



# State of Management of HAE in Europe



**HAEi**

International Patient Organization  
for C1 Inhibitor Deficiencies



These pictures are of the same woman; during a facial attack and outside of an attack.

“ It took years for me to get a diagnosis. In that time, I lost time at school, was dismissed from jobs, and had two unnecessary operations—all because no one recognized that I had HAE. ”



## Section 1: Background

# Facing up to hereditary angioedema

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Hereditary angioedema (HAE) is a rare, potentially life threatening inherited disorder with symptoms of severe, painful, and recurring attacks of edema (swelling). HAE patients often suffer for many years and may be subject to unnecessary medical procedures and surgery prior to receiving an accurate diagnosis. While HAE cannot yet be cured, intelligent use of available treatments can help patients lead a relatively normal life.

### What is HAE?

HAE affects between one in 10,000 and one in 50,000 people worldwide.<sup>1,2</sup> HAE is hereditary because the genetic defect is passed on in families. If a parent has HAE, their child has a 50 per cent chance of inheriting the disorder.<sup>1</sup> The absence of family history does not rule out the HAE diagnosis, however, scientists report that as many as 25 per cent of HAE cases result from patients who had a spontaneous mutation of the C1-inhibitor gene at conception. These patients can pass the defective gene to their offspring.<sup>3</sup>

People with HAE experience attacks of severe swelling that affect various body parts including the hands, feet, face, airway (throat) and internal organs. Swelling of the throat is the most dangerous aspect of HAE because the airway can be closed and cause death by suffocation. Throat attacks must be treated as an emergency and patients must seek prompt medical attention as soon as throat involvement is suspected. Studies reveal that more than 50 per cent of patients will endure at least one throat attack in their lifetime.<sup>4,5</sup>

Almost all HAE patients experience abdominal attacks.<sup>6</sup> Swelling in the abdomen involves severe and excruciating pain, vomiting, and diarrhea.<sup>1,7,8</sup> Approximately one third of patients with undiagnosed HAE undergo unnecessary surgery during abdominal attacks because the symptoms mimic a surgical emergency.<sup>1</sup> Swelling of the face, hands, feet and other body parts is disfiguring, extremely painful and debilitating. It is not uncommon for HAE attacks to involve more than one body part.

Untreated, an average attack lasts for between 24 and 72 hours, but some attacks may go on for over a week.<sup>7</sup> The majority of patients experience their first attack during childhood or adolescence.<sup>5</sup> Most attacks occur spontaneously with no apparent reason. However, anxiety, stress, minor trauma, certain medical, surgical and dental procedures and illnesses such as colds and flu have been cited as triggers. ACE Inhibitors (a blood pressure control medication) and estrogen-derived medications (birth control pills and hormone replacement drugs) have also been shown to cause HAE attacks.

Patients often report a “tightness” sensation at the site where the swelling then occurs thirty minutes to several hours later. In some cases, this sensation can be felt 12 to 24 hours before the swelling begins. Approximately one quarter of HAE patients experience a flat, non-itching red blotchy rash both before and during an attack.

## What causes HAE?

HAE patients have a defect in the gene that controls a blood protein called C1-inhibitor, and therefore the disorder is also commonly referred to as C1-inhibitor deficiency. The genetic defect results in production of either inadequate or nonfunctioning C1-inhibitor protein. Normal C1-inhibitor helps to regulate the complex biochemical interactions of blood based systems involved in fighting disease, inflammatory response and coagulation. Because the defective C1-inhibitor does not adequately perform its regulatory function, a biochemical imbalance can occur and produce an unwanted peptide — called bradykinin — that induces the capillaries to release fluids into surrounding tissues, thereby causing swelling.

As shown in Table 1 there are two forms of HAE. The most common form of the disease — Type I — is characterized by low quantitative levels of C1-inhibitor and affects about 85 per cent of patients. Type II HAE affects the other 15 per cent of patients who have normal or elevated levels of C1-inhibitor, but the protein does not function properly. The two types are symptomatically indistinguishable and affect men and women equally.<sup>8</sup> Several investigators have noted a familial (and therefore inherited) angioedema in patients with normal levels of C1-inhibitor. Often found under the designation of 'HAE Type III', this form of angioedema is yet to be fully understood.

