NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Review Proposal Project (RPP) decision paper

Partial review of TA375; Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for moderate rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed

Final recommendation post consultation
A partial review of TA375 for patients with moderate disease only will be planned into the appraisal work programme

1. Background

This guidance was issued in January 2016.

At the Guidance Executive meeting of 03 April 2019, it was agreed that we would consult on the recommendations made in the GE proposal paper. A four-week consultation has been conducted with consultees and commentators and the responses are presented below.

2. Proposal put to consultees and commentators

We propose that a partial review of TA375 for patients with moderate disease only should be planned into the appraisal work programme. To consult on this proposal.

3. Rationale for selecting this proposal

TA375 includes optimised positive recommendations for patients with severe disease only. It concluded that biological disease-modifying antirheumatic drugs (DMARDs) are not a cost-effective use of NHS resources for people with moderate active disease because the committee's preferred median ICER was around £51,100 per QALY gained.

Although TA375 included biosimilar infliximab, since its publication, new biosimilars for adalimumab and etanercept have become available and there have been changes in the confidential prices paid by NHS England for all treatments considered in TA375. The availability of cheaper treatments may reduce the committee's preferred ICER to £20,000 to £30,000 per QALY gained for people with moderate active disease (that is, the range that is considered a cost-effective use of NHS resources). No new evidence has been found to address the other uncertainties identified in TA375.

It is therefore proposed that a partial review of TA375 for people with moderate active disease only should be planned into the appraisal work programme because the price reductions may change the existing, negative recommendations in TA375 for patients with moderate disease.

4. Summary of consultee and commentator responses

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.

Respondent: AbbVie **Response to proposal:** Agree AbbVie is not aware of any further data that could help inform this update, although would recommend the modifications made in TA485 to the model developed by the assessment group in TA375 be adopted in this update. AbbVie recommend that the Chartered Society of Physiotherapy is included in the stakeholder matrix	**Comment from Technology Appraisals** Thank you, your comments have been noted. NICE will review the cost-effectiveness model and its assumptions during the appraisal. The Chartered Society of Physiotherapy has been added to the stakeholder matrix.

Respondent: Amgen **Response to proposal:** Agree there has been a significant reduction in the cost of adalimumab which will result in improved cost-effectiveness for the treatment of rheumatoid arthritis across different levels of disease. As you indicated that the main driver for the review is the price reduction for the treatments included in the original appraisal, we fully support the proposal that: 1. NICE takes a pragmatic approach to the update without going through a full appraisal process 2.A partial update of TA375 should be planned into the appraisal work programme focussing on the population with moderate active disease only.	**Comment from Technology Appraisals** Thank you, your comments have been noted. No action required.

Respondent: Biogen **Response to proposal:** Agree Biogen fully supports the proposal to undertake this review. The current confidential acquisition costs for each of the Biogen Biosimilar molecules is a considerable reduction compared to the anti-TNF molecule list prices currently outlined in TA375 and hence provides a significant opportunity to reassess the cost-effectiveness of these molecules in the moderate rheumatoid arthritis patient population. Biogen estimates that since the launch of its three anti-TNF biosimilars, the savings generated to the NHS will reach circa [redacted] by the end of 2019.	**Comment from Technology Appraisals** Thank you, your comments have been noted. No action required.

Respondent: Eli Lilly and Company Limited **Response to proposal:** Agree Lilly would like to request the inclusion of baricitinib (Olumiant; TA466) in any review of treatments for rheumatoid arthritis that would reconsider patients with moderate disease activity. As you may be aware, we originally provided data for moderate patients in our submission for TA466. Whilst we recognise this consultation is focussed on TA375, baricitinib (TA466) was appraised using the same approaches as required by the appraisal committee for TA375 and therefore should be treated in the same way. [redacted] [redacted] Baricitinib has characteristics that make it suitable for use in the wider population of patients with moderate rheumatoid arthritis. As a small molecule, baricitinib does not induce the production of anti-drug antibodies unlike the tumour necrosis