National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Lanadelumab for the long-term prevention of angioedema attacks in hereditary angioedema types I and II

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Shire	Shire feel that this is an appropriate topic to refer for appraisal however it should be recognised that the Single Technology Appraisal (STA) does not adequately account for orphan medicines such as lanadelumab and rare conditions like hereditary angioedema (HAE).	Landelumab does not fulfil the criteria for Highly Specialised Technologies as described in the Interim Process and Methods of the Highly Specialised Technologies and will be appraised as a Single Technology Appraisal.
	British Association of Dermatologists	Yes.	No comment

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	HAE UK	Yes, this is an appropriate subject for NICE to assess.	Comment noted. No action required.
Wording	Shire	No further comments.	Comment noted. No action required.
	British Association of Dermatologists	Yes.	Comment noted. No action required.
	HAE UK	Yes.	Comment noted. No action required.
Timing Issues	Shire	People are constantly at risk of mortality and morbidity from this condition. Lanadelumab can ameliorate these risks and it is [redacted]. Therefore, there is an urgent need to evaluate this drug so that it can be made available to meet patient needs as soon as it is licensed.	Comments noted. NICE will schedule the appraisal of lanadelumab in a timely manner i.e. close to the marketing authorisation being granted
	HAE UK	I believe the license has yet to be approved?	Comments noted. NICE will schedule the appraisal of lanadelumab in a timely manner i.e. close to the marketing authorisation being granted

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Shire	Shire suggests rewording “The swellings usually occur in the airway, the mouth and the gut” as airway attacks are less common, the most common being the gastro-intestinal and peripheral. There is a list of risk factors for attacks but it should be noted that many attacks do not have an apparent cause. It should be noted that attacks are unpredictable in timing and severity, and that severity and frequency of previous attacks does not predict severity and frequency of future attacks. Second bullet point of page 1 should be “type II is defined by normal level of...” Shire notes that the prevalence figures differ from those in the recent NHS England Clinical Commissioning Policy, where the reported prevalence is 1 in 50,000 to 100,000 people, and recommends that the figures in the scope should be adjusted to be consistent and thus reflective of the best evidence.	Comment noted. The background section of the scope has been revised.
	British Association of Dermatologists	Adequate.	Comment noted. No action required.
	HAE UK	Reasonable, but fails to account for the extreme pain of severe swellings and potential life-threatening episodes of laryngeal swellings.	Comment noted. The background section of the scope has been revised.

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The technology/ intervention	Shire	Shire suggests rewording as “Lanadelumab is administered subcutaneously as a 2 mL injection.”	Comment noted. The technology section of the scope is not meant to report on the dosage of the technology. No change to o the scope required.
	British Association of Dermatologists	Yes.	Comment noted. No action required.
	HAE UK	In so far as it goes.	Comment noted. No action required.
Population	Shire	The population is appropriately defined and in line with the submitted licence indication; should the licence wording be revised, Shire will inform NICE and will reconsider the population.	Comment noted. No action required.
	British Association of Dermatologists	Yes.	Comment noted. No action required.
	HAE UK	I would suggest that population should be defined as having failed prophylaxis with attenuated androgens and having one or more clinically significant swellings per month.	Comment noted. Clinical experts explained that they would usually prescribe attenuated androgens as a first-line treatment. However, because attenuated androgens

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			can cause infertility in females, it would not be prescribed to adolescents or women who have not completed their family. In such instances, clinicians would prescribe either a C1-eterase inhibitor or anti-fibrinolytics, although the latter is not used routinely by all clinicians. Clinicians agreed that HAE attacks were considered "frequent" when they occurred at least 1/month. No change was made to the scope
Comparators	Shire	Shire feel that attenuated androgens do not represent a valid comparator and that lanadelumab is likely to be used as an alternative to C1-esterase inhibitors. There is a lack of robust data to support the use of attenuated androgens in the treatment of HAE; furthermore the available evidence does	Comment noted. Clinical experts explained that they would usually prescribe

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		not allow a valid comparison with Lanadelumab (or C1-esterase inhibitors) to be made. The only comparator should be C1-esterase inhibitors in a long-term prevention setting.	attenuated androgens as a first-line treatment. However, because attenuated androgens can cause infertility in females, it would not be prescribed to adolescents or women who have not completed their family. In such instances, clinicians would prescribe either a C1-eterase inhibitor or anti-fibrinolytics, although the latter is not used routinely by all clinicians. No change was made to the scope
	British Association of Dermatologists	Yes.	Comment noted. No action required.
	HAE UK	Yes. C1-INH either on demand or prophylactically best alternative	Comment noted. No action required.

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Outcomes	Shire	Time to first attack should also be included in the list of outcomes.	Comment noted. It was agreed that 'Time to first attack' should not be included as it would be captured by the outcome measure 'frequency of attacks'. More specific outcomes can be considered under the broad scope outcomes, as part of the full appraisal. No change was made to the scope.
	British Association of Dermatologists	Yes.	Comment noted. No action required.
	HAE UK	Fail to note the substantial social benefits of treating long term conditions effectively, e.g. improved life chances of uninterrupted education, facility to enter full time occupations etc.	Comment noted. The reference case described in more detail in the NICE methods for technology appraisal.
Economic analysis	Shire	No further comments.	Comment noted. No action required.
	HAE UK	None.	Comment noted. No action required.
	Shire	No further comments.	Comment noted. No action required.