Table 1: Hereditary angioedema subtypes<sup>1</sup>

Type	Cause	Affects
Type 1	Low quantitative/antigenic levels of C1-inhibitor	85 per cent of cases
Type 2	Normal or raised levels of quantitative/antigenic C1-inhibitor, but the protein is non functional (as measured by the C1-inhibitor function assay)	15 per cent of cases

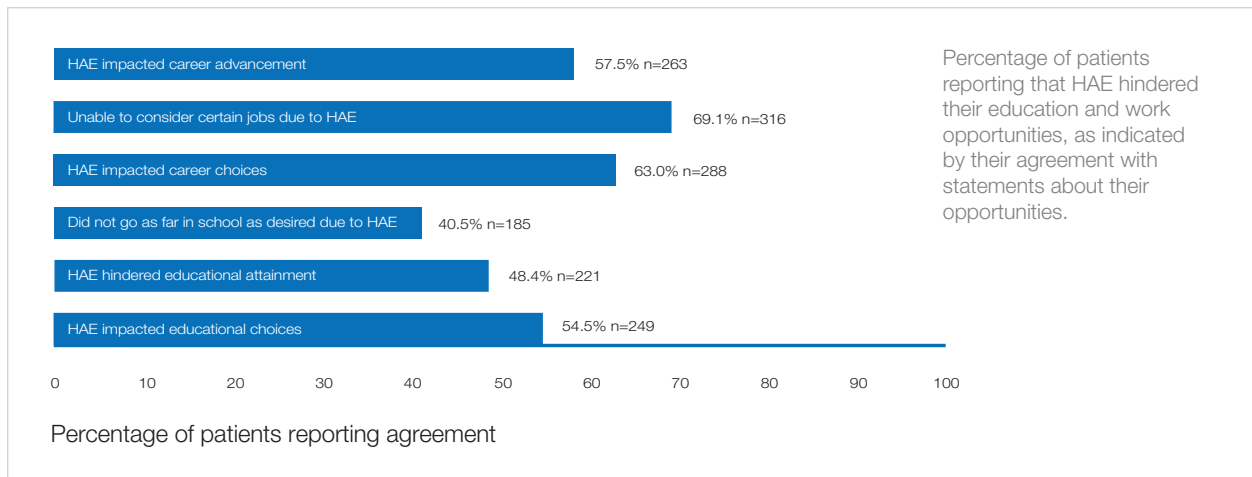
## How does HAE affect patients?

Untreated patients have attacks every 7 to 14 days on average, with a frequency ranging from virtually never to every three days.<sup>1,5</sup> There is considerable variation in the severity of HAE, even among affected family members.<sup>8</sup>

Because a typical attack lasts several days before it subsides, people with HAE may be debilitated by their symptoms for up to 100 days, or more than three months, of the year.<sup>9</sup> HAE imposes a substantial humanistic burden and patient's quality of life is significantly diminished by missed days of work, school, and leisure activities. HAE patients suffer from decreased physical and mental health, including depression.<sup>10</sup> In addition, HAE can cause patients to withdraw from education, work and social activities.

