12th Nordic Bradykinin Meeting

Copenhagen September 14, 2023

HAE | Takeda

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Introduction

Angioedema (AE) is a clinical syndrome characterized by localized swelling of the subcutaneous layer of the skin or the submucosal layer of the gastrointestinal or respiratory tracts. Hereditary angioedema (HAE) is an autosomal dominant disorder caused by a mutation in the C1 esterase inhibitor gene. The latter is a rare disease characterized by unpredictable, potentially life-threatening attacks, resulting in significant physical and emotional burdens for patients and their families.

On September 14, 2023, Takeda arranged the 12th Nordic Bradykinin Meeting in Copenhagen, Denmark. The meeting was a hybrid event that gathered healthcare professionals from the Nordic and Baltic countries both physically and virtually. This report summarises the presentations given.

Dr Johanna Mandelin, Division of Dermatology and Venereology, Helsinki University Central Hospital, Finland

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What is HAE – introduction to the area and today's meeting

Professor Björn R Lúðvíksson, Department of Immunology, National University Hospital, Reykjavik, Iceland

Björn Lúðvíksson gave a swift introduction to the pathophysiology, clinical characteristics and management of HAE.

The C1 esterase inhibitor (C1-INH) is a protease inhibitor belonging to the serpin superfamily. Its main function is to inhibit the complement system to prevent spontaneous activation, but also to regulate the contact system (Law RH et al. Genome Biol 2006; 7: 216).

The international WAO/EAACI guideline for managing HAE distinguishes two classes of AE: bradykinin-induced and mast cell mediator-induced (Maurer M et al. World Allergy Organ J 2022; 15: 100627). The former includes AE with C1-INH deficiency/defect and AE with normal C1-INH, both of which can be inherited or acquired. When the condition has no known mediator, it is classified as idiopathic AE.

In HAE, three different types are distinguished. Type I, accounting for 80–85% of cases, has decreased C1-INH protein and function, while type II has a normal or increased C1-INH protein but decreased function. HAE with normal C1-INH, previously named type III, is caused by mutations in genes like factor XII (FXII), the angiopoietin or plasminogen gene, or no identified cause (Bova M et al. Int Arch Allergy Immunol 2018; 175: 126–35).

The prevalence of HAE is estimated to 1:10,000–150,000, with no racial or gender predilection. Edema usually manifests in the second decade of life but may also be seen in young children. Attacks left untreated can last for up to eight days before resolution but resolve on the average within 2–5 days (Jean-Baptiste M et al. Orphanet J Rare Dis 2022; 17: 232).

Clinical picture

About every other HAE patient experiences prodromal symptoms in the form of fatigue, a tingling sensation, muscle ache, local discomfort or erythema marginatum, a characteristic skin rash. The majority of attacks are peripheral but can also be abdominal, orofacial, laryngeal or genitourinary, and 15–30% of patients have multi-location attacks (Hofman ZL et al. Clin Rev Allergy Immunol 2016; 50: 34–40, Zeerleder S, Levi M. Ann Med 2016; 48: 256–67). Long-term complications of HAE include musculoskeletal pain and autoimmunity (Triggianese P et al. Isr Med Assoc J 2014; 16: 622–4).

Treatment options

Treatments that replace C1-INH, either plasma-derived or manufactured, have been available for decades. More recently, bradykinin receptor antagonists and kallikrein inhibitors have been introduced, and several novel targets are currently under investigation, including prekallikrein inhibitors and activated FXII inhibitors (Valerieva A, Longhurst HJ. Front Allergy 2022; 3: 952233).

Estrogen can have detrimental effects on HAE patients by decreasing C1-INH, decreasing ACE and increasing FXII. Attenuated androgens have the opposite effect but are nevertheless not a favourable treatment option due to their side effects.

With the introduction of highly effective therapies and the phasing out of androgens, HAE treatment has undergone a revolution over the past decade. Patients are also increasingly engaged in their own treatment. Nevertheless, a significant proportion of patients are still missing school or work and score their general health below average. Factors to consider when deciding on HAE treatment are shown in Figure 1.

Patient involvement

In Iceland, one strategy for increased patient involvement is HAEXpert, an interactive mobile app and web-based tool with a self-reported disease scoring system and recording capabilities for a personalised treatment recommendation plan. A severity score is calculated based on the patient's daily registrations. HAExpert also records quality of life (QoL).

- Patient preference
- Attack frequency and severity
- Access to emergency treatment
- Comorbid conditions
- Patient's experience with on-demand therapy
- Achievement of control
- Ability to administer
- Adverse effects
- Impact on QoL

Figure 1. Common examples of concerns related to HAE treatment decision-making (Banerji A et al. J Asthma Allergy 2021; 14: 119–125).

HAE in pediatric and elderly patients

Dr Emel Aygören-Pürsün, University Hospital Frankfurt, Germany

Different patient groups have their own challenges and special features. Emel Aygören-Pürsün concentrated on the very young and the elderly HAE patients.

Childhood and adolescence are critical periods in life for every individual's further well-being and success. In patients with HAE, symptoms can occur early in life and may include laryngeal attacks; death from suffocation has been described as early as age three (Minafra FG et al. Clin Rev Allergy Immunol. 2022; 62: 232–9). A study investigating the location of the first HAE manifestation in 70 pediatric patients found that subcutaneous and abdominal attacks were most common, while multi-site attacks were not seen (Fig. 1).

Dominating trigger factors in the pediatric population are mechanical trauma, infection and psychological stress (Farkas H et al. J Allergy Clin Immunol Pract 2020; 8: 2379–83). Nevertheless, children should not be limited in their activities and lifestyle to avoid activities that might trigger attacks (Maurer M et al. World Allergy Organ J 2022; 15: 100627).

Early diagnosis of childhood HAE can be difficult but is of vital importance as death due to laryngeal edema is seven-fold higher in undiagnosed patients (Bork K et al. J Allergy Clin Immunol 2012; 130: 692–7). Like adults, pediatric HAE patients have been shown to have more anxiety and lower QoL compared to healthy controls (Kessel A et al. Pediatr Allergy Immunol 2017; 28: 692–8).

Pediatric management

The WAO/EAACI guideline recommends that the treatment goals in all patients are to achieve total control of the disease and to normalize patients' lives (Maurer M et al. World Allergy Organ J 2022; 15: 100627). In Europe, on-demand therapeutic options from age two are plasma-derived or recombinant C1-INH and icatibant. For short-term prophylaxis, plasma-derived or recombinant C1-INH can be used, also from age two. For long-term prophylaxis, plasma-derived C1-INH is approved from age six and berotralstat from age 12 (Khan DA et al. J Allergy Clin Immunol Pract 2021; 9: 2170–84). Lanadelumab is now indicated from age 2 (Takhzyro SmPC).

In the US, lanadelumab is approved from age two based on the recently published SPRING study (Maurer M et al. J Allergy Clin Immunol Pract 2023, Online ahead of print), and studies are ongoing to evaluate the effects of berotralstat and garadacimab in that age group.

