

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

**Tofacitinib for treating moderate to severe active rheumatoid arthritis  
after the failure of disease-modifying anti-rheumatic drugs**

**Draft scope**

**Remit/appraisal objective**

To appraise the clinical and cost effectiveness of tofacitinib within its marketing authorisation for treating rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs

**Background**

Rheumatoid arthritis is an inflammatory autoimmune disease that typically affects the synovial tissue of the small joints of the hands and feet but can affect any synovial joint, causing swelling, stiffness, pain and progressive joint destruction. It is a systemic disease and can affect the whole body, including the lungs, heart and eyes. Rheumatoid arthritis is usually a chronic relapsing condition which has a pattern of flare-ups followed by periods of lower disease activity; however, for some people, the disease is constantly progressive. Rheumatoid arthritis is associated with increased mortality and increasing disability, which has a severe impact on quality of life. Severity of disease can be classified into 3 categories, based on the disease activity score (DAS28) scoring system. A DAS28 greater than 5.1 indicates high disease activity or severe disease, between 3.2 and 5.1 indicates moderate disease activity, and less than 3.2 indicates low disease activity

The prevalence of rheumatoid arthritis in the UK is estimated to be 0.44% in males and 1.16% in females<sup>1</sup>; which is approximately 441,000 people in England (119,000 males and 322,000 females)<sup>1,2</sup>. There are approximately 17,500 people diagnosed with rheumatoid arthritis every year in England<sup>3</sup>. It can develop at any age, but the peak age of onset in the UK is about 45–75 years<sup>1</sup>.

There is no cure for rheumatoid arthritis and treatment aims to improve quality of life and to prevent or reduce joint damage. Treatment for rheumatoid arthritis usually includes: non-steroidal anti-inflammatory drugs which reduce pain, fever and joint swelling/inflammation, and disease modifying anti-rheumatic drugs (DMARDs). DMARDs may be broadly classed as either non-biological or biological. Non-biological DMARDs include methotrexate, leflunomide and sulfasalazine, while the latter group includes, but is not limited to, tumour necrosis factor (TNF) inhibitors. DMARDs slow the disease process and reduce joint damage. Corticosteroids may also be used to control inflammation, although the long-term use of corticosteroids can increase the

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risk of conditions such as osteoporosis and diabetes. The main aim of management in early disease is to suppress disease activity and induce disease remission, prevent loss of function, control joint damage, maintain pain control and enhance self-management. In established disease, management should address complications and associated comorbidity; and the impact of the condition on the patient's quality of life.

For people with newly diagnosed rheumatoid arthritis, NICE Clinical Guideline (CG 79) recommends a combination of DMARDs (including methotrexate and at least one other DMARD plus short term glucocorticoids) as first-line treatment, ideally beginning within 3 months of the onset of persistent symptoms. Where combination therapies are not appropriate (for example where there are comorbidities or pregnancy) DMARD monotherapy is recommended. Where the disease has not responded to intensive combination therapy with conventional DMARDs, NICE Technology appraisal guidance 375 recommends biological DMARDs (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept) in combination with methotrexate for severe rheumatoid arthritis only. For those people with severe rheumatoid arthritis who cannot take methotrexate because it is contraindicated or because of intolerance, the guidance recommends that adalimumab, etanercept, certolizumab pegol or tocilizumab monotherapy can be used.

Where the disease has not responded adequately or in the case of intolerance to other DMARDs, including at least one TNF inhibitor (a subgroup of biological DMARDs), rituximab in combination with methotrexate is recommended for severe active disease only (NICE Technology appraisal guidance 195). Where rituximab is contraindicated or withdrawn because of an adverse event, adalimumab, etanercept, infliximab, abatacept, golimumab, tocilizumab and certolizumab pegol each in combination with methotrexate are recommended as options (NICE Technology appraisal guidance 195, 225, 247 and 415). Where rituximab therapy cannot be given because methotrexate is contraindicated or has been withdrawn due to an adverse event, adalimumab, etanercept and certolizumab pegol, each as a monotherapy, can be used (NICE Technology appraisal guidance 195 and 415).

### **The technology**

Tofacitinib (Xeljanz, Pfizer) is an oral Janus kinase inhibitor preventing full activation of lymphocytes thereby interrupting the inflammatory process. Tofacitinib is not a biological DMARD.

Tofacitinib does not currently have a UK marketing authorisation for the treatment of moderate to severe active rheumatoid arthritis after the failure of DMARDs. It has been studied in combination with methotrexate and as a monotherapy in adults whose rheumatoid arthritis has had an inadequate response to, or who are intolerant to conventional non-biological DMARDs

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including methotrexate. It has also been studied in adults whose rheumatoid arthritis has had an inadequate response to, or who are intolerant to, TNF inhibitors. In the studies tofacitinib has been compared with placebo, adalimumab plus methotrexate and adalimumab monotherapy.