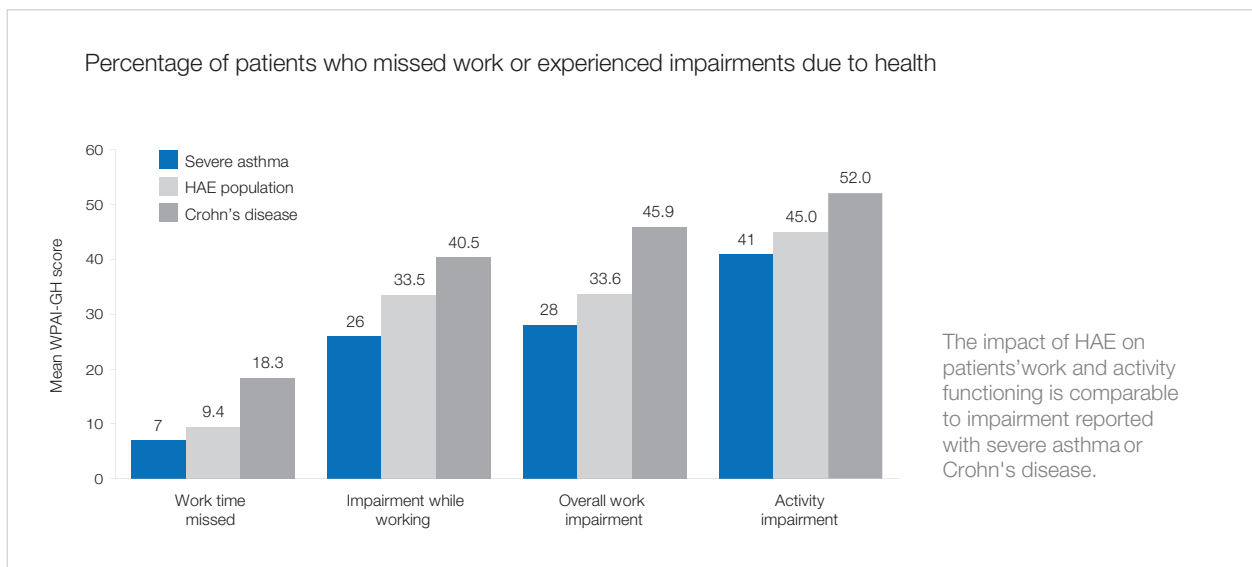
## HAE impact on patients

Figure 1: Missed opportunities due to hereditary angioedema (HAE)<sup>10</sup>



Two-fifths of people with HAE are clinically depressed, and they are twice as likely as the general population to be taking psychoactive drugs. The burden of HAE related to productivity impairment is similar to that seen in data from patients with better-recognized chronic diseases such as severe asthma and Crohn's disease.<sup>10</sup>

Figure 2: Work productivity and activity impairment—general health instrument (WPAI-GH)<sup>10</sup>



“ Patients with the deficiency of C1-inhibitor are not just an interesting model for study... they are critically ill. Many have ancestors that died suddenly from suffocation. Patients live in constant dread of life threatening laryngeal obstruction. ”<sup>9</sup>

## What are the costs of HAE?

The economic burden associated with HAE has a significant effect on patients, healthcare systems and society. A recent study conducted in the United States of America showed the substantial economic costs associated with both acute attacks and the ongoing chronic (long term) nature of the disorder.<sup>11</sup> The study indicated that total costs for an HAE patient could be as high as USD100,000 each year, and that almost all costs increase with disease severity.

However, the study may underestimate the real costs of HAE. The study was performed before acute therapy was available in the US. Over two thirds of patients in the study did not seek immediate medical help for attacks, probably because of their past experience of frequent misdiagnosis and limited treatment options. Nor did the study take into account the cost of inappropriate procedures or other unnecessary treatments commonly experienced by people with HAE.

## How is HAE diagnosed?

It is important that HAE patients receive an accurate diagnosis early in life. Various studies reveal that the risk of death, mainly due to suffocation during laryngeal attacks, can be as high as 30-40 per cent in undiagnosed patients.<sup>9</sup>

Delays in diagnosis are common in patients with hereditary angioedema. The average time between the onset of symptoms and the diagnosis was 22 years as of 1977 and was still more than 10 years as of 2005. The diagnosis should be suspected in any patient who presents with recurrent angioedema or abdominal pain in the absence of hives, which could suggest allergic angioedema.<sup>9</sup>

The diagnosis is complicated because HAE is extremely rare and most physicians may never see a patient with the disorder. In addition, most cases of angioedema are caused by an allergic reaction. Abdominal attacks may be mistaken for conditions such as appendicitis and often results in unnecessary exploratory surgery. Often, patients are misdiagnosed as having psychosomatic symptoms and are inappropriately referred for psychiatric evaluation.

**Table 2: Diagnosing hereditary angioedema<sup>3</sup>**

### Typical signs and symptoms of HAE include:

- Recurrent episodes of angioedema and abdominal attacks without urticaria (itching)
- Episodic attacks, with intervals between periods of swelling
- Onset of attacks in childhood or young adulthood, worsening around the time of puberty
- Prolonged attacks (typically 76-96 hours in duration)
- Family history of attacks (in 75 per cent of patients)
- Attacks do not respond to antihistamines or corticosteroids

Diagnosis must be confirmed by laboratory tests for C1-INH and other blood parameters

## Treatment of HAE

Because HAE is a non-allergic form of angioedema, symptoms do not respond to treatments for allergic reactions, such as antihistamines, corticosteroids and epinephrine. In the past, treatment was limited to tranexamic acid and pain medicines (including morphine) for acute attacks (attacks that are in progress), and anabolic steroids (such as danazol) for long-term attack prevention. Anabolic steroids are effective in reducing attack frequency in many patients, but are associated with significant side effects. Because anabolic steroids are male hormones, their side effects can be particularly severe in female patients. In addition, these drugs cannot be given to pregnant women and children.