Challenges in the elderly

The increasing prevalence of comorbidities in elderly patients may affect the severity of HAE, and the higher risk for polypharmacy increases the risk for adverse drug reactions (Farkas H et al. Lancet 2001; 358: 1695–6). A Swedish nationwide longitudinal register study including 239 individuals with HAE and matched controls shows an increased risk of all cardiovascular diseases, in particular hypertension and thromboembolic disease (Sundler Björkman L et al. Clin Transl Allergy 2022; 12: e12135).

Modern long-term prophylactic agents have effect in elderly patients. This has been shown in subgroup analyses from the HELP study on lanadelumab (Johnston DT et al. Clin Exp Allergy 2021; 51: 1391–5) and the COMPACT study on subcutaneous C1-INH (Li HH et al. Allergy Asthma Clin Immunol. 2019; 15: 49).

To conclude, it is reassuring to know that for both very young and elderly patients, safe and effective therapeutic options are available with the goal of normalizing their lives.

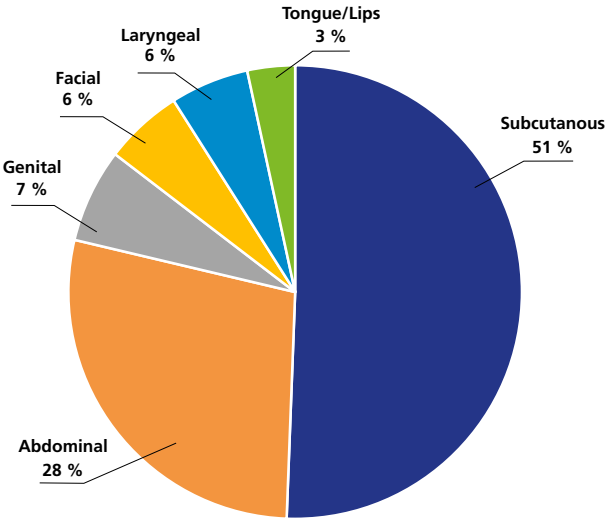


Figure 1. Distribution of the locations of more than 3,000 HAE attacks in 70 pediatric patients with C1-INH HAE (Farkas H et al. J Allergy Clin Immunol Pract 2020; 8: 2379–83).

Family planning in HAE

Dr Maria Karlsson, Division of Dermatology, Karolinska University Hospital, Solna, Sweden

Maria Karlsson talked about family planning and prenatal diagnostics in HAE in Sweden, stressing the importance of informing patients about the possibility of becoming a parent without passing the disease on to the child.

Finding time to discuss personal relations and family planning during a routine visit can be a challenge, but we do need to bring up the question. For some patients, the conviction that they do not want to pass the disease on to a child can even affect their willingness to enter into a relationship. Clinical experience shows that even boys in their late teens can worry about their possibilities for a future family.

Traditionally, prenatal genetic diagnostics for patients who risk having children with a severe genetic disease was performed through placenta sampling in pregnancy week 11–12 or amniocentesis in week 15–16. Today, however, these methods have been replaced by preimplantation genetic testing (PGT), a method combining *in vitro* fertilization (IVF) with genetic diagnostics of embryonic stem cells before implantation in the uterus.

PGT involves several time-consuming steps and it is therefore advisable that patients be referred in good time. The ten steps in PGT are shown in Figure 1.

The PGT process

Regardless of which of the partners has HAE, the PGT process is the same: it is always the woman who undergoes the procedure. The hormone stimulation phase involves several ultrasound check-ups to establish how the eggs are maturing so that harvesting can be done at the right time and the risk of over-stimulation avoided. Eggs are usually fertilized through intracytoplasmatic sperm injection (ICSI).

When the eggs have been incubated for 5–6 days, embryo biopsy is performed and the embryos with and without the mutation are identified by genetic analysis. Statistically, 50% of the embryos should have the mutation, but this is not always the case. Embryos without the mutation are then cryo-preserved.

After adjusting to the menstrual cycle and possible need for additional hormone stimulation, one embryo is thawed and placed in the uterus. Remaining embryos are kept cryo-preserved for new attempts and possible siblings. After two weeks, a pregnancy test will confirm whether the implantation has been successful. In Sweden, the state will cover the cost for three attempts.

PGT pros and cons

The risk for diagnostic mistakes is very low but can nevertheless happen, so once pregnancy is established, the couple is offered traditional foetal diagnostic tests.

There are no additional risks for children conceived through PGT compared with routine IVF (internetmedicin.se/behandlingsoversikter/gynekologi-obstetrik/preimplantatoriskgenetiskdiagnostik).The medical risks for the woman are very low but a (<3%) risk of overstimulation that can lead to fluid retention and risk of lung edema, heart failure and circulation collapse does exist.

The advantage of PGT compared to foetal diagnostics is that the pregnancy can begin with the knowledge that the expected child does not carry the mutation. The disadvantages are that it is time consuming and stressful. In addition, the procedure requires high technological competence and is costly. Importantly, the decision to proceed with PGT should be made after considering all aspects of the procedure and evaluating the chances of success.

To date, more than 15,000 children worldwide have been born following PGT. Although the technique has been practised in Sweden for more than 20 years, only one of the approximately 500 PGT births during this period can be ascribed to HAE.

1. Clinical Genetics perform the diagnostics to identify the mutation (blood test)
2. Referral to reproduction clinic to evaluate the chances of a successful pregnancy
3. The woman starts hormone stimulation
4. Several ultrasound check-ups to monitor the maturation of eggs
5. Egg harvesting with aspiration of mature eggs
6. Fertilization of the eggs, usually performed by intracytoplasmatic sperm injection (ICSI). Cells are incubated for 5–6 days
7. Embryo biopsy at day 5–6 when containing 100 cells (3–10 cells removed)
8. Genetic analysis and embryo selection
9. When suitable, one embryo is thawed and placed in the uterus
10. Pregnancy test in 14 days

Figure 1. The ten steps in preimplantation genetic testing (PGT) (Parikh FR et al. J Hum Reprod Sci 2018; 11: 306–14).

The clinical management of hereditary angioedema

Professor Marcus Maurer, Institute of Allergology, Charité – Universitätsmedizin Berlin and Fraunhofer Institute for Translational Medicine and Pharmacology, Immunology and Allergology, Berlin, Germany

Marcus Maurer discussed the burden of HAE and how the condition is managed clinically.

HAE is a rare disease and therefore still often overlooked. Of 100 patients with AE who make their way into our clinics, only one or two have bradykinin-mediated AE – and not all of those are HAE. As opposed to mast cell-mediated AE, HAE does not come with wheals, and only HAE manifests with abdominal attacks (Caballero T et al. Allergy Asthma Proc 2014; 35: 47–53).

Health between attacks

The burden of HAE is high even when the number of attacks is low. Patients have an increased risk of depression, and both health-related QoL and productivity are reduced (Lumry WR et al. Allergy Asthma Proc 2010; 31: 407–14).

HAE impacts many aspects of QoL (Fig. 1). Major fears among HAE patients include sudden airway closure, intolerable pain and transmission of HAE to children (Huang SW. Allergy Asthma Proc 2004; 25: 127–31). Effective treatment will not only prevent attacks but subsequently also the depression, the anxiety and the fears.

