NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Anakinra for treating Still's disease [ID1463]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Anakinra for treating Still's disease [ID1463]

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document** from **Swedish Orphan Biovitrum Ltd ("Sobi")**

   Consultee and commentator comments on the Appraisal Consultation Document
   None received.

   Comments on the Appraisal Consultation Document from experts:
   None received.

   Comments on the Appraisal Consultation Document received through the NICE website
   None received.

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Anakinra for treating Still's disease

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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 number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	SOBI	Treatments for rare diseases will never achieve the standard of extensive data generation seen in common diseases. We are grateful to see that the rarity of this disease has been acknowledged, although a little surprised that the interpretation of clinical evidence for a well established treatment, which has been repurposed for a rare disease, is seemingly held to the same standard as for new drugs in common diseases. Anakinra, earlier in the treatment pathway and without the requirement of prior csDMARD use, is considered the standard of care in a number of European countries, including the Netherlands (for which the study by ter Haar et al. reports findings in Dutch practice) and Scotland (SMC2104).2,3Care for NHS patients with Still's disease in England and Wales will continue to fall short of this current standard of care, putting them at risk of progressive joint and systemic damage (also acknowledged in the ACD).	Thank you for your comments. The committee considered all the available clinical evidence. See sections 3.4 to 3.6 of the FAD.
2	Consultee	SOBI	The known continuum of Still's disease, in which sJIA and AOSD are understood to be the same disease presenting at different ages, does not appear to have been taken into account in the Committee's conclusions. No clinical evidence was presented that would support the suggestion that biologics should follow only after failure of two DMARDs in adults. We understand that current NHS policies mean that tocilizumab is available to sJIA and AOSD patients at different stages, and therefore, based on a cost-minimisation analysis framework, NICE's decision is to allow clinicians to choose between both biologic therapies following treatment with csDMARD(s). However, as a direct consequence of the assumptions forced by a cost minimisation model, sJIA and AOSD patients will not be able to access biologic therapies at the same point in time.	As acknowledged in the comment, the committee is only able to recommend anakinra as a cost-effective option at the positions in the pathway that tocilizumab is currently used in the NHS. See section 3.14 of the FAD.
3	Consultee	SOBI	The ACD highlights several limitations with the submitted economic model, most of which are either directly or indirectly linked to the limited clinical evidence base to inform the model (and so a number of simplifying assumptions were unavoidably made within the model). In one of these comments, it is stated that, with the exception of remission, the benefits of remaining on a given treatment were not captured in the model (ACD Section 3.7). It is understood that this relates to the fact that patients remaining on a given treatment may accrue benefits in terms of symptom control which are not captured within a specific utility value. We acknowledge that in the economic model, no change in utility value was captured between patients with benefits in terms of symptom control versus those without symptom control. However, the main benefit outside of remission, which is explicitly captured within the model, is the delayed time to, or potential avoidance	This has been clarified in section 3.7 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			of, “unresolved” disease. This health state was associated with a lower utility value and increased medical resource use. We therefore wish to clarify that while the comment raised in relation to potentially-omitted benefits from the model is partially true, it does not acknowledge that another key aspect of the model was that continued treatment for symptom control is associated with a higher utility through avoiding “unresolved” disease (either indefinitely, or for a certain period of time).	
4	Consultee	SOBI	The clinical evidence base consistently fails to support the efficacy of csDMARDs for the treatment of Still’s disease. We are concerned that the ACD focusses on an exploratory datapoint from the Nordström et al study, as erroneous reassurance on the efficacy of csDMARDs prior to anakinra. The analysis appears to set aside studies, submitted during review, which directly and consistently challenges the efficacy of csDMARDs in Still’s disease. The recently-published Single Hub and Access point for paediatric Rheumatology in England (SHARE) consensus recommendations, on the diagnosis and treatment of sJIA, confirmed no proven benefit of methotrexate in the treatment of systemic features of the disease	Section 3.8 notes the difference in clinical expert opinion on this point and acknowledges the uncertainty.
5	Consultee	SOBI	The ACD explains that, based on the limitations of the cost-utility analysis submitted, and that the efficacy of anakinra and tocilizumab are considered to be broadly similar (on a population level), a cost-minimisation analysis is sufficient for decision-making. The use of tocilizumab in current NHS practice is based on NICE TA238 (for sJIA, published in December 2011), and the NHS England clinical commissioning policy 170056P (for AOSD, published in June 2018).6,8 Whilst we acknowledge the reasons behind the decision to consider a cost-minimisation analysis, we note that by definition, this means that it would not be possible for the Committee to make a recommendation for anakinra to be used outside of where tocilizumab is currently used in NHS practice. It is our view that any alternative economic modelling approach, that could address the limitations highlighted within the ACD, would not be possible due to the limited evidence base. For example, the ability to reflect a non-constant rate of treatment discontinuation would be impossible robustly to estimate with available evidence. This impasse means that it is unlikely the committee would ever be able to make a decision outside of a cost-minimisation framework, which is extremely disappointing for patients that may benefit from accessing anakinra earlier in the treatment pathway.	Comment noted. The reasons for using a cost minimisation approach are outlined in section 3.11 of the FAD.