As shown in Table 3, other therapies are available to prevent attacks and treat attacks once they have begun.

Table 3: Treating hereditary angioedema		
Drug names	Class of drug	Administered
<b>Acute treatment</b>		
Berinerit Cetor Cinryze*	C1-inhibitor concentrate (human plasma derived)	Intravenous (in the vein)
Ruconest (rhucin)	Recombinant C1-inhibitor	Intravenous (in the vein)
Firazyr (icatibant)	B2 Bradykinin Receptor Antagonist	Subcutaneous (under the skin)
Kalbitor (ecallantide)*	Kallikrein Inhibitor	Subcutaneous (under the skin)
<b>Prophylactic treatment</b>		
Danazol (danocrine)	Anabolic Steroids	Oral
	C1-inhibitor concentrate	Intravenous (in the vein)

\* Cinryze and Kalbitor are not yet authorized by the European Medicines Agency (EMA)

Patients typically receive treatment for attacks at a clinic or hospital. However, several studies have suggested that home treatment can be safe and reduce the severity and duration of attacks. Self-treatment can help patients regain control of and improve the quality of their lives, and avoid costly admission the hospital.<sup>1</sup>

A recent survey highlights wide variations in patients' access to treatment, including self-treatment, within Europe.



## Case history

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I am 25 years old; I'm married and have a little boy aged three years. I first noticed swelling in my hands and feet when I was about 11 years old, but it got worse when I was about 14. I took so much time off school that I did not do well in my examinations. I managed to find a job in an office, but found it very stressful and my attacks came more often. I left after about six months and since then I've just had short bits of temporary work.

My HAE doesn't just affect me. When I have an attack, my mother has to look after me and my little boy, as my husband can't take time off work. Things have got a lot better recently. When I feel an attack coming on, I inject myself with icatibant, which helps a lot. When my little boy goes to school, I'll see if I can get a full-time job.

## Case history

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I am 46 years old and have attacks twice every week. Mostly the attacks involve the abdomen—but I also have frequent laryngeal attacks. Until I turned 36 I was treated with anabolic steroids, which had very little effect on my attacks and their frequency and severity. I went through rescue tracheotomy several times—and was completely disabled, unable to work or attend social activities.

At the age of 36 I got in touch with a HAE specialist who immediately prescribed C1-inhibitor concentrate to me. I also learned self administration—and now I treat myself every three days at the early signs of an attack. Shortly after changing my therapy I could resume my full time job and suddenly lead a normal social life as well. The right treatment changed my life—and made it worth living again!





## Section 2: Survey

# The reality of hereditary angioedema in Europe

While HAE cannot yet be cured, intelligent use of available treatments can help to prevent the onset of symptoms and effectively manage attacks. However, a recent survey among patient organizations representing more than 11,600 patients in 12 countries\* revealed that HAE is all too often under-recognized, under-diagnosed, and under-treated.