Treatment goals

We know that HAE is a devastating disease, but the disability and impairment it brings is individual. Every patient has unique needs, impairments and expectations, and to understand what they are, we need to listen to our patients.

According to the updated and revised WAO/EAACI HAE guideline, the goals for HAE treatment are to achieve total control of the disease and to normalize patients' lives (Maurer M et al. World Allergy Organ J 2022; 15: 100627). To achieve this, the guidelines recommend that patients are treated by a specialist with specific expertise in managing HAE.

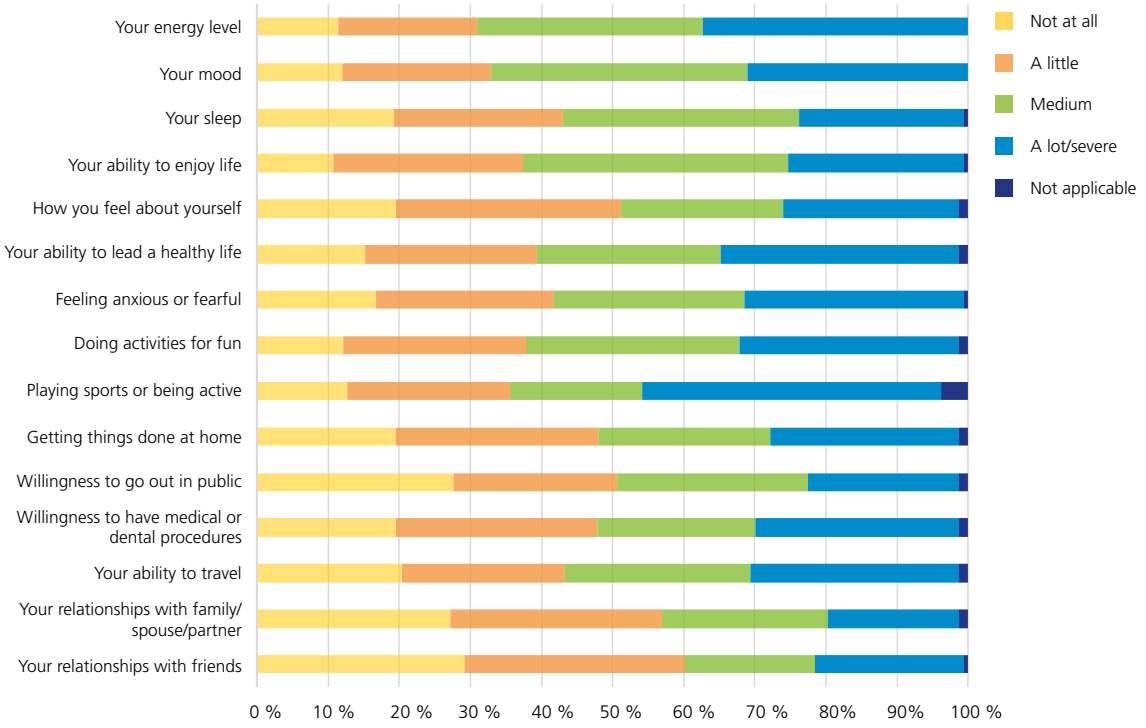


Figure 1. The multi-faceted disease burden of HAE and its impact on various domains (Banerji A. Ann Allergy Asthma Immunol 2013; 111: 329–36).

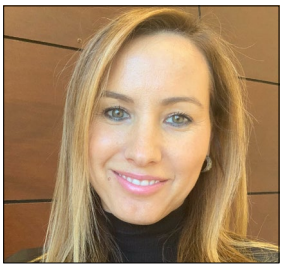
Evaluation tools

To establish whether a treatment works, we need to measure its effects on disease activity, QoL and disease control. The Angioedema Control Test (AECT) is a very simple, easy-to-use tool with only four questions and a maximum score of 16 (moxie-gmbh.de). The Angioedema Quality of Life Questionnaire (AE-QoL) contains 17 questions designed to assess symptom-specific QoL impairment. Its maximum score is 100 (Weller K et al. Allergy 2013; 68: 1185–92).

Long-term prophylaxis is (currently) the only way to achieve the above treatment goals in patients with HAE. Three modern long-term prophylactic options are available and recommended by the guideline: pdC1-INH, lanadelumab, and berotralstat. Shared decision-making will identify the right treatment for each patient.

The ACARE program is a joint initiative by GA²LEN and HAE International (HAEi) for developing and accrediting an interactive network of centres of reference and excellence in AE. The ACARE network facilitates scientific projects and studies, and it informs and educates medical professionals on AE through its websites, social media channels, and education programs for physicians including webinars, preceptorships and AE schools (acare-network.com).

Registration for the expert panel and author group for the next update and revision of the international HAE guideline is open for those interested in joining (acare-network.com/guidelines). The next guideline revision and update will include recommendations on how to diagnose and treat AE patients with normal C1-INH. As no clinical trial data are available regarding this group, everyone who treats even only one patient with HAE that is not type 1 or 2 is encouraged to share their results by publishing them or entering them in the ACARE registry, CARE (chronic-angioedema-registry.com).



Follow-up of HAE patients: what do we need to measure and how?

Dr Anna Sala Cunill, Vall d'Hebron University Hospital, Barcelona, Spain

Achieving the goals of HAE management requires not only effective therapy but also objective tools to ascertain and prove the effect. In addition, the way patients are followed up must be optimized, as frequent visits to the hospital have a negative impact on QoL. Anna Sala Cunill talked about evaluation tools and value-based healthcare.

To optimize care for HAE patients and achieve the treatment goals – total disease control and a normalized life – QoL and disease activity should be routinely monitored with validated patient-reported outcome (Bork K et al. Allergy Asthma Clin Immunol 2021; 17: 40).

Some of the main challenges in today's healthcare are a growing, ageing population and shortage of healthcare professionals. To meet these challenges, we need to make the transition from evidence-based medicine to value-based healthcare.

Value in healthcare

Value in healthcare is a measure of the quality of healthcare services and the results delivered in relation to the costs incurred. Value in healthcare encompasses the balance between the effectiveness, safety, patient experience, and efficiency of healthcare interventions.

One way of increasing the value in HAE care is early detection and attack prevention. Another is patient education and empowerment through support services. Value can also be increased by accurate and understandable information and shared decision-making. A further important measure is coordinated care and long-term management through collaboration between different healthcare providers. In this way, all relevant aspects of the patient's condition can be addressed, avoiding duplication of services and enhancing the efficiency of the system.

Shared decision-making is a key component of individualized treatment plans (Banerji A et al. J Asthma Allergy 2021; 14: 119–125). Decisions should be built on a mutual understanding of the patient's needs and goals, as well as potential benefits and harms of the treatment option. The 3D model is one way of achieving this (Fig. 1).

Validated patient-reported outcome tools should be routinely used to measure disease activity, QoL and disease control (Bork K et al. Allergy Asthma Clin Immunol 2021; 17: 40).

