

National Institute for Health and Care Excellence

Health Technology Evaluation

Sebetralstat for treating acute attacks of hereditary angioedema in people 12 years and over [ID6284]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	KalVista Pharmaceuticals	Yes, this is appropriate for appraisal under the single technology appraisal evaluation route.	Comment noted, no action required.
	British Society for Allergy and Clinical Immunology	The evaluation and proposed evaluation route is appropriate.	Comment noted, no action required.
	The Royal College of Pathologists	The evaluation and proposed evaluation route is appropriate.	Comment noted, no action required.
Wording	KalVista Pharmaceuticals	Yes	Comment noted, no action required.
	British Society for Allergy and	Yes, it does.	Comment noted, no action required.

Section	Stakeholder	Comments [sic]	Action
	Clinical Immunology		
	The Royal College of Pathologists	Yes, it does.	Comment noted, no action required.
	HAE	Yes	Comment noted, no action required.
Timing issues	KalVista Pharmaceuticals	<p>This evaluation is urgent and timely guidance is a high priority for patients with HAE and for the NHS.</p> <p>HAE is a rare inherited disease characterised by uncontrolled swellings (known as attacks) that may affect various parts of the body including the skin, mucous tissues in the abdomen and respiratory tract. The condition can be fatal.</p> <p>HAE impairs patients' ability to perform daily activities, proportional to pain/swelling severity, with patients reporting lower productivity, missed time from work or school and potentially resulting in missed career and educational opportunities. As such, many patients with HAE experience a significant psychological burden, including anxiety and depression.¹</p> <p>Treatments for HAE aim to prevent and/or treat HAE attacks as they occur, to reduce morbidity and mortality in order to improve health-related quality of life for HAE sufferers.</p> <p>Current on-demand treatments are administered intravenously or subcutaneously (administered either by healthcare professionals or by patients/carers following sufficient training) and create challenges to compliance with treatment guidelines for various reasons, for example:</p> <ul style="list-style-type: none"> • Prefer to treat at home: 72%² • Find on-demand treatment bulky: 32%² • Lack of privacy: 23%³ 	<p>Comment noted.</p> <p>NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme.</p> <p>The committee will consider unmet need during the development of the appraisal. No action required.</p>

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		<ul style="list-style-type: none"> • Fear of needles: 11%.³ <p>Sebetralstat is in clinical development as the first in class (plasma kallikrein inhibitor) and first oral on-demand treatment of HAE, to meet the current unmet need for a non-injectable treatment option.</p> <p>A safe and effective oral on-demand therapy can help ease the burden of treatment that people living with HAE are currently experiencing. Oral administration can help increase the likelihood of carrying treatment at all times, encouraging treatment of all attacks at the onset, resulting in a better sense of control over the disease and better clinical outcomes.⁴</p> <p>Of note, on 20th February 2024, sebetralstat was awarded the Innovation Passport by the MHRA, which is the first step in the UK ILAP (Innovative Licensing and Access Pathway) pathway to accelerate sebetralstat's time to reach the UK market.</p> <p>¹ Chong-Neto HJ. A narrative review of recent literature of the quality of life in hereditary angioedema patients. World Allergy Organ J. 2023 Mar 20;16(3):100758. doi: 10.1016/j.waojou.2023.100758</p> <p>² Betschel S, van Kooten S, Heckmann M, Danese S, Goga L, Guilarte M. HAE Patients Decision to Carry On-demand Treatment When Away from Home. Abstract presented at: 13th C1-inhibitor Deficiency & Angioedema Workshop, May 4-7, 2023; Budapest, Hungary. Allergy Asthma Clin Immunol. 2024;153(2) Suppl 1 A-4A: AB1-AB386. doi:10.1016/j.jaci.2023.11.287</p> <p>³ Grumach A, van Kooten S, Heckmann M, Danese S, Goga L, Garcez T. Understanding the complex decision-making associated with on-demand treatment of hereditary angioedema (HAE) attacks. Abstract presented at: EAACI 2023 Hybrid Congress, June 9-11, 2023; Hamburg, Germany. Allergy. 2023;78(suppl 1): 504. doi:10.1111/all.15922</p> <p>⁴ Valerieva A, Jones D, van Kooten S, et al. Treatment of HAE Attacks with Anticipated Future Oral On-demand Therapies as Reported by Patients. Abstract presented at: EAACI 2024, May 31-June 3, 2024; Valencia, Spain. In Press.</p>	

