 90 mg per 24 hours in adults). It was further noted that there is no clinical feature or lab marker (except for a small percentage of cases in which a gene is identified) that can predict response to icatibant.
How would you consider nonclinical benefits or burdens (e.g., accessibility, mode of administration, impact on patient autonomy, and so forth) alongside clinical risk-benefit when deciding whether to prescribe icatibant?	The panellists emphasized the importance of access to timely treatment to expedite recovery. They noted that the mode of administration is an important factor in treatment decisions. A treatment that is easy and quick to administer and readily

Questions	Responses
	accessible (not reliant on the hospital emergency department) will reduce the disease burden and is an important consideration when deciding whether to prescribe icatibant. The most common adverse reaction is injection site reaction. In the treatment of all HAE attacks, the potential benefit far outweighs any risks.
If both Berinert and icatibant were available for treating acute attacks in patients with HAE nC1-INH, what would be the treatment of choice, given the current data regarding the efficacy and safety of these agents (disregarding the mode of administration)?	The panellists indicated that all patients with HAE should have access to both Berinert and icatibant to treat acute attacks; they are both considered first-line treatments for all patients. Some patients have very severe/life-threatening attacks and may not respond fully to 1 initial dose of either Berinert or icatibant, and as such, the other should always be available to treat the attack. For certain patients, icatibant would likely be the treatment of choice for acute attacks. One panellist emphasized that mode of administration is an important part of decision-making and cannot be disregarded. Given that HAE is a lifelong condition, chronic venous access is an important concern. Lack of access will require a central line, resulting in a lifelong need for line replacements and risk of complications (infection — including sepsis, thrombi, and emboli). Therefore, the mode of administration is important in decision-making, including for the initial choice for acute treatment.
Are there groups of patients who currently do not have access to Berinert? What is the impact of not accessing Berinert when required? Does the availability of icatibant help address any inequities in access to therapy for patients with HAE nC1-INH?	The panellists indicated that there is inequity in access to Berinert for several groups of patients. Patients in remote and some rural areas of Canada have difficulty obtaining Berinert because they are far from a facility accredited to carry Berinert. Even patients who are proficient at starting IVs may not be able to do so during an attack. Inaccessibility to rural ERs in these cases will mean inaccessibility to Berinert infusion. In addition, other groups of patients who cannot use blood products (e.g., Jehovah's Witnesses) can be considered as lacking access to Berinert. Other patients (or caregivers) have difficulty self-administering Berinert and thus do not have timely access to it. The impact of not having access to Berinert can be significant, leading to unmanaged angioedema attacks, increased morbidity and mortality (e.g., potential for untreated laryngeal attack), and reduced quality of life. There is also inequity in access to icatibant because icatibant is available as first-line treatment for acute attacks in patients with HAE types I and II. Availability of icatibant addresses this issue for types I and II but not patients with normal C1-INH. The availability of icatibant would help address the inequities in access to therapy in these patients because it can be self-administered and may be more readily available in various settings, allowing patients to manage their symptoms more effectively without needing specialized medical facilities.

Questions	Responses
Should there be a defined treatment sequence for HAE nC1-INH? Should icatibant be considered as a first-line or second-line option for treating acute attacks, and what factors can help determine first-line vs. second-line therapy (i.e., as compared to Berinert)?	The panellists reiterated that patients should have access to both icatibant and Berinert as first-line treatments for acute attacks in patients with HAE nC1-INH because they are both considered effective in this setting. Individual patient circumstances and clinical judgment should guide the treatment strategy. Factors influencing the choice between first-line and second-line therapy include the severity of attacks, patient preferences, history of treatment response, accessibility, and potential side effects, which should be determined after shared decision-making. In pregnant patients and children younger than 2 years, C1 inhibitor replacement may be trialled before icatibant. The panellists emphasized that access to both icatibant and Berinert is crucial because treatment with both may be required for very severe attacks.
Patient characteristics	
Are there subgroups of patients who would benefit more from the use of icatibant (other than rural patients who have difficulty accessing Berinert) for the treatment of acute attacks in HAE nC1-INH? Are there patients with certain disease characteristics (e.g., laryngeal vs. nonlaryngeal symptoms; diagnosed vs. idiopathic) who would benefit more from treatment with icatibant?	The panellists noted that all patients should have access to both icatibant and Berinert. The panellists acknowledged that certain subgroups of patients may benefit more from icatibant for treating acute attacks of HAE nC1-INH. Patients experiencing laryngeal symptoms could benefit from icatibant's rapid action. Those with idiopathic HAE or those who have not responded well to traditional therapies may find icatibant more effective due to its different mechanism of action. Patients with frequent attacks may also prefer icatibant for its self-administration option, enabling quicker relief and better management of attacks. Those with ethical objections to the use of blood products would benefit from the use of icatibant. In addition, patients with certain pathogenic variants (e.g., PLG) would likely benefit more from icatibant due to the mechanism of action. However, they noted that there is no marker that will reliably and consistently predict which patients will respond. A trial of icatibant would identify those who respond. All patients with HAE have a risk of laryngeal attack that requires rapid treatment. Therefore, all patients with HAE would benefit from access to icatibant that can be self-administered, enabling quicker relief and better management of attacks.

