NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Anakinra for treating Still's disease

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of anakinra within its marketing authorisation for treating Still's disease.

Background

Still's disease is a rare systemic inflammatory disorder which can affect adults (adult-onset Still's disease) or children (systemic juvenile idiopathic arthritis). The symptoms of Still's disease can develop quickly or over time and include a daily fever which usually peaks in the late afternoon/early evening, joint and muscle pain and swelling (commonly in the knees, wrists and ankles) and a pink rash. Signs and symptoms are highly variable between individuals. Adult-onset Still's disease can take 2 forms, systemic or arthritis-predominant. In the systemic form, the predominant symptoms are acute onset characterised by fever, weight loss and other systemic manifestations. The arthritis-predominant form is characterised by slow onset and symptoms mainly affecting the joints. The cause of Still's disease is unknown although it is thought that abnormalities in a particular part of the immune system causes episodes of inflammation to occur in the body. It may be difficult to diagnose Still's disease because diagnosis is usually based on clinical evaluation, patient history, identification of characteristic findings, and exclusion of other possible disorders, rather than specific tests or laboratory findings that may differentiate it from similar disorders.

Still's disease affects between 400 and 800 adults[1] and around 1,000 children in England.[2] Adult-onset Still's disease primarily affects young adults[3] while systemic idiopathic juvenile arthritis affects children under 16 years old, with onset usually between 3–5 years old, and the disease resolving before adulthood in about 50% of patients.[4]

Treatment aims to induce and maintain remission of symptoms; controlling pain, fever and inflammation, and reducing joint damage, disability and loss of function, thereby improving quality of life. Still's disease, including adult-onset Still's disease and systemic juvenile idiopathic arthritis, is treated initially with combinations of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics and corticosteroids, before progressing to non-biological disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate. If symptoms are not adequately controlled with non-biological DMARDs, biological therapies such as tocilizumab or TNF-alpha inhibitors may be used.

In systemic juvenile idiopathic arthritis, NICE technology appraisal guidance 238 recommends tocilizumab (monotherapy or in combination with

methotrexate) for children and young people aged 2 years and older whose disease has responded inadequately to NSAIDs, systemic corticosteroids and methotrexate. It is not recommended when the disease continues to respond to methotrexate or has not yet been treated with methotrexate. There is no NICE technology appraisal guidance for adult-onset Still's disease.

The technology

Anakinra (Kineret, Swedish Orphan Biovitrum) is a recombinant Interleukin-1 receptor antagonist (IL-1Ra) that blocks the biological activity of cytokine IL-1, thereby controlling active inflammation. It is administered by subcutaneous injection.

Anakinra has a marketing authorisation in the UK for treating Still's disease. It is indicated 'in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above for the treatment of Still's disease, including Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease (AOSD), with active systemic features of moderate to high disease activity, or in patients with continued disease activity after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids.' Anakinra can be given as monotherapy or in combination with other anti-inflammatory drugs and disease-modifying anti-rheumatic drugs (DMARDs).

Anakinra also has a marketing authorisation in the UK for treating rheumatoid arthritis and cryopyrin-associated period syndromes (CAPS).

Interventions	Anakinra as monotherapy or in combination with other anti-inflammatory drugs and DMARDs
Population	People with Still's disease (including Systemic Juvenile Idiopathic Arthritis and Adult-Onset Still's Disease).
Comparators	For previously untreated disease: • NSAIDs and systemic corticosteroids For disease previously treated with NSAIDs or systemic corticosteroids • DMARDs For disease previously treated with DMARDs: • Tocilizumab (only for systemic juvenile idiopathic arthritis that has responded inadequately to methotrexate) • TNF-alpha inhibitors
Outcomes	The outcome measures to be considered include: • disease activity (including disease flares and remission)

	• fever • physical function • blood markers for inflammation • glucocorticoid tapering • rash • mortality • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.
Other considerations	If the evidence allows, the following subgroups will be considered: • People with systemic juvenile idiopathic arthritis or adult-onset Still's disease • Level of disease activity Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals** 'Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis' (2015). NICE Technology Appraisal 373. Review date December 2018. 'Tocilizumab for the treatment of systemic juvenile idiopathic arthritis' (2011). NICE Technology Appraisal 238. Currently under review.