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	British Society for Allergy and Clinical Immunology	Although there are approved treatments for treating acute attacks in hereditary angioedema, all licensed therapies are injectable medications – which can result in pain from the injections as well as difficulty/anxiety/hesitancy/delay in the treatment being administered. An oral treatment option for acute attacks is a significant step forward, and this is an important evaluation for that reason.	<p>Comment noted.</p> <p>NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme.</p> <p>The methods of administration will be discussed during the appraisal. It will also be discussed if all benefits of sebetralstat were captured in the cost-effectiveness analyses. No action required.</p>
	The Royal College of Pathologists	Although there are approved treatments for treating acute attacks in hereditary angioedema, all licensed therapies are injectable medications – which can result in pain from the injections as well as difficulty/anxiety/hesitancy/delay in the treatment being administered. An oral treatment option for acute attacks is a significant step forward, and this is an important evaluation for that reason.	<p>Comment noted.</p> <p>NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation</p>

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			<p>and introduces the technology in the UK. NICE has scheduled this topic into its work programme.</p> <p>The methods of administration will be discussed during the appraisal. It will also be discussed if all benefits of sebetralstat were captured in the cost-effectiveness analyses. No action required.</p>
	HAE UK	There is an extreme urgency for this particular technology	<p>Comment noted.</p> <p>NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme. No action required.</p>

Section	Stakeholder	Comments [sic]	Action
Additional comments on the draft remit	-	-	-

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	KalVista Pharmaceuticals	<p>The background is well written and mostly clear; we have provided a revised draft of the first two paragraphs of the background (at the bottom of the Comment 2 table) that include the following for clarity and completeness:</p> <ul style="list-style-type: none"> Added that the controlled enzyme cascade relates to the kallikrein-kinin system Slight amendment to “swellings usually occur in the mouth” to “often occur” Rearranged the order of the swellings to position the airway swellings last <p>Amended “most angioedema attacks” to “many” that are associated with “known triggers such as” trauma, etc, and included that “often a specific trigger cannot be identified”.</p>	<p>Comments noted.</p> <p>The background section of the scope provides a brief overview of the disease. More detailed information will be explored at the submission stage.</p> <p>The scope has been updated to remove the statement that suggests most angioedema attacks are associated with known triggers.</p>
	British Society for Allergy and	<p>It should be noted that peripheral swelling can be significantly disruptive, affecting work or schooling, and resulting in days off sick or missing school. Although angioedema attacks can be triggered by various different things, it is not accurate that most of them have a known trigger. They are very often</p>	<p>Comments noted.</p> <p>The background section of the scope provides a</p>

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	Clinical Immunology	<p>random and unpredictable, as mentioned subsequently, and the unpredictability is a significant burden for patients.</p> <p>Type III HAE has been re-classified in the latest guidelines, and is old nomenclature – this is now known as HAE with normal C1 inhibitor, or HAE with one of the other recognised genetic mutations.</p> <p>Avoidance of trigger factors is not helpful for unpredictable random attacks, which can be frequent.</p>	<p>brief overview of the disease. The scope has been updated to state that HAE attacks are associated with disfiguration, severe pain, inability to perform daily activities and feelings of fear and anxiety. More detailed information will be explored at the submission stage.</p> <p>The scope has been updated to remove the statement that suggests most angioedema attacks are associated with known triggers.</p> <p>The scope has been updated to include the updated nomenclature for Type III HAE.</p>