Tools to facilitate data collection

The fourth healthcare revolution, Healthcare 4.0, has evolved to meet diverse requirements in the healthcare domain. It is transforming medicine through artificial intelligence, precision medicine and telemedicine, technologies that can provide better health and healthcare, often at lower cost and higher value (Gupta A, Singh A. Wirel Pers Commun 2023; 129: 933–52). Implementation of Healthcare 4.0 supports the transition from a hospital-centred system to a patient-centred organization in which multiple departments, roles and responsibilities are merged to provide optimal patient healthcare outcomes.

One way of minimising the number of health visits is to have patients use a mobile app such as HAE TrackR to register swells, triggers and treatments (www.haetrackr.org). If everything is stable and working well, the patient does not need to come to the hospital for every visit, or the meeting can be virtual instead of physical. A chatbot can also be used.

'The liquid hospital' concept envisions the expansion of healthcare provision beyond the traditional hospital structure. Its aim is to include connectivity, telemedicine, internet-of-things technologies, and social media in the management of disease (Rovira-Simón J et al. Future Healthc J 2022; 9: 34–40).

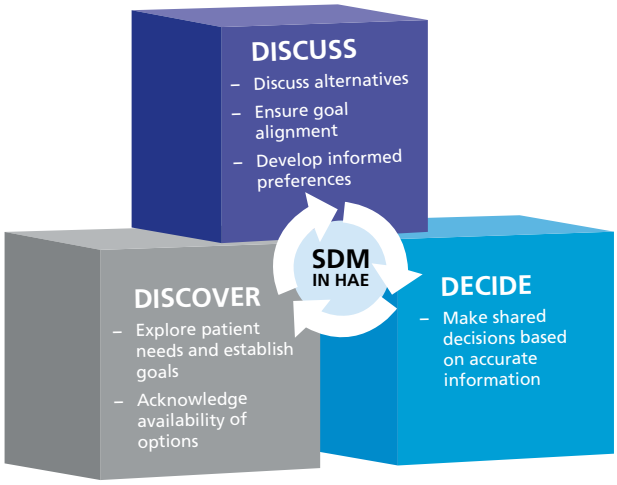


Figure 1. The 3D model (Discover, Discuss, Decide) for shared decision-making (SDM) in HAE (Banerji A et al. J Asthma Allergy 2021; 14: 119–125).

Nordic panel discussion

Dr. Shailajah Kamaleswaran, Department of Dermatology,
Odense University Hospital, Denmark

Dr Johanna Mandelin, Division of Dermatology and Venereology,
Helsinki University Central Hospital, Finland

Dr Martin Kropp, Department of Dermatology,
Falun Hospital, Sweden

Professor Marcus Maurer, Institute of Allergology, Charité – Universitätsmedizin Berlin and Fraunhofer Institute for Translational Medicine and Pharmacology, Immunology and Allergology,
Berlin, Germany

Professor Björn R Lúðvíksson, Department of Immunology, National University Hospital, Reykjavik, Iceland

Sharing experiences and learning from each other is one way of improving HAE care. A panel of Nordic experts discussing HAE-related topics was moderated by Marcus Maurer.

What is the biggest challenge in your country regarding HAE patients?

Johanna Mandelin: HAE patients with normal C1-INH.

Marcus Maurer: Finding a mutation that has not been described. As an increasing number of us are doing genetic testing, we need guidance on what to do in these cases.

Martin Kropp: We have all the opportunities we need diagnostic-wise; constraints are more financial, primarily concerning long-term prophylaxis.

Shailajah Kamaleswaran: Side effects from long-term prophylaxis. We have had two patients who have developed rash, ANA positivity and joint pain.

Björn Lúðvíksson: ANA positivity is a comorbidity that is rather often seen in the elderly and sometimes also in the middle-aged population. Musculoskeletal problems and joint effusions often seem to subside when the dose of the C1-INH is increased.

Marcus Maurer: Musculoskeletal problems are also common in the general population, which means there is a lot of noise when you look at the rather small HAE population.

Is androgen treatment a problem?

Martin Kropp: We have quite a few patients on androgens who are satisfied with their treatment and don't want to switch. In addition, the Swedish authorities require that patients have at least four attacks per month to get modern long-term prophylaxis subsidized.

Marcus Maurer: We don't use androgens anymore. It prevents attacks but the long-term side effects are gruesome. Germany has no restrictions concerning the number of attacks for modern long-term treatment to be started.

Do you recommend testing C4 and C1 inhibitor and activity for patients with AE of any age, even without a family history, during the initial consultation?

All said yes.

Marcus Maurer: Stand-alone recurrent AE requires that HAE is excluded.

Björn Lúðvíksson: We might test C4 and C1 inhibitor function first and move on to activity testing if those are positive. On the other hand, genetic testing is getting increasingly accessible and affordable and will probably be the standard procedure within 2–3 years.

How can we optimize treatment with modern prophylaxis to keep costs down while maintaining complete response?

Marcus Maurer: In our experience, the possibilities to reduce the dose or increase the time between doses do not apply to C1-INH or berotralstat, while lanadelumab offers the opportunity to individualize treatment intervals. This is done by continuously

increasing the dosing interval by three days, starting from the third dose.

Shailajah Kamaleswaran: We do the same, but wait for three months before starting to increase the dosing interval.

Björn Lúðvíksson: We believe that using apps like HAEXpert more efficiently will make patients more actively involved and allow them to adjust the treatment to their needs: increasing their dose before stressful events or periods and decreasing it when things are quiet.

How to decide if long-term prophylaxis is necessary?

Marcus Maurer: We decide on a patient-by-patient basis without any restrictions.

Martin Kropp: Sweden requires that the patient has at least four attacks per month to get lanadelumab reimbursed.

Shailajah Kamaleswaran: Denmark has the same situation as Sweden, but it is not fair to the patients so we will have to look into it again.

Johanna Mandelin: Finland has no such requirements, but subcutaneous C1-INH is not reimbursed.

Björn Lúðvíksson: We were initially instructed to follow the Swedish guidelines but refused. We challenged the cost efficiency calculations and won.

Marcus Maurer: Cost efficiency is a difficult issue: can we really measure the effects in money? But it is valuable to be able to show that the treatment is worth the cost beyond the humanistic benefit through reduced on-demand medication, ER room visits, work missed…

Shailajah Kamaleswaran: Most patients with only one attack per month or so do not want to be on long-term prophylaxis. Living a normal life and being free from attacks are two different things. A patient who has an abdominal attack every six months may find it totally unacceptable while a patient whose hands swell up once every month might not be bothered.

Marcus Maurer: Agreed. In Berlin, about 60% of HAE patients are on long-term prophylaxis. The main factor that drives the decision not to use long-term prophylaxis is the patient. For some, 'long-term' translates into 'life-long' which can be deterring, so it may be better to offer them the opportunity to try prophylactic treatment and emphasize that they can stop if they don't like it.

What is your approach when you discuss treatment options with patients?

