# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Proposed Health Technology Appraisal

## Upadacitinib for treating moderate to severe rheumatoid arthritis

## Draft scope (pre-referral)

### Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of upadacitinib within its marketing authorisation for previously treated moderate to severe active rheumatoid arthritis.

### 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 has a severe impact on quality of life and it is estimated that approximately one-third of people stop work within 2 years because of the disease, and this prevalence increases thereafter. 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[1]; which is approximately 441,000 people in England (119,000 males and 322,000 females)[1,2]. There are approximately 17,500 people diagnosed with rheumatoid arthritis every year in England[2,3,4]. It can develop at any age, but the peak age of onset in the UK is about 45–75 years[4].

There is no cure for rheumatoid arthritis and treatment aims to improve quality of life and to prevent or reduce joint damage. 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. For people with newly diagnosed rheumatoid arthritis, NICE clinical guideline 79 ('Rheumatoid arthritis in adults: management') recommends a combination of conventional disease modifying anti-rheumatic drugs (DMARDs; including methotrexate, leflunomide and sulfasalazine) 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, 466, 480 and 485 recommend biological DMARDs (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept and sarilumab) or other immunomodulatory therapies (baricitinib and tofacitinib) each 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, tocilizumab, baricitinib, sarilumab or tofacitinib 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, biological DMARDs (adalimumab, etanercept, infliximab, abatacept, golimumab, tocilizumab, certolizumab pegol and sarilumab) or other immunomodulatory therapies (tofacitinib and baricitinib) each in combination with methotrexate are recommended as options (NICE Technology appraisal guidance 195, 225, 247 ,415, 466, 480 and 485). Where rituximab therapy cannot be given because methotrexate is contraindicated or has been withdrawn due to an adverse event, biological DMARDs (adalimumab, etanercept, certolizumab pegol and sarilumab) or other immunomodulatory therapies (tofacitinib and baricitinib) each as a monotherapy, can be used (NICE Technology appraisal guidance 195, 415, 466, 480 and 485).

### The technology

Upadacitinib (brand name unknown, AbbVie) is a Janus-kinase (JAK) 1 inhibitor that blocks the JAK-signal transducer and activator of transcription (STAT) pathway and inflammatory responses. It is administered orally.

Upadacitinib does not currently have a marketing authorisation in the UK for rheumatoid arthritis. It has been studied in clinical trials compared to, and in combination with, conventional DMARDs and as monotherapy in adults whose disease did not respond adequately to conventional or biological DMARDs. It has also been studied in separate clinical trials in combination with conventional DMARDs, compared with both abatacept (a biological DMARD) and adalimumab (a TNF inhibitor, a subgroup of biological DMARDs).

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| **Intervention(s)** | Upadacitinib (as monotherapy and in combination with other conventional DMARDs, including methotrexate) |

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| **Population(s)** | 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 |
| **Comparators** | For moderate active rheumatoid arthritis that has not responded adequately to therapy with conventional DMARDs:<br>• Combination therapy with conventional DMARDs (including methotrexate and at least one other DMARD, such as sulfasalazine and leflunomide)<br>• Conventional DMARD monotherapy with dose escalation<br>• Best supportive care (only where conventional DMARDs are not appropriate due to intolerance)<br>For severe active rheumatoid arthritis that has not responded adequately to therapy with conventional DMARDs only:<br>• Biological DMARDs in combination with methotrexate (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept or sarilumab)<br>• Adalimumab, etanercept, certolizumab pegol, tocilizumab or sarilumab (each as monotherapy)<br>• Tofacitinib or baricitinib (monotherapy or in combination with methotrexate)<br>For severe active rheumatoid arthritis that has not responded adequately to therapy with DMARDs including at least one TNF inhibitor:<br>• Rituximab in combination with methotrexate<br>When rituximab is contraindicated or withdrawn due to adverse events:<br>• Adalimumab, etanercept, infliximab, abatacept tocilizumab, certolizumab pegol, golimumab or sarilumab, each in combination with methotrexate<br>• Adalimumab, etanercept, certolizumab pegol or sarilumab (each as monotherapy)<br>• Tofacitinib or baricitinib (monotherapy or in combination with methotrexate) |

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| **Outcomes** | The outcome measures to be considered include:<br>• disease activity<br>• physical function<br>• joint damage, pain<br>• mortality<br>• fatigue<br>• radiological progression<br>• extra-articular manifestations of disease<br>• adverse effects of treatment<br>• 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.<br>If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out.<br>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.<br>Costs will be considered from an NHS and Personal Social Services perspective.<br>The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.The availability and cost of biosimilar products should be taken into account. |
| **Other considerations** | 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).<br>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. |

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| **Related NICE recommendations and NICE Pathways** | **Related Technology Appraisals**:<br>Sarilumab for moderate to severe rheumatoid arthritis (2017) NICE Technology Appraisal 485. Review Date November 2020<br><br>Tofacitinib for moderate to severe rheumatoid arthritis (2017) NICE Technology Appraisal 480. Review Date October 2020<br><br>Baricitinib for moderate to severe rheumatoid arthritis (2017) NICE Technology Appraisal 466. Review Date August 2020.<br><br>Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor (2016) NICE Technology Appraisal 415. Review Date October 2019<br><br>Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (2016) NICE Technology Appraisal 375 (previously TA130, TA186 and TA280). Review Date January 2019<br><br>Tocilizumab for the treatment of rheumatoid arthritis (2012) NICE Technology Appraisal 247. Guidance on static list.<br><br>Golimumab for the treatment of rheumatoid arthritis after the failure of previous diseasemodifying anti-rheumatic drugs. (2011) NICE Technology Appraisal 225. Guidance on static list.<br><br>Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. (2010) NICE Technology Appraisal TA195. Guidance on static list.<br><br>**Terminated appraisals:**<br>Sirukumab for previously treated moderate to severe active rheumatoid arthritis NICE technology appraisals guidance [ID1002] (suspended appraisal)<br>Rituximab for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs NICE technology appraisals guidance [ID333] (suspended appraisal) |

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| | **Related Guidelines:**<br>Rheumatoid arthritis in adults: the management of rheumatoid arthritis in adults (2015) NICE guideline CG79. Review date to be confirmed.<br>**Related Quality Standards:**<br>Rheumatoid arthritis in over 16s (2017) NICE Quality Standard QS33.<br>**Related NICE Pathways:**<br>'Rheumatoid arthritis' (2015). NICE pathway |
| **Related National Policy** | NHS England (2017) Manual for Prescribed Specialised Services 2017/18.Adult highly specialist rheumatology services [section 5, page 24-26]<br>Department of Health and Social Care, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1-5. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017<br>National Service Frameworks for Older People: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/198033/National_Service_Framework_for_Older_People.pdf |

**Questions for consultation**

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

Where do you consider upadacitinib 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 upadacitinib 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 upadacitinib 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 upadacitinib 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 Symmons D et al. (2002) The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. Rheumatology 41 (7): 793-800.

2.Office for National Statistics (2016) 'Population Estimates by Age and Sex'. Accessed June 2018.

3. Symmons D et al. (2012) The incidence of rheumatoid arthritis in the UK: comparisons using the 2010 ACR/EULAR classification criteria and the 1987 ACR classification criteria. Results from the Norfolk Arthritis Register. Annals of the Rheumatic Diseases 72: 1315-1320.

4. Arthritis Research UK (2018) Musculoskeletal Calculator. Accessed June 2018.