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	The Royal College of Pathologists	<p>It should be noted that peripheral swelling can be significantly disruptive, affecting work or schooling, and resulting in days off sick or missing school.</p> <p>Although angioedema attacks can be triggered by various different things, it is not accurate that most of them have a known trigger. They are very often random and unpredictable, as mentioned subsequently, and the unpredictability is a significant burden for patients.</p> <p>Type III HAE has been re-classified in the latest guidelines, and is old nomenclature – this is now known as HAE with normal C1 inhibitor, or HAE with one of the other recognised genetic mutations.</p> <p>Avoidance of trigger factors is not helpful for unpredictable random attacks, which can be frequent.</p>	<p>Comments noted.</p> <p>The background section of the scope provides a brief overview of the disease. The scope has been updated to state that HAE attacks are associated with disfigurement, severe pain, inability to perform daily activities and feelings of fear and anxiety. More detailed information will be explored at the submission stage.</p> <p>The scope has been updated to remove the statement that suggests most angioedema attacks are associated with known triggers.</p> <p>The scope has been updated to include the</p>

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			updated nomenclature for Type III HAE.
	HAE UK	In general accurate	Comment noted. No action required.
	Takeda	<p>We consider that treatment goals for patients with HAE should be highlighted in the background information. International guidelines recommend that the goal of treatment is to achieve complete control of the disease; i.e. patients should have no angioedema attacks. In addition to eliminating attacks, restoring a normal quality of life is a key aim of treatment. Long-term prophylactic treatments have significantly reduced attack rates and have allowed many patients to achieve disease control and reduce QoL impairment.¹</p> <p>1. Maurer, M. et al. (2022) 'The international WAO/EAACI guideline for the management of hereditary angioedema – the 2021 revision and update', World Allergy Organization Journal, 15(3), p. 100627.</p>	<p>Comments noted.</p> <p>The background section of the scope provides a brief overview of the disease. More detailed information will be explored at the submission stage. No action required.</p>
Population	KalVista Pharmaceuticals	Yes	Comment noted, no action required.
	British Society for Allergy and Clinical Immunology	The population needs to specify which types of hereditary angioedema are included	<p>Comment noted.</p> <p>The population in the scope is intended to be broad to cover the final marketing authorisation. No action required.</p>
	The Royal College of Pathologists	The population needs to specify which types of hereditary angioedema are included	<p>Comment noted.</p> <p>The population in the scope is intended to be broad to cover the final</p>

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			marketing authorisation. No action required.
	HAE UK	The population is generally accepted as 1 in 30,000 to 1 in 50,000	Comment noted. This estimate has been updated in the scope with a UK-based estimate.
Subgroups	KaVista Pharmaceuticals	None suggested in the draft scope and we agree that there are no subgroups of people in whom sebetralstat should be examined separately	Comment noted. No action required.
	British Society for Allergy and Clinical Immunology	Paediatric patients may stand to gain greater benefit due to greater fear/hesitancy with injectable therapies	Comment noted. If evidence allows the company can present subgroups in their submission for the committee to consider. Committee will consider the relevance of these subgroups in line with NICEs methods outlined in the CHTE 2022 manual.
	The Royal College of Pathologists	Paediatric patients may stand to gain greater benefit due to greater fear/hesitancy with injectable therapies	Comment noted. If evidence allows the company can present subgroups in their submission for the committee to consider.

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			Committee will consider the relevance of these subgroups in line with NICEs methods outlined in the CHTE 2022 manual.
Comparators	KalVista Pharmaceuticals	Yes	Comment noted. No action required.
	British Society for Allergy and Clinical Immunology	Comparators are standard treatments currently used in the NHS, and are appropriate.	Comment noted. No action required.
	The Royal College of Pathologists	Comparators are standard treatments currently used in the NHS, and are appropriate.	Comment noted. No action required.
	HAE UK	My understanding is that this technology is a rescue medication ie is used as soon as a patient 'feels' and attack is happening and used much in the same way as Icatibant. However, this technology is such that patients could carry this with them at all times and it is not a subcutaneous painful technology. It would appear from the published data seen from clinical trials so far, that this oral therapy has extremely rapid response to onset of symptoms and therefore substantially fulfils an empty position of relevant, fast acting, portable and immediate acute treatment	Comment noted. Sebetralstat is anticipated to be licensed for the treatment of acute attacks of HAE. The mode of administration and unmet need will be considered during the appraisal.
	Takeda	We consider the comparators listed to be relevant to UK clinical practice.	Comment noted. No action required.