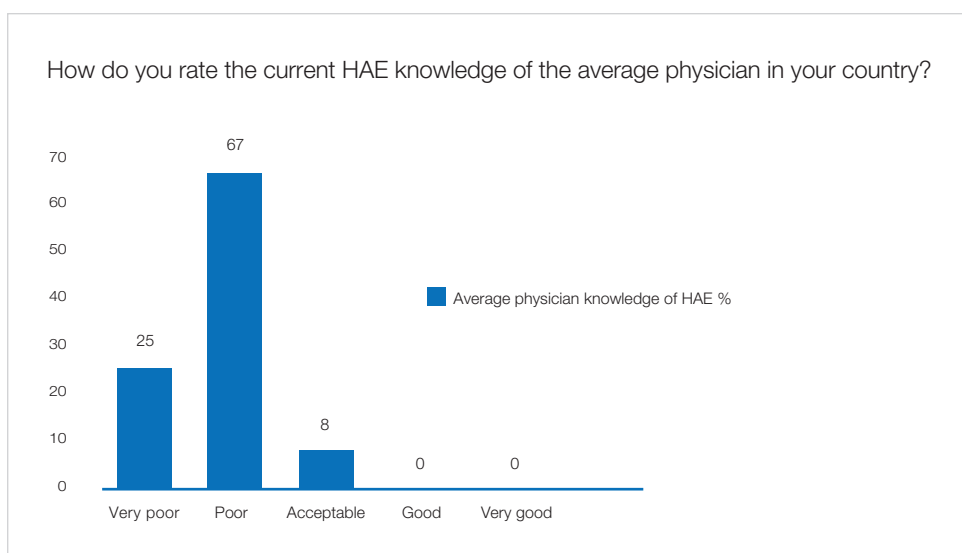
### Under-recognized

Because HAE is a rare disorder, the general knowledge of the average physician is very limited. The knowledge of the average health professional is rated:

- Poor or very poor by 92 per cent of respondents
- Adequate by 8 per cent of respondents
- No respondent rated professional knowledge as good or very good

### Average physicians' knowledge of HAE

Figure 3: Physician knowledge as rated by respondents



\* The survey was conducted in June 2010 among organizations representing patients with HAE in Austria, Czech Republic, Denmark, Finland, France, Germany, Hungary, Norway, Spain, Ukraine and the United Kingdom. Outside Europe the survey also included Israel. The HAE population of 11,600 is extrapolated, based on an average prevalence of one in 30,000.

HAE patients who visit hospital accident and emergency departments during an acute attack often do not receive appropriate treatment because physicians are not familiar with HAE. In the emergency department setting, inaccurate diagnosis is likely to result in delayed and/or inappropriate treatment (including exploratory surgery), and the patients risks unnecessary pain, suffering and, in some cases, death.

Low levels of professional awareness and knowledge are a particular concern in four of the 12 countries surveyed without a center of expertise in managing the condition. Specialist knowledge is critical in serious, rare disorders such as HAE, to ensure that patients receive an appropriate treatment designed to improve their quality of life and reduce their risk of disability and death.

“ Emergency-care doctors must know how to identify HAE, as I never know when my symptoms may develop into a laryngeal attack that could kill me.”

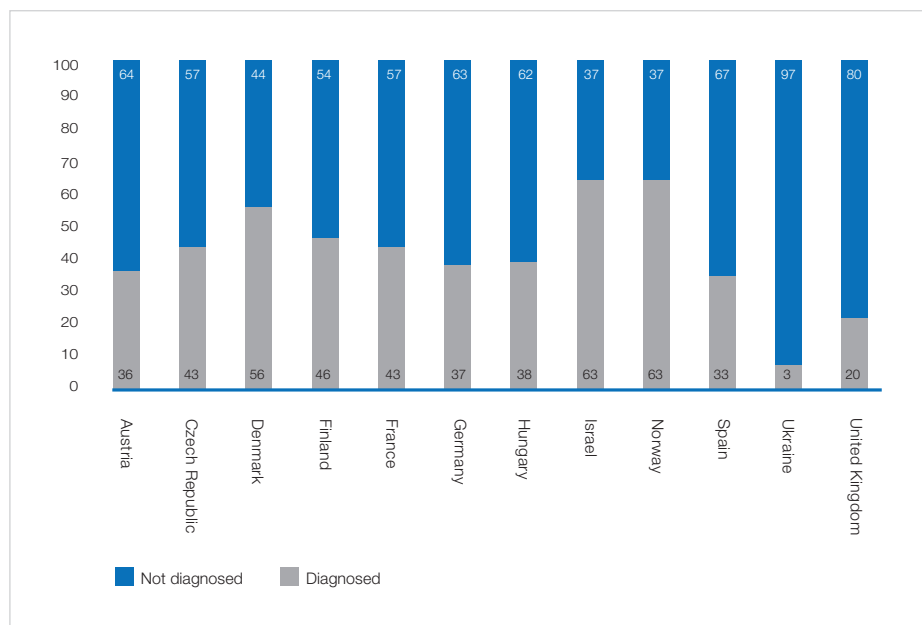
### Under-diagnosed

Respondents estimate that across Europe, less than two fifths of patients with HAE have received a formal diagnosis of their condition. There are alarming implications for the remaining three fifths of patients, given the high risk of serious and life-threatening complications associated with the disorder.