NICE National Institute for Health and Care Excellence

Anakinra for treating Still's disease [ID1463]

Consultation on the appraisal consultation document – deadline for comments **5pm** on **Wednesday 27 January 2021**. Please return to: **NICE DOCS**

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Swedish Orphan Biovitrum Ltd ("Sobi")
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments
1	Treatments for rare diseases will never achieve the standard of extensive data generation seen in common diseases. We are grateful to see that the rarity of this disease has been acknowledged, although a little surprised that the interpretation of clinical evidence for a well established treatment, which has been repurposed for a rare disease, is seemingly held to the same standard as for new drugs in common diseases. Anakinra, earlier in the treatment pathway and without the requirement of prior csDMARD use, is considered the standard of care in a number of European countries, including the Netherlands (for which the study by ter Haar *et al.* reports findings in Dutch practice) and Scotland (SMC2104).[2,3] Care for NHS patients with Still's disease in England and Wales will continue to fall short of this current standard of care, putting them at risk of progressive joint and systemic damage (also acknowledged in the ACD).

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2	The known continuum of Still's disease, in which sJIA and AOSD are understood to be the same disease presenting at different ages, does not appear to have been taken into account in the Committee's conclusions. No clinical evidence was presented that would support the suggestion that biologics should follow only after failure of two DMARDs in adults. We understand that current NHS policies mean that tocilizumab is available to sJIA and AOSD patients at different stages, and therefore, based on a cost-minimisation analysis framework, NICE's decision is to allow clinicians to choose between both biologic therapies following treatment with csDMARD(s). However, as a direct consequence of the assumptions forced by a cost minimisation model, sJIA and AOSD patients will not be able to access biologic therapies at the same point in time.
3	The ACD highlights several limitations with the submitted economic model, most of which are either directly or indirectly linked to the limited clinical evidence base to inform the model (and so a number of simplifying assumptions were unavoidably made within the model). In one of these comments, it is stated that, with the exception of remission, the benefits of remaining on a given treatment were not captured in the model (ACD Section 3.7). It is understood that this relates to the fact that patients remaining on a given treatment may accrue benefits in terms of symptom control which are not captured within a specific utility value. We acknowledge that in the economic model, no change in utility value was captured between patients with benefits in terms of symptom control versus those without symptom control. However, the main benefit outside of remission, which is explicitly captured within the model, is the delayed time to, or potential avoidance of, "unresolved" disease. This health state was associated with a lower utility value and increased medical resource use. We therefore wish to clarify that while the comment raised in relation to potentially-omitted benefits from the model is partially true, it does not acknowledge that another key aspect of the model was that continued treatment for symptom control is associated with a higher utility through avoiding "unresolved" disease (either indefinitely, or for a certain period of time).
4	The clinical evidence base consistently fails to support the efficacy of csDMARDs for the treatment of Still's disease. We are concerned that the ACD focusses on an exploratory datapoint from the Nordström *et* al study, as erroneous reassurance on the efficacy of csDMARDs prior to anakinra. The analysis appears to set aside studies, submitted during review, which directly and consistently challenges the efficacy of csDMARDs in Still's disease. The recently-published Single Hub and Access point for paediatric Rheumatology in England (SHARE) consensus recommendations, on the diagnosis and treatment of sJIA, confirmed no proven benefit of methotrexate in the treatment of systemic features of the disease.[4]
5	The ACD explains that, based on the limitations of the cost-utility analysis submitted, and that the efficacy of anakinra and tocilizumab are considered to be broadly similar (on a population level), a cost-minimisation analysis is sufficient for decision-making. The use of tocilizumab in current NHS practice is based on NICE TA238 (for sJIA, published in December 2011), and the NHS England clinical commissioning policy 170056P (for AOSD, published in June 2018).[6,8] Whilst we acknowledge the reasons behind the decision to consider a cost-minimisation analysis, we note that by definition, this means that it would not be possible for the Committee to make a recommendation for anakinra to be used outside of where tocilizumab is currently used in NHS practice. It is our view that any alternative economic modelling approach, that could address the limitations highlighted within the ACD, would not be possible due to the limited evidence base. For example, the ability to reflect a non-constant rate of treatment discontinuation would be impossible robustly to estimate with available evidence. This *impasse* means that it is unlikely the committee would ever be able to make a decision outside of a cost-minimisation framework, which is extremely disappointing

	for patients that may benefit from accessing anakinra earlier in the treatment pathway.

References

1. Sobi. anaSTILLS study data (Sobi data on file). 2020.
2. Ter Haar NM, van Dijkhuizen EHP, Swart JF, van Royen-Kerkhof A, El Idrissi A, Leek AP, et al. Treatment to Target Using Recombinant Interleukin-1 Receptor Antagonist as First-Line Monotherapy in New-Onset Systemic Juvenile Idiopathic Arthritis: Results From a Five-Year Follow-Up Study. Arthritis Rheumatol Hoboken NJ. 2019 Jul;71(7):1163–73.
3. Scottish Medicines Consortium (SMC). SMC advice 2104: anakinra (Kineret) [Internet]. Scottish Medicines Consortium. 2018 [cited 2021 Jan 7]. Available from: https://www.scottishmedicines.org.uk/medicines-advice/anakinra-kineret-fullsubmission-smc2104/
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6. National Health Service (NHS). Clinical Commissioning Policy: Anakinra/tocilizumab for the treatment of Adult-Onset Still's Disease refractory to second-line therapy (adults) [Internet]. 2018 [cited 2019 Sep 22]. Available from: https://www.england.nhs.uk/publication/clinical-commissioning-policy-anakinra-tocilizumab-for-the-treatment-of-adult-onset-stills-disease-refractory-to-second-line-therapy-adults/
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8. National Institute for Health and Care Excellence (NICE). TA238: Tocilizumab for the treatment of systemic juvenile idiopathic arthritis [Internet]. 2011 [cited 2019 Jun 25]. Available from: https://www.nice.org.uk/guidance/ta238

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Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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