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Outcomes	KalVista Pharmaceuticals	<p>The outcomes listed are mostly appropriate. However, KalVista would like to request clarity on the “severity of angioedema attacks” outcome.</p> <p>PGI-S was a tool used in the phase 3 KONFIDENT study to broadly measure the baseline severity of treated attacks (classification of attacks included mild, moderate, severe or very severe).</p> <p>KalVista can report the patient numbers based on baseline severity of attack classification in the KONFIDENT trial.</p> <p>Please could NICE clarify what their expectation is for the “severity of angioedema attacks” outcome and what analyses are expected.</p> <p>Of note, severity is also indirectly captured within the following three other outcomes listed in the NICE draft scope:</p> <ol style="list-style-type: none"> 1. Time to beginning of symptom relief 2. Duration of angioedema attacks 3. Reduction in symptoms of angioedema attacks. <p>Our understanding is that while routine severity assessment would be insightful for HAE, there are currently no suitable and easy to use severity tools that are in widespread use in clinical practice.</p>	<p>Comments noted.</p> <p>The list of outcomes presented presents a summary of the main outcomes and is not intended to be an exhaustive list. The company is invited to include the outcomes commonly used in clinical practice in HAE, in relation to ‘severity of angioedema attacks’ within its evidence submission. No action required.</p>
	British Society for Allergy and Clinical Immunology	<p>Yes, outcomes are appropriate.</p> <p>Carer disutility should be considered as well if possible.</p>	<p>Comments noted.</p> <p>The key outcomes relevant to the population are outlined in the scope but this is not an exhaustive list. Where relevant, the organisation is welcome to provide the evidence on all outcomes that are important for people</p>

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			with the condition during the evaluation. No action required.
	The Royal College of Pathologists	Yes, outcomes are appropriate. Carer disutility should be considered as well if possible.	Comments noted. The key outcomes relevant to the population are outlined in the scope but this is not an exhaustive list. Where relevant, the organisation is welcome to provide the evidence on all outcomes that are important for people with the condition during the evaluation. No action required.
	HAE UK	Add 'time to patient feeling normal ie return to pre-attack stasis	Comment noted. Duration of angioedema attacks have been included in the outcomes. The list of outcomes is not intended to be exhaustive at this stage. Where relevant, the organisation is welcome to provide the evidence on all outcomes that are

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			important for people with the condition during the evaluation. No action required.
	Takeda	<p>The outcomes listed are appropriate; additionally, frequency and duration of hospitalisation should be considered to capture important health-related impacts of this technology. Regular monitoring of patients is important and highlighted in treatment guidelines to ensure outcomes are effectively understood.¹</p> <p>1. Maurer, M. et al. (2022) 'The international WAO/EAACI guideline for the management of hereditary angioedema – the 2021 revision and update', World Allergy Organization Journal, 15(3), p. 100627.</p>	<p>Comments noted.</p> <p>Frequency and duration of hospitalisation has been added as an outcome to the scope. The key outcomes relevant to the population are outlined in the scope but this is not an exhaustive list. Where relevant, the company and consultees are welcome to provide the evidence on all outcomes that are important for people with the condition during the evaluation.</p>

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Equality	KalVista Pharmaceuticals	No equality issues to raise	Comment noted. No action required.
	HAE UK	This technology should be available to all HAE patients with all Types of HAE. The remit could perhaps include the consequences of oral medication over needle administered which can be painful, difficult to manage if already experiencing swellings, and can quickly and easily be taken.	Comment noted. We have noted your comments on the equality impact assessment (EIA) form. Sebetralstat will be appraised within its marketing authorisation or a population for whom the company provides evidence if this is narrower than the marketing authorisation.
Other considerations	KalVista Pharmaceuticals	None	No action required.
Questions for consultation	KalVista Pharmaceuticals	<p>Question: Where do you consider sebetralstat will fit into the existing care pathway for the treatment of acute attacks of hereditary angioedema?</p> <p>Answer: We consider sebetralstat will be an option for the on-demand treatment of HAE attacks alongside currently available C1-esterase inhibitors for on-demand treatment (Berinert, Cinryze, Ruconest) and icatibant.</p> <p>Question regarding prescribing and follow up</p>	<p>Comments noted.</p> <p>The positioning of the technology in the treatment pathway will be considered by the committee during the appraisal. No action required</p>

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		Answer: [Option C] We can confirm that sebetralstat will be prescribed in secondary care with routine follow-up in secondary care.	
	British Society for Allergy and Clinical Immunology	Sebetralstat should fit into the existing pathway where other NICE TA medications sit i.e. prescribed within specialised immunology services and routine follow-up by the same service. C1 inhibitors and icatibant are the only effective licensed therapies for treatment of acute attacks of HAE. A small minority of patients do increase the dose of their attenuated androgens for acute attacks – this is not recommended in guidelines and there is no evidence for the efficacy of this approach. Sebetralstat should be considered for managed access as well.	Comments noted. The positioning of the technology in the treatment pathway will be considered by the committee during the appraisal. No action required
	The Royal College of Pathologists	Sebetralstat should fit into the existing pathway where other NICE TA medications sit i.e. prescribed within specialised immunology services and routine follow-up by the same service. C1 inhibitors and icatibant are the only effective licensed therapies for treatment of acute attacks of HAE. A small minority of patients do increase the dose of their attenuated androgens for acute attacks – this is not recommended in guidelines and there is no evidence for the efficacy of this approach. Sebetralstat should be considered for managed access as well.	Comments noted. The positioning of the technology in the treatment pathway will be considered by the committee during the appraisal. No action required
Additional comments on the draft scope	KalVista Pharmaceuticals	Please find below our proposed first two paragraphs of the background after some minor suggested amendments (as detailed above): <i>“Hereditary angioedema (HAE) is a rare genetic disorder, associated with the deficiency of the protein C1-esterase inhibitor, which is a regulator of inflammatory pathways. Normally, C1-esterase inhibitor controls the enzyme cascade reactions of the kallikrein-kinin system so that uncontrolled swelling of the subcutaneous and submucosal tissues do not occur. In patients with HAE, at times of physiological or psychological stress, the function of the C1-</i>	Comments noted. The background section of the scope provides a brief overview of the disease. More detailed information will be explored at the submission stage.

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		<p><i>esterase inhibitor is insufficient, resulting in the accumulation of excessive fluid (oedema) and localised oedematous swellings. The swellings often occur in the mouth, the gut (affecting the submucosal tissues) and the deep tissues of the skin (affecting the dermis and subcutaneous tissues) causing significant impact, for example if the hands, feet or genitals are affected. The swellings can also occur in the airway, causing potentially life-threatening difficulty with breathing.”</i></p> <p><i>“Many angioedema attacks are associated with known triggers such as trauma, medical procedures, emotional stress, menstruation, oral contraceptive use, infections, or the use of medications such as ACE inhibitors, but often a specific trigger cannot be identified. Attacks are unpredictable; the severity and frequency of previous attacks do not predict severity and frequency of future attacks. Attacks usually last approximately 2 to 5 days before resolving spontaneously.”</i></p>	The scope has been updated to remove the statement that most angioedema attacks are associated with known triggers.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

Genetic Alliance UK

Neonatal and Paediatric Pharmacists Group