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

Final 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

There are approximately 441,000 people with rheumatoid arthritis in England (119,000 men and 322,000 women) with around 17,500 people diagnosed every year[1, 2, 3]. It can develop at any age, but the peak age of onset in the UK is about 45–75 years[1].

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 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 marketing authorisation in the UK for treating people with moderate to severe rheumatoid arthritis. However, the Committee for Human Medicinal Products recommended the granting of a marketing authorisation for tofacitinib in combination with methotrexate for treating adult patients with moderate to severe active rheumatoid arthritis who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs. It can also be given as a monotherapy in case

of intolerance to methotrexate or when treatment with methotrexate is inappropriate. Tofacitinib is administered orally.

Intervention(s)	Tofacitinib (monotherapy and in combination with methotrexate)
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	People with moderate active rheumatoid arthritis: • Combination therapy with conventional DMARDs (including methotrexate and at least one other DMARD) • Conventional DMARD monotherapy with dose escalation • Best supportive care (only where conventional DMARDs are not appropriate because of intolerance) People with severe active rheumatoid arthritis that has not responded adequately to therapy with conventional DMARDs only: • Biological DMARDs in combination with methotrexate (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept) • Adalimumab, etanercept, certolizumab pegol, or tocilizumab (each as monotherapy in case of intolerance to methotrexate or when treatment with methotrexate is inappropriate) People with severe active rheumatoid arthritis that has not responded adequately to therapy with DMARDs including at least one TNF inhibitor: • Rituximab in combination with methotrexate • When rituximab is contraindicated or withdrawn because of adverse events: - Abatacept, adalimumab, certolizumab pegol, etanercept, infliximab, tocilizumab, or golimumab, each in combination with methotrexate - Adalimumab, etanercept or certolizumab pegol (each as monotherapy when rituximab therapy cannot be given because

	methotrexate is contraindicated or has been withdrawn due to an adverse event)
Outcomes	The outcome measures to be considered include: • disease activity • physical function • joint damage, pain • mortality • fatigue • radiological progression • extra-articular manifestations of disease • 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 should be taken into account. The availability and cost of biosimilars 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). 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	**Related Technology Appraisals:** Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor (2016) NICE Technology Appraisal TA415. Review date: October 2019. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (review of TA guidance 130, 186, 224, 234 and part review of TA guidance 225 and 247) (2016) NICE Technology Appraisal TA375. Review date: January 2019. Tocilizumab for the treatment of rheumatoid arthritis (rapid review of technology appraisal guidance 198) (2012) NICE technology appraisal TA247. Guidance on static list. Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease modifying anti-rheumatic drugs (2011) NICE technology appraisal TA225. Guidance on static list. 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. **Ongoing Technology Appraisals**: NICE technology appraisal ID979, Publication expected Sep 2017, 'Baricitinib for treating moderate to severe rheumatoid arthritis. **Related Guidelines:** Rheumatoid arthritis in adults: management (2009) NICE guideline CG79. Review date: August 2018. **Related Quality Standards:** Rheumatoid arthritis in over 16s (2013) Quality Standard QS33. **Related NICE Pathways:** Rheumatoid arthritis (2015) NICE Pathway.
Related National Policy	NHS England Manual for prescribed specialised services 2016/2017. Adult highly specialist rheumatology services) [section 5, page 80-82]: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf

	NHS England & BMJ Group (2012) Shared Decision Making Sheets: Rheumatoid Arthritis. Department of Health, NHS Outcomes Framework 2016-2017 (2016) Domains 1–5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf 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

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'.