The estimated wide variation in the rate of diagnosis in the 12 countries surveyed is an additional cause for concern:

- In one country virtually no patients have received a diagnosis
- In one country, 20% of patients are diagnosed
- In four countries, 33% of patients are diagnosed
- In three countries, 40% of patients are diagnosed
- In only three countries, more than 50% of patients diagnosed

**Figure 4: Percentage of patients diagnosed or not, as estimated by respondents**



## Under-treated

Several treatments are available that prevent HAE episodes and effectively treat acute attacks (see page 7). Once authorized by EU regulatory authorities, a drug ought to be available for patients throughout Europe, but the survey highlights wide variations among countries:

- Patients in one country have no access to any treatment
- In other countries, patients' access to treatment can be as high as 80 per cent and as low as 10 per cent

“ My doctors cannot give me some HAE treatments even though they are available in nearby countries. ”

The availability of self-administered home treatment is important for patients with HAE. It means that they can give themselves routine preventive treatment, or they can treat themselves at the first sign of an acute attack. But, again, patients' access to the full range of treatments varies within Europe:

- In one country, patients have no access to either preventive or acute treatments
- In two countries, patients have access to acute treatment, but only if the attack is life-threatening
- In five countries, patients have access to acute treatments at home or through an accident and emergency department
- In five countries, patients have both preventive and acute treatments available at home

## Calling for action

This survey of patient organizations in 12 countries highlights lack of professional awareness and knowledge about HAE, widespread under-diagnosis and huge variations in access to approved treatments. This is unacceptable.

The diagnosis, treatment and care of patients with rare diseases like HAE are now priorities for European action and collaboration (see panel). Patients with HAE are now responding to this Europe-wide initiative with a call to action to their governments, health professionals, health authorities and fellow citizens.

“ My life was transformed when I was finally referred to a specialist. Now I am cared for by doctors who know about HAE. ”

## HAE: the European dimension

In June 2009 the European Council adopted recommendations on action in rare diseases\*, which are intended to:

- Support and strengthen the adoption before 2013 of national plans and strategies for rare diseases
- Improve the recognition and visibility of rare diseases
- Encourage more research into rare diseases
- Forge links between centers of expertise and professionals in different countries. This will be through the creation of European reference networks, in order to share knowledge and expertise and, where necessary, to identify where patients should go when such expertise cannot be made available to them

In achieving these ends, the role of patient organizations is particularly important.

The aims of this European Council initiative are to bring together resources for rare diseases that are currently fragmented across individual countries in the EU, and to help patients and professionals to collaborate across Member States in order to share and co-ordinate expertise and information.

The European Council defines rare diseases, including those of genetic origin, as life-threatening or chronically debilitating diseases that are of such low prevalence that special combined efforts are needed to address them so as to prevent significant disability and premature death, or a considerable reduction in an individual's quality of life or socio-economic potential. Low prevalence is generally defined as less than five per 10,000 people in the European Union.

\*Council Recommendation of 8 June 2009 in the field of rare diseases (2009/C 151/02).  
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF> (accessed 22 November 2010)

“ Being able to treat myself means that I keep my job and stay out of hospital. This is better for me and the health service. ”

## Section 3: Call to action

### HAE: a European call to action

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HAE patients want to have access to a treatment that allows them to lead a normal life. They want to control their symptoms so they can feel safe and fulfil their life's potential at school, work and in their relationships.

#### **Patients throughout Europe call for:**

- Governments, health authorities and health professionals to recognize that HAE is a serious, disabling, potentially life-threatening and chronic condition that must receive timely, accurate diagnosis and effective treatment.
- Professional education that enables health professionals to recognize HAE symptoms, diagnose the condition, and appropriately treat attacks, and understand the importance of specialist referral and ongoing care.
- Public and patient education that increases HAE awareness, and encourages patients to;
  - seek information on currently available treatment options.
  - form a partnership with their HAE treating physician.
- A treatment plan that meets each patient's individual needs and considers home treatment as a viable option.
- Co-operation among key stakeholders — patients, scientists, specialist doctors and industry — to continue research, including clinical trials, to improve treatment and ultimately to find a cure for HAE.
- Co-operation among national governments, regulatory authorities and industry to ensure continuing and, where appropriate, improved access to all available treatments.

# Appendix

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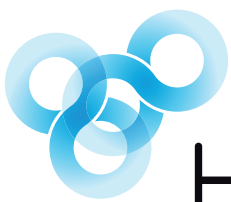
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“ There is very little home treatment. Only a few doctors accept that patients can treat themselves, and few patients are aware of the option. ”



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