Johanna Mandelin: I explain that there is now medication available that does not require intravenous administration. I tell them that the medication is long-term and that it will only have effect as long as they take it: if they don't like it, they can always stop. That's important for many patients.

Martin Kropp: You have to give the patient time and talk about it several times. They think about it and perhaps talk to their relatives, and after some time they are ready to try.

Marcus Maurer: Families often have an opinion on how HAE should be dealt with, and this can have a strong influence on the decision. In such cases, it can make sense to have family meetings.

Björn Lúðvíksson: It's important to tell patients about patient organizations. These can provide information about treatment options. An issue that is rarely discussed is the consequences of having recurrent inflammatory attacks in, for example, the abdomen or the respiratory tract. It may lead to some kind of remodelling.

Marcus Maurer: Agreed. We completely ignore what the infiltrate at the site of the attack will do in terms of susceptibility of that location to experience the next attack. Also, we know from chronic inflammatory diseases like asthma and atopic dermatitis that repeated inflammation drives more inflammation and higher susceptibility in the tissues to inflammatory stimuli. The Berlin Angioedema Center of Reference and Excellence (ACARE) has initiated the CAUSTO project to investigate these issues by taking biopsies from attack sites.

Are there any recordings in the ACARE registry about lanadelumab during pregnancy?

Marcus Maurer: No. We do not encourage it, instead we switch patients to C1-INH prophylaxis. But when it has happened, the pregnancies have been uneventful.

ACE inhibitors are not the only family of drugs that is problematic. Are beta blockers, calcium antagonists and angiotensin 2 receptor blockers considered safe?

Marcus Maurer: They are, at least in terms of HAE.

Is it safe to combine one biologic for HAE with another biologic for a different indication?

Johanna Mandelin: I have no experience from this in HAE, but based on that in dermatology, I would say yes.

Shailajah Kamaleswaran: We never combine two biologics.

Björn Lúðvíksson: I have done this in various conditions but it's necessary to look at the mechanisms targeted, so a complicated yes.

Marcus Maurer: I do this but only after taking the mechanisms into consideration. Some double biologics do not make sense be-

cause there is so much overlap in the target that the result will probably be the same with only one of them. In some cases, you can instead treat two conditions with one biologic.

Do you inform your patients about the ultimate treatment goal for HAE?

All said yes.

Marcus Maurer: Telling the patient that the goal is a normal life with no attacks and asking questions to establish the patient's personal goals is the perfect framework for presenting the different treatment options.

Do HAE patients have a higher prevalence of oncological diseases, and should oncology screening be done more frequently?

Marcus Maurer: No.

Björn Lúðvíksson: No as well, with the exception of those who have been on androgens.

Shailajah Kamaleswaran: Yes if there is suspicion of acquired C1 inhibitor deficiency.

What are you excited about regarding the future for HAE?

Johanna Mandelin: Better diagnostics.

Martin Kropp: Oral on-demand treatment. Marcus Maurer agreed and said there are a couple exciting programs ongoing. One targets kallikrein and the other is a bradykinin 2 receptor antagonist.

Shailajah Kamaleswaran: Having a discussion about when to stop long-term medication, as attack rates decrease with age. *Marcus Maurer* said that to ensure that the treatment effect is maintained, it may be more reasonable to reduce the treatment rather than stopping it.

Björn Lúðvíksson: Empowering our patients to take charge of their own health and available treatment options by using e-health applications.

What about genetic therapy?

Marcus Maurer: That's happening right now. In Berlin, we currently have two patients undergoing gene editing with CRISPR-Cas9 plus ongoing studies on gene silencing.

HAE with normal C1 inhibitor: mutations in factor XII and plasminogen

Adjunct Professor Allen Kaplan, Medical University of South Carolina, Charleston, USA

Allen Kaplan described two forms of HAE with normal C1 inhibitor and the mechanisms behind them.

Of the different forms of HAE with normal C1 inhibitor, factor XII mutation (HAE-FXII) and plasminogen mutation (HAE-PLG) are the only two in which the causal mechanism is known. Both alter protease activity in a gain-of-function manner.

HAE-FXII

Patients with HAE-FXII most frequently have a point mutation in the gene encoding factor XII that affects the amino acid threonine to which a carbohydrate is attached. As threonine is eliminated, so is the carbohydrate, resulting in a smaller-sized factor XII (Björkqvist J et al. J Clin Invest 2015; 125: 3132–46). Consequently, the mutation can be detected with a simple SDS electrophoresis gel.

Plasmin cleaves at the mutated site at a very rapid rate followed by kallikrein cleavage of the usual site. This accelerated activation of the shorter FXII overwhelms the opposing function of C1-INH, increasing the amount of bradykinin produced. Like factor XII fragment (β factor XIIa) it has lost the heavy chain binding site for 'surfaces' so prekallikrein activation proceeds, but factor XI activation does not, i.e. the intrinsic coagulation cascade is not activated.

HAE-PLG

HAE-PLG was first reported by Bork and colleagues (Allergy 2018; 73: 442–50) but only recently was the mechanism by which bradykinin is released in this condition discovered (Dickeson SK et al. Blood 2022; 139: 2816–29).

When plasmin derived from mutant plasminogen is added to plasma, bradykinin evolves. To investigate the driving force behind this evolution, the different steps in the bradykinin-forming cascade (Fig. 1) were systematically investigated.

The first step to be ruled out was the need for factor XII. Mutated plasmin activated factor XII-deficient plasma just as well as it activated normal plasma, and mutated plasmin was also found to activate factor XII no more successfully than unmutated. When a potent inhibitor of activated factor XII was employed, bradykinin formation by the mutated factor XII (above) was completely inhibited but the mutated plasmin was not. The need for prekallikrein could also be ruled out: when mutated plasmin was added to plasma deficient in prekallikrein, bradykinin formation was normal. This left only kininogen itself.

In CI-INH deficiency, high molecular weight kininogen (HK) is cleaved but not low-molecular weight kininogen (LK). When the ability of mutated plasmin to cleave these kininogens was tested, both were activated to produce bradykinin. Indeed, liberation of bradykinin was faster when HK was cleaved by mutated plasmin than by unmutated plasmin, and even more so with LK. In addition, the cleavage of LK with mutated plasmin continues until the molecule is digested into small pieces.

These experiments were done with the same molar concentrations of LK and HK, but since the amount of LK exceeds that of HK in plasma by about three-fold, the former can be expected to be the major contributor to bradykinin formation in HAE-PLG.

Plasma kallikrein preferentially cleaves HK to produce bradykinin while tissue kallikrein prefers LK. Tissue kallikrein's mechanism is a two-step process in which the product of the first step is the 10-amino acid peptide lysyl-bradykinin. In the next step, aminopeptidase P cleaves off the N-terminal Lys, resulting in the 9-amino-acid peptide bradykinin. Mutated plasmin, on the other hand, cleaves both HK and LK directly to produce bradykinin.