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Equality and Diversity	HAE UK	No comment.	Comment noted. No action required.
Other considerations	HAE UK	Consideration of cost savings of long term effective treatment by increasing contribution to society.	Comment noted. The reference case described in more detail in the NICE methods for technology appraisal.
Innovation	Shire	Lanadelumab, a first in class, monoclonal antibody against active plasma kallikrein, offers a more effective and convenient therapy for patients suffering from HAE due to its unique mechanism of action, target selectivity, long half-life allowing sustained control of plasma kallikrein activity with infrequent dosing (once every 2 weekly or 4 weekly self-administration in 2 mL subcutaneous injection), favourable safety profile, highly statistically significant and clinically meaningful efficacy results, including a high proportion of subjects (up to 77%) who remained attack free over 16 week assessment period once steady-state was achieved, and improvement in HRQoL demonstrated in a 26 week prevention study and supported by data during an additional 6 months of exposure. As such, lanadelumab has been demonstrated to bring significant benefit over existing therapies for HAE patients and therefore should be considered innovative. This is also reinforced by the current EMA accelerated review. Applications are eligible for accelerated assessment if the CHMP decides the product is of major interest for public health and therapeutic innovation. There are limitations in currently available treatments for routine prevention of HAE:	Comments noted. Innovation will be considered in more detail as part of the full appraisal. No action required.

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		C1-esterase inhibitors: • Administration is 2-3 times per week. • Less efficacious in attack reduction (Shire; Data on file). • Class warnings (transmissible infectious agents, thromboembolic events and hypersensitivity), plasma-derived.	
	British Association of Dermatologists	**Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Yes. **Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** No	Comments noted. No action required.
	HAE UK	Effective prophylaxis by treating cause rather than replacing missing protein (HELP study). Considerable benefit of sub-cutaneous administration in terms of training and skill (generally accepted).	Comments noted. Innovation will be considered in more detail as part of the full appraisal.
Questions for consultation	Shire	**How many people with types I and II HAE would be expected to have treatment with lanadelumab in England each year?** Over a 3 year period it is expected that between 55 and 100 patients will be treated with lanadelumab.	Comment noted. No action required.

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		Do you consider that the use of lanadelumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Due to the difficulty in quantifying the impact of anxiety and acute events on patients' quality of life, some benefits of an effective treatment are likely to exist outside the QALY calculations. Furthermore, due to the difficulty in identifying long term data on mortality associated with each attack, the benefit of an effective treatment on mortality is unlikely to be captured by the QALY calculations.	Comment noted. Committee will consider whether there are significant and substantial HRQoL as part of any future appraisal of lanadelumab.
	Barts Health NHS Trust	**Is the population in the scope defined appropriately?** Based on the populations in the clinical trials, yes, but other populations not included in the trial could benefit such as HAE-III or HAE-N **The clinical trial recruited people with hereditary angioedema types I or II who have at least 1 attack every 4 weeks. Would people with less frequent attacks be given the treatment?** This should be considered on individual case basis rather than purely based on the number of attacks. E.g. based on severity of attack, are the attacks life threatening? **Which treatments are considered to be established clinical practice in the NHS for long-term prevention of the acute attacks in people with types I and II HAE? In particular is Cinryze considered established clinical practice in the NHS for the long-term prevention of angioedema attacks in people with types I and II HAE?** Cinryze is considered an established option for prophylaxis and is prescribed based on NHSE commissioning policy. (Clinical Commissioning Policy: Plasma-derived C1-esterase inhibitor for prophylactic treatment of hereditary angioedema (HAE) types I and II Reference: NHS England: 16045/P).	Lanadelumab will appraised as part of its marketing authorisation. Population in scope has been amended. Comparators in scope have been amended.

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		How many people with types I and II HAE would be expected to have treatment with lanadelumab in England each year? 20-40.	The number of people eligible for treatment with lanadelumab is unknown as it is dependent on the definition of 'frequent' angioedema attacks. Estimates vary from approximately 50 -1000.
		Are the subgroups suggested in 'other considerations' appropriate? Patient unable to tolerate alternative medications. e.g. patients with high risk of thromboembolism, patient on C1 esterase inhibitor concentrate prophylaxis requiring increasing doses with suboptimal response	More specific outcomes can be considered under the broad scope outcomes, as part of the full appraisal
		Do you consider lanadelumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Absolutely. The most innovative product in the market. Majority of the patients in our cohort (4/5) benefitted immensely.	Innovation will be considered in more detail as part of the full appraisal.

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		Do you consider that the use of lanadelumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? A long term comparison between lanadelumab and other available treatments has not been made but patients report life changing experiences that would probably be difficult to quantify. I would suggest interviewing some of the patients on the trial in the UK performed at Barts Health NHS Trust. I would be happy to approach the patients and if they consent provide you with their details.	Committee will consider whether there are significant and substantial HRQoL as part of any future appraisal of lanadelumab
Additional comments on the draft scope	British Association of Dermatologists	We support the appraisal and feel Lanadelumab will be a much needed additional therapy for long-term prophylaxis of angioedema attacks in hereditary angioedema types I and II. Clinical trial evidence supports the effectiveness of lanadelumab which has few side effects.	Comment noted

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

None