	Terminated appraisals 'Canakinumab for treating systemic juvenile idiopathic arthritis' (2013). NICE Technology Appraisal 302. **Appraisals in development (including suspended appraisals)** 'Canakinumab and tocilizumab for treating systemic juvenile idiopathic arthritis' NICE technology appraisals guidance [ID983]. Publication date to be confirmed. **Related Guidelines** 'Rheumatoid arthritis in adults: management' (2009 updated 2015). NICE guideline CG79. Review date to be confirmed. **Related NICE evidence summaries** 'Systemic juvenile idiopathic arthritis: canakinumab' (2014). NICE evidence summary: new medicines 36. **Related NICE Pathways** Musculoskeletal conditions (2013) NICE pathway http://pathways.nice.org.uk/pathways/musculoskeletal-conditions
Related National Policy	NHS England (2018) Clinical Commissioning Policy: Anakinra/tocilizumab for the treatment of Adult Onset Still's Disease refractory to second-line therapy (adults). https://www.england.nhs.uk/wp-content/uploads/2018/07/1609-anakinra-and-tocilizumab-for-aosd.pdf NHS England (2017) Manual for Prescribed Specialised Services 2017/18. Chapter 138: Stem cell transplantation service for juvenile idiopathic arthritis and related connective tissue disorders (children). https://www.england.nhs.uk/wp-content/uploads/2017/10/prescribed-specialised-services-manual-2.pdf Department of Health and Social Care (2016) NHS Outcomes Framework 2016-2017: Domains 2, 3 and 4. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 NHS England (2015) Clinical Commissioning Policy Statement: Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis (JIA) and Appendix A. https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/e03pd-bio-therapies-jia-oct15.pdf and https://www.england.nhs.uk/commissioning/wp-

	content/uploads/sites/12/2015/07/appx-a-jia-e03Pd.pdf NHS England (2013) A13/S/a 2013/14 NHS standard contract for specialised rheumatology services (adult). https://www.england.nhs.uk/wp-content/uploads/2013/06/a13-spec-rheumatology.pdf NHS England (2013) B09/S/a 2013/14 NHS standard contract for specialised immunology (all ages). https://www.england.nhs.uk/wp-content/uploads/2013/06/b09-spec-immun.pdf

Questions for consultation

At which stage in therapy do you anticipate anakinra would be used?

Are people with systemic juvenile idiopathic arthritis that has continued into adulthood likely to be covered by this appraisal?

How is active disease defined? How might features of moderate to high disease activity be defined and differentiated?

Which treatments are considered to be established clinical practice in the NHS for systemic juvenile idiopathic arthritis and adult-onset Still's disease?

Have all relevant comparators for anakinra been included in the scope?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom anakinra is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider anakinra will fit into the existing NICE pathway for musculoskeletal conditions?

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 proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which anakinra is licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. 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 tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider anakinra 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)?

Do you consider that the use of anakinra can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made.

- Would it be appropriate to use the cost comparison methodology for this topic?

- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?

- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?

- Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

[1] NHS England (2018) Clinical Commissioning Policy: Anakinra/tocilizumab for the treatment of Adult-Onset Still's Disease refractory to second-line therapy (adults). Accessed July 2018.
[2] NICE Evidence Summary: New Medicines 36 (2014) Systemic juvenile idiopathic arthritis: canakinumab. Accessed July 2018.
[3] Orphanet Adult-onset Still disease. Accessed July 2018.
[4] Ophanet Systemic-onset juvenile idiopathic arthritis. Accessed July 2018.