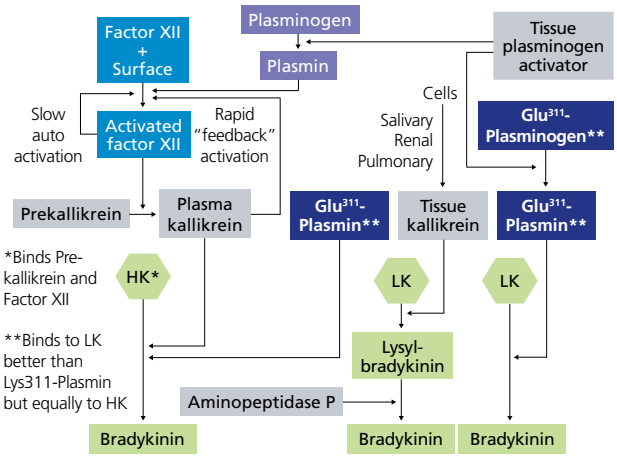


Figure 1. Pathways of bradykinin formation. In HAE with plasminogen mutation (HAE-PLG), conversion of mutated plasmin (Glu311-plasmin) to mutated plasminogen (Glu311-plasminogen) leads to direct digestion of both low (LK) and high molecular-weight kininogen (HK) to produce bradykinin (Kaplan AP. Blood 2022; 139: 2732–3).

History of HAE and treatment evolution

Professor Marc Riedl, HAEA Angioedema Center, University of California, San Diego, USA

Marc Riedl gave a long-term perspective on where HAE has been and where it may be heading, focusing on the evolution of HAE management.

JL Milton is often credited with publishing the first real descriptions of AE (Edinb Med J 1876; 22: 513–26) but already in 1586, Italian physician Marcello Donati described an attack in his book 'De Medica Historia Mirabili Libri Sex'. In 1882, Heinrich Quincke described several cases of acute localized skin edema and in 1888, Sir William Osler published what is probably the first comprehensive clinical and genetic description of HAE.

In the 1960s, the mechanisms behind the condition began to reveal themselves and a few years later, subtypes 1 and 2 were recognized (Rosen FS et al. Science 1965; 148: 957–8).

Therapeutics development

Treatment to prevent attacks was introduced in the 1970s, primarily tranexamic acid and danazol. In the early 1980s, with the recognition of the protein deficiency, two different groups reported that administration of plasma-derived C1-INH during attacks could lead to rapid symptom resolution (Agostoni A et al. Ann Allergy 1980; 44: 299–301, Gadek JE et al. N Engl J Med 1980; 302: 542–6). A few years later, the ability to create complementary DNA clones, plus the recognition that these genes lead to translation of protein that could be cloned and studied, made it possible to really begin to untangle the pathophysiology behind HAE.

In 1989, the prophylactic benefit of C1-INH in both hereditary and acquired AE was demonstrated (Bork K, Witzke G. J Allergy Clin Immunol 1989; 83: 677–82). These findings were soon followed by larger studies that helped improve the understanding of the natural history, complications, issues and variability of symptoms in HAE.

A decade or so later came the recognition of the C1-INH protein's role in multiple pathways: the contact system, the complement system and the fibrinolytic system. Yet some controversy remained as to why swelling occurs, until one seminal paper by Han and colleagues revealed bradykinin as the primary mediator (Han ED et al. J Clin Invest 2002; 109: 57–1063). This led to the development of specific targeted therapies: C1-INH concentrates for both acute and prophylactic treatment, the bradykinin B2 receptor antagonist icatibant, the kallikrein inhibitor ecallantide and recombinant C1-INH.

In the next wave of clinical trials, prevention was the dominating strategy. This includes subcutaneous C1-INH (Longhurst H et al. N Engl J Med 2017; 376: 1131–40), lanadelumab (Banerji A et al. JAMA 2018; 320: 2108–21) and berotralstat (Zuraw B et al. J Allergy Clin Immunol 2021; 148: 164–172). Many new therapies are also under investigation, including monoclonal antibodies, oral targeted therapy, RNA-targeted therapy and gene therapy (Chen M, Riedl MA. Immunol Allergy Clin North Am 2017; 37: 585–95). This evolution allows us to individualize care and maximize treatment benefits and QoL for our patients. It should be borne in mind, however, that these opportunities are not available to patients in all parts of the world.

Assessing QoL

Part of the evolution of HAE management is recognising that the burden of disease exceeds the burden of attacks. The condition affects both patients and families chronically and QoL is affected also between attacks (e.g. Bork K et al. Allergy Asthma Clin Immunol 2021; 17: 40). In addition, the treatment can be a burden. In recent years, ways to measure disease control and QoL have improved (Fig. 1).

	HAE-AS	AAS	HAE-QoL	AE-QoL
Number of items (questions)	12 (once)	1-6 (everyday)	25 (once)	17 (once)
Recall period	6 months	1 day	6 months	4 weeks
Applicable in HAE 1/2	+	+	+	+
Applicable in other forms of recurrent angioedema	–	+	–	+
Assessment	Retrospective	Prospective	Retrospective	Retrospective
High level of patient compliance required	–	+	–	–
Clinical important difference published	–	+	–	+
Cost-free use in routine management and investigator-initiated clinical research	+	+	+	+

Figure 1. Characteristics of relevant patient-reported outcome measures for disease activity and QoL impairment in HAE (Bygum A et al. Front Med (Lausanne) 2017; 4: 212).

Real-world data on lanadelumab

Professor Marcus Maurer, Institute of Allergology, Charité – Universitätsmedizin Berlin and Fraunhofer Institute for Translational Medicine and Pharmacology, Immunology and Allergology, Berlin, Germany

Gradual extension of injection intervals with lanadelumab can minimize the burden of therapy without losing efficacy. Marcus Maurer presented experiences from Berlin.

In the phase III HELP trial, 300 mg every two weeks reduced the attack rate to 0.16 per four weeks compared to 1.88 with placebo when steady state had been achieved. The proportion of patients free from attacks on lanadelumab from steady state until the end of the study (days 70–182) was 76.9% (Banerji A. et al. JAMA 2018; 320: 2108–21).

The Berlin experience

To date, more than 100 patients have been treated with lanadelumab at Charité – Universitätsmedizin Berlin. Some have discontinued because they have become or wanted to become pregnant and a few did not experience satisfactory efficacy, but no patient discontinued due to intolerance or safety issues.

The first 34 patients have been assessed and evaluated (Buttgereit T et al. J Allergy Clin Immunol Pract 2021; 9: 3744–51). Of these, six were from the open-label extension of the HELP trial, six were on on-demand treatment with icatibant and the remaining 22 were on long-term prophylaxis with C1-INH or tranexamic acid.

The 'Berlin protocol' is used in all lanadelumab-treated patients. Patients who are free from attacks are gradually transitioned from dosing every two weeks to dosing every four weeks by continuously increasing the interval by three days, starting from the third dose.

The first dose is given at the clinic while the second is administered by the patient at home two weeks later. If no attack then occurs, this second two-week interval is regarded as indicative of complete response, and the patient adds an extra three days before taking the third dose. If the patient still remains free from attacks, he or she continues to add another three days until a four-week interval is reached. If an attack occurs, the patient goes back to the step that was protective and keeps to that interval for some time before re-attempting the protocol.