HAE = hereditary angioedema; PLG = plasminogen gene; q.6.h. = every 6 hours; RCT = randomized controlled trial; vs. = versus.

Panel Discussion

This section aims to synthesize the deliberations of the expert panel that are related to the implementation advice for icatibant in the treatment of acute attacks of HAE with normal C1-INH.

Table 2: Summary of Implementation Advice for Treatment With Icatibant for Acute Attacks of HAE With Normal C1-INH

Criteria	Implementation advice
Initiation	
Patient population eligibility: What group of patients should be eligible for icatibant treatment?	All patients who have been diagnosed with HAE with normal C1 inhibitor would benefit from icatibant. Initiation should be based on a confirmed diagnosis of HAE with symptoms consistent with angioedema, including all the following: history of observed documented episodic HAE, normal C1 level or function, and a lack of response to mast cell treatments (e.g., antihistamines, corticosteroids, epinephrine). **Discussion points:** The panel discussed family history and genetic testing as diagnostic components and discussed their limitations. They noted that although a positive genetic test and family history are useful to confirm a diagnosis of HAE, the absence of these elements does not rule out a diagnosis of HAE. Genetic testing can be a helpful component in diagnosis; however, the panel noted several challenges, including a lack of feasibility due to limited testing accessibility and the presence of unknown genetic variants. It was noted that as much as a third of patients do not have mutations in commonly investigated known loci, and full genome sequencing may be required to identify new mutations (some mutations are unique to 1 family). Full genome sequencing is costly and not readily available to all patients. There are also sporadic cases of HAE with no family history of the disease. Therefore, genetic testing and the presence of family history are not necessary for diagnosis of HAE with normal C1-INH and should not prevent access to icatibant.
Renewal/Continuation	
What should be the minimum treatment response required to continue icatibant treatment?	There was consensus among the panellists that patients should ideally report symptom improvement within 6 hours of icatibant administration to be considered responders to treatment. However, they noted that this is based on the definition of response used in clinical trials of icatibant in patients with HAE with C1-INH deficiency.[9] There is no established definition of an acceptable time to response to treatment in the setting of HAE with normal C1-INH. Importantly, it was noted that, given the variability of clinical presentation, attack characteristics, and response among patients with HAE with normal C1-INH, some patients may have a longer time to response (> 6 hours). Patients should have a minimum of 3 doses to assess clinical efficacy. Response should be based on a subjective response (i.e., patient-reported symptoms). **Discussion points:** The panellists discussed objective vs. subjective response and noted several challenges in the feasibility of requiring an objective response to determine treatment response. There

Criteria	Implementation advice
	are no current standardized scoring systems for response in acute attacks. The panellists discussed circumstances in which it may be possible to obtain evidence of an objective response (e.g., airway, limbs, facial attacks) and when it may not be (e.g., abdominal attacks). In addition, given that the goal of icatibant availability to patients is self-administration and preventing hospitalizations or emergency department visits, an objective assessment of response by a health care provider after each attack would not be performed in most cases. However, the panellists indicated that treating physicians routinely document a subjective response during patient visits and can assess overall response to treatment used in acute attacks. The panel discussed the number or maximum number of doses that may be required per month/year/lifetime for a given patient. They noted that acute HAE attacks are unpredictable, and given the variability in the frequency of attacks, it is impossible to predict the number of doses icatibant patients need to manage acute symptoms. Some patients belonging to a diagnosed family may not have yet had a first attack but need to have access to (or carry) icatibant in the event of an attack. Other patients may have infrequent attacks based on their attack history and may require a few doses of icatibant per year, whereas others with more frequent attacks would need more doses of icatibant to manage acute symptoms. The panellists noted that most patients are also on prophylactic treatment, but for those with consistently frequent acute attacks, more effective long-term prophylactic treatments should be considered.
Discontinuation	
When should icatibant be discontinued?	Patients should be reassessed by the prescriber every 6 months (initially for the first year), then every 12 months. **Discussion points:** The panellists noted that the assessment interval depends on the frequency of attacks. For some patients with infrequent attacks, yearly assessments may be sufficient, whereas others with more frequent attacks are assessed more often by the treating physician.
Prescribing	
Should icatibant be prescribed only by specialist physicians?	Icatibant should be prescribed by or in consultation with a physician with experience treating HAE. **Discussion points:** The panellists noted that some patients in remote areas with limited or no access to HAE specialists may be treated by a general practitioner with experience in treating HAE or after consulting with a HAE expert/specialist.

HAE = hereditary angioedema; vs. = versus.

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