<b>Intervention(s)</b>	Tofacitinib (monotherapy and in combination with methotrexate)
<b>Population(s)</b>	Adults with moderate to severe, active rheumatoid arthritis whose disease has responded inadequately to, or who are intolerant of one or more disease modifying anti-rheumatic drugs (DMARDs), including conventional or biologic DMARDs
<b>Comparators</b>	<p>People with moderate active rheumatoid arthritis:</p> <ul style="list-style-type: none"> <li>• Combination therapy with conventional DMARDs (including methotrexate and at least one other DMARD, such as sulfasalazine and leflunomide)</li> <li>• Conventional DMARD monotherapy with dose escalation</li> <li>• Best supportive care (only where conventional DMARDs are not appropriate due to intolerance)</li> </ul> <p>People with severe active rheumatoid arthritis that has not responded adequately to therapy with conventional DMARDs only:</p> <ul style="list-style-type: none"> <li>• Biological DMARDs in combination with methotrexate (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept)</li> <li>• Adalimumab, etanercept, certolizumab pegol, or tocilizumab (each as monotherapy)</li> </ul> <p>People with severe active rheumatoid arthritis that has not responded adequately to therapy with DMARDs including at least one TNF inhibitor:</p> <ul style="list-style-type: none"> <li>• Rituximab in combination with methotrexate</li> <li>• When rituximab is contraindicated or withdrawn due to adverse events: <ul style="list-style-type: none"> <li>- Abatacept, adalimumab, certolizumab pegol, etanercept, infliximab, tocilizumab, or golimumab, each in combination with methotrexate</li> <li>- Adalimumab, etanercept or certolizumab pegol (each as monotherapy)</li> </ul> </li> </ul>
<b>Outcomes</b>	The outcome measures to be considered include:

	<ul style="list-style-type: none"> <li>• disease activity</li> <li>• physical function</li> <li>• joint damage, pain</li> <li>• mortality</li> <li>• fatigue</li> <li>• radiological progression</li> <li>• extra-articular manifestations of disease</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life.</li> </ul>
<p><b>Economic analysis</b></p>	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>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.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.</p> <p>The availability and cost of biosimilars should be taken into account.</p>
<p><b>Other considerations</b></p>	<p>If the evidence allows the following subgroups will be considered. These include people with moderate disease activity (DAS28 between 3.2 and 5.1) and severe active disease (DAS28 greater than 5.1).</p> <p>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.</p>
<p><b>Related NICE recommendations</b></p>	<p>Related Technology Appraisals:</p> <p>Technology Appraisal No 415, Oct 2016, 'Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor'. Review date: October 2019</p>

	<p>Technology Appraisal No 375, Jan 2016, ‘Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab for the treatment of rheumatoid arthritis (review of TA guidance 130, 186, 224, 234 and part review of TA guidance 225 and 247)’. Review date: January 2019</p> <p>Technology Appraisal No. 247, Feb 2012, ‘Tocilizumab for the treatment of rheumatoid arthritis (rapid review of technology appraisal guidance 198)’. Guidance on static list.</p> <p>Technology Appraisal No. 225, Jun 2011, ‘Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease modifying anti-rheumatic drugs’. Guidance on static list.</p> <p>Technology Appraisal No. 195, Aug 2010, ‘Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor’. Guidance on static list.</p> <p>Ongoing Technology Appraisals:</p> <p>NICE technology appraisal ID975, Publication expected Sep 2017, ‘Baricitinib for treating moderate to severe rheumatoid arthritis.</p> <p>Related Guidelines:</p> <p>Clinical Guideline No. 79, February 2009. Last updated in Jan 2015 and another update in development. Expected publication Aug 2018.</p> <p>Related Quality Standards:</p> <p>Quality Standard No. 33, Apr 2013, ‘Quality standard for rheumatoid arthritis’ (2009). Review Proposal Date unknown. <a href="http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp">http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp</a></p> <p>Related NICE Pathways:</p> <p>NICE Pathway: Rheumatoid arthritis, Pathway created: Apr 2013 and updated Oct 2016. <a href="https://pathways.nice.org.uk/pathways/rheumatoid-arthritis">https://pathways.nice.org.uk/pathways/rheumatoid-arthritis</a></p>
<b>Related National Policy</b>	<p>NHS England Manual for prescribed specialised services 2016/2017. Adult highly specialist rheumatology services) [section 5, page 80-82]: <a href="https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf">https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf</a></p> <p>NHS England &amp; BMJ Group (2012) <a href="#">Shared Decision</a></p>

	<p><a href="#">Making Sheets: Rheumatoid Arthritis.</a></p> <p>Department of Health, NHS Outcomes Framework 2016-2017 (2016) Domains 1–5.  <a href="https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf">https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf</a></p> <p>National Service Frameworks for Older People:  <a href="https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/198033/National_Service_Framework_for_Older_People.pdf">https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/198033/National_Service_Framework_for_Older_People.pdf</a></p>
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### Questions for consultation

Have all relevant comparators for tofacitinib 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 tofacitinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider tofacitinib will fit into the existing NICE pathway, [Rheumatoid arthritis](#)?

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 tofacitinib will be 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 tofacitinib 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 tofacitinib 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.

NICE could appraise this technology through its Single Technology Appraisal Process. However, NICE has just consulted on an additional technology appraisal process known as the Abbreviated Appraisal Process (ATA). More information on the draft ATA process is available at <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/abbreviated-technology-appraisal-process-consultation>. We welcome comments on the appropriateness and suitability of considering the new ATA process for appraising this topic. Information on the Institute's Technology Appraisal processes is available at <http://www.nice.org.uk/article/pmg19/chapter/1-Introduction>.

- Is the new technology likely to be similar in its clinical efficacy and resource use to the comparator?
- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) in TA375/TA415/TA247 still clinically relevant?
- Is there any substantial new evidence for the comparator technology/ies that has not been considered in TA375/TA415/TA247? Are there any important ongoing trials reporting in the next year?

### References

1. Arthritis Research UK (2016) '[How common is rheumatoid arthritis?](#)' Accessed January 2017.
2. Office for National Statistics (2016) '[Population Estimates by Age and Sex](#)'. Accessed January 2017
3. NICE (2013) '[Support for commissioning for rheumatoid arthritis](#)'.