Patients appreciate this possibility to individualize their treatment, and 89% reach the four-week interval without any interruption. Some patients continue to increase the interval even further, but this is off label and not encouraged.

Improved QoL

QoL monitoring during the transition showed a clinically meaningful improvement in AE-QoL score for a majority of treated patients (Fig. 1).

A caveat with effective long-term prophylaxis is that patients need to be reminded to always have rescue medication with them and how to use it.

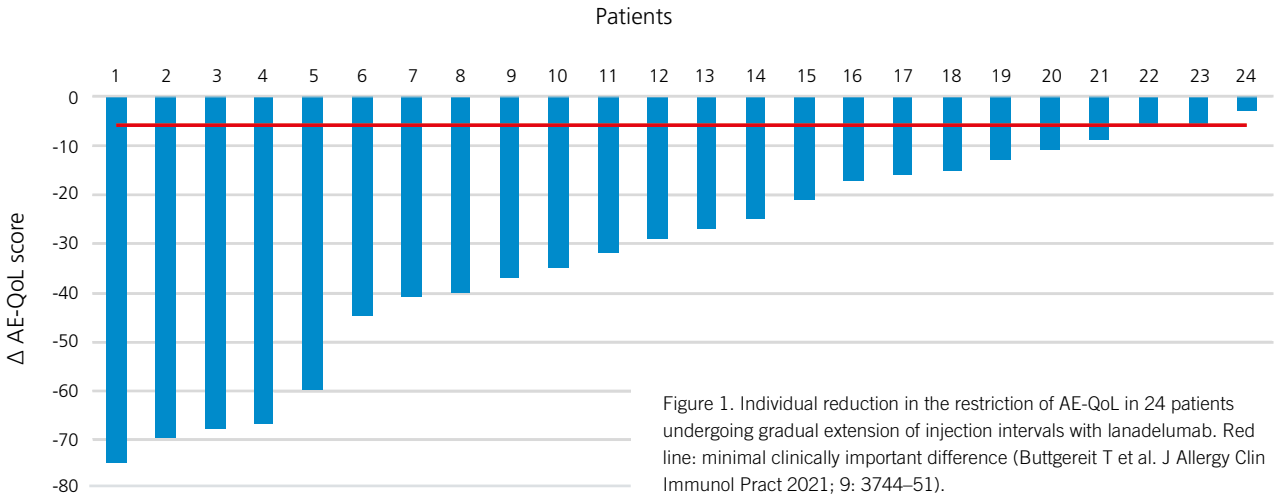


Figure 1. Individual reduction in the restriction of AE-QoL in 24 patients undergoing gradual extension of injection intervals with lanadelumab. Red line: minimal clinically important difference (Buttgereit T et al. J Allergy Clin Immunol Pract 2021; 9: 3744–51).

News in the 'angioedema world'

Professor Marcus Maurer, Institute of Allergology, Charité – Universitätsmedizin Berlin and Fraunhofer Institute for Translational Medicine and Pharmacology, Immunology and Allergology, Berlin, Germany

Marcus Maurer presented ACARE, the network for AE centres of reference and excellence.

ACARE is a joint initiative by the Global Allergy and Asthma European Network (GA²LEN) and HAE International (HAEi) for developing and accrediting an interactive network of centres of reference and excellence in AE (acare-network.com). There are currently 88 certified ACAREs in 36 countries with 15 applicants waiting. The goal is to have at least one ACARE in every country. ACARE has also partnered with national AE societies such as French CRéAk, Italian ITACA and Asia–Pacific APAAACI, and collaborates with centres of reference and excellence around the world.

The ACARE network facilitates scientific projects and studies. Participants choose what projects they want to participate in, or develop their own projects, and the steering committee guides and helps them with the organization. The practical work is carried out by the ACARE office team. ACARE also has activities aimed to inform and educate medical professionals, develop guidelines, establish the CARE registry, and organize meetings. Some of its projects and activities are described below.

Scientific projects

Every ACARE project has a project lead, a steering committee and a roadmap. The office team helps to keep the project on track, find funding and ensure that recruitment goals are met. They also provide medical writers and help with getting the results published.

- IMAGINE I and II offer free genetic testing to all ACAREs with the aim of identifying gene mutations in patients with recurrent idiopathic AE and HAE.
- SHAERPA aims to stop androgen treatment in patients with HAE by characterizing reasons and protocols, and developing advice for patients and physicians.
- DANCE aims to develop a global consensus on the definition, acronyms, nomenclature and classification of AE.
- PROMUSE focuses on describing the level of perception, knowledge and limitations of the use of patient-reported outcome measures (PROMs), while PROMUSE-PAT looks at the patient perspective on PROMs.
- HAPY is a newly-started project aimed to identify the influence of pregnancy on HAE.

ACARE activities

10 Questions is a tool that can help patients with recurrent swellings to determine the cause and find the correct treatment (ten-questions.net). It is now available in seven languages. Anyone interested in having it in their own language is welcome to contact ACARE.

The *CARE Registry* (chronic-angioedema-registry.com) is a global registry for all patients with AE with the aim to improve knowledge on recurrent AE and its epidemiology, types and subtypes, underlying causes, comorbidities, trigger factors, treatment response, costs and impact of disease.

Educational programs include free webinar series such as 'Make a difference'. Anyone who has a good topic to discuss at such a webinar is welcome to contact ACARE. Other examples are 'INTERACT', which is an educationally focused masterclass on the management of recurrent AE, and live regional-specific preceptorships. The ACARE LevelUp program (acare-network.com/levelup-2) offers education in various formats (Fig. 1).

Plans for the future

Future activities include an ACARE session at the UCARE conference in December 2023, a bradykinin symposium in Berlin in September 2024, and support of the revision and update of the international HAE guideline to which registration for the expert panel is still open (acare-network.com/guidelines). In addition, a global AE Forum is planned for September 2025.

- **7 Educational** formats:
  - 3 Online masterclasses
  - 30 Journal clubs
  - 6 Webinars
  - 36 Podcast episodes "All things angioedema" – first episode coming soon
  - 6 Newsletters
  - Website
  - Social media
- **81 Events** over an 18-month period
- Programming created by **internationally renowned physicians**
- Interactive, international, comprehensiv environment
- Giving **healthcare professionals** a platform to learn, network, collaborate and share best clinical practicesin angioedema

Figure 1. The ACARE LevelUp program (acare-network.com).

▼ Detta läkemedel är föremål för utökad övervakning. Detta kommer att göra det möjligt att snabbt identifiera ny säkerhetsinformation. Hälso- och sjukvårdspersonal uppmanas att rapportera varje misstänkt biverkning till: Läkemedelsverket, Box 26, 751 03 Uppsala, www.lakemedelsverket.se

CINRYZE® (human C1-esterashämmare) 500 IE, pulver och vätska till injektionsvätska, lösning. **Rx (F)** Subventioneras endast för akut behandling av svåra anfall av hereditärt angioödem. **Farmakoterapeutisk grupp:** läkemedel som används vid hereditärt angioödem, C1-hämmare, framställt av plasma. **ATC-kod:** B06AC01. **Indikation:** Behandling och prevention av angioödemattacker före ingrepp hos vuxna, ungdomar och barn (2 år och äldre) med hereditärt angioödem. Rutinmässig prevention av angioödemattacker hos vuxna, ungdomar och barn (6 år och äldre) med allvarliga och återkommande attacker av hereditärt angioödem, som är intoleranta mot eller får otillräckligt skydd av orala preventionsbehandlingar, eller patienter där upprepad akut behandling inte är tillräckligt. Cinryze-behandling bör sättas in under övervakning av en läkare med erfarenhet av vård av patienter med hereditärt angioödem. **Kontraidikationer:** Överkänslighet mot den aktiva substansen eller mot något hjälpämne. **Varningar och försiktighet:** För att underlätta spårbarhet av biologiska läkemedel ska läkemedlets namn och tillverkningssatsnummer dokumenteras.Tromboshändelser har rapporterats hos nyfödda och spädbarn som genomgått ingrepp med hjärtbypass och samtidigt fått höga doser (off-label) av ett annat läkemedel för C1-esterashämning (upp till 500 enheter(*)/kg) för att förhindra kapillärläckage-syndrom. Patienter med kända riskfaktorer för tromboshändelser (inklusive kvarkatetrar) bör övervakas noga. *(*) [Tidigare angivna potensvärden motsvarade en intern referensstandard varigenom 1 enhet (E) motsvarar den genomsnittliga mängden C1 esterashämmare i 1 ml normal humanplasma.] En internationell referensstandard (IE) har nu införts där IE också definieras som mängden C1 esterashämmare i 1 ml normal humanplasma.* Risken för att överföra smittämnen kan inte uteslutas helt när läkemedelsprodukter som beretts av humant blod eller plasma administreras. Lämplig vaccination (hepatit A och B) bör övervägas för patienter som regelbundet/upprepade gånger får en C1-esterashämmare som härrör från human plasma. I likhet med alla biologiska läkemedel kan överkänslighetsreaktioner uppkomma. Symtomen vid överkänslighetsreaktioner kan likna angioödemattacker. Detta läkemedel innehåller 11,5 mg natrium per injektionsflaska, motsvarande 0,5 % av WHOs högsta rekommenderat dagligt intag (2 gram natrium för vuxna). Cinryze ska endast ges till gravida kvinnor om det är tydligt indikerat. Ett beslut måste fattas om man ska avbryta amningen eller avbryta/avstå från behandling med Cinryze efter att man tagit hänsyn till fördelen med amning för barnet och fördelen med behandling för kvinnan. Cinryze kan ha mindre effekt på förmågan att framföra fordon och använda maskiner.

För fullständig information och priser, se www.fass.se.
Datum för översyn av produktresumé: 09/2022

Firazyr® (ikatibant) 30 mg, injektionsvätska, lösning i förfylld spruta. **Farmakoterapeutisk grupp:** Andra hematologiska medel, medel som används för behandling av hereditärt angioödem. **ATC-kod:** B06AC02. **Rx. (F). Subventionsbegränsning:** Subventioneras endast för akut behandling av svåra anfall av hereditärt angioödem. **Indikation:** Firazyr är avsett för symptombehandling av akuta anfall av hereditärt angioödem (HAE) hos vuxna, ungdomar och barn 2 år och äldre, med brist på C1-esterasinhibitor. **Kontraindikationer:** Överkänslighet mot den aktiva substansen eller mot något hjälpämne. **Varningar och försiktighet:** Patienter med laryngeala anfall ska tas om hand på lämplig medicinsk enhet efter injektion tills läkaren anser att det är säkert att skriva ut patienten. Vid ischemiska tillstånd skulle teoretiskt sett en försämring av hjärtfunktionen och en minskning av blodflödet i kranskärlen kunna uppstå. Försiktighet bör därför iakttas vid administrering av Firazyr till patienter med akut ischemisk hjärtsjukdom eller instabil angina pectoris. Försiktighet bör iakttas vid administrering av ikatibant till patienter veckorna efter en stroke. ACE-hämmare är kontraindicerade för HAE-patienter på grund av en möjlig förhöjning av bradykininhalten. Firazyr bör endast ges till gravida kvinnor om de förväntade fördelarna uppväger den potentiella risken för fostret (t.ex. för behandling av potentiellt livshotande laryngeala anfall). Det rekommenderas att ammande kvinnor som vill ta Firazyr inte ammar under 12 timmar efter behandlingen. Patienter bör uppmanas att inte köra eller använda maskiner om de känner sig trötta eller yra. **För patienter som aldrig tidigare har fått Firazyr ska den första behandlingen ges på medicinsk enhet eller under vägledning av läkare.**

För fullständig information och aktuella priser, se www.fass.se.
Datum för översyn av produktresumé: 04/2023.

TAKHZYRO (lanadelumab) 150 och 300 mg, injektionsvätska, lösning och lösning i förfylld spruta. **Farmakoterapeutisk grupp:** Övriga hematologiska medel, läkemedel använda vid ärftligt angioödem. **ATC-kod:** B06AC05. **Rx, (F). Subventionsbegränsning:** Subventioneras endast för rutinmässig prevention av recidiverande anfall av hereditärt angioödem (HAE) hos patienter i åldern 12 år och äldre med svår sjukdomsbild och minst fyra HAE-anfall i månaden. **Indikation:** TAKHZYRO är avsett för rutinmässig prevention av recidiverande anfall av hereditärt angioödem (HAE) hos patienter i åldern 2 år och äldre. **Kontraindikationer:** Överkänslighet mot den aktiva substansen eller mot något hjälpämne. **Varningar och försiktighet:** För att underlätta spårbarhet av biologiska läkemedel ska läkemedlets namn och tillverkningssatsnummer dokumenteras. Överkänslighetsreaktioner har observerats. I händelse av en allvarlig överkänslighetsreaktion måste administreringen av TAKHZYRO avbrytas omedelbart och lämplig behandling initieras. TAKHZYRO är inte avsett för behandling av akuta HAE-anfall. I händelse av ett genombrottsanfall av HAE ska individanpassad behandling initieras med ett godkänt, anfallskuperande läkemedel. Lanadelumab kan öka aktiverad partiell tromboplastintid (aPTT) till följd av interaktion mellan lanadelumab och aPTT-analysen. Användning av lanadelumab bör undvikas under graviditet. Det är känt att humant IgG utsöndras i bröstmjölk under de första dagarna efter förlossningen, vilket minskar till låga koncentrationer kort därefter. Följaktligen kan en risk för det ammade barnet inte uteslutas under denna korta tid. Därefter kan lanadelumab användas under amning om kliniskt behov föreligger.

För fullständig information och priser, se www.fass.se.
Datum för översyn av produktresumé: 11/2023.
Kontakt: Takeda Pharma AB, infosweden@takeda.com, tel. 08-731 28 00, **www.takeda.se**

Takeda Pharma AB
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112 51 Stockholm

C-APROM/SE/HAE/0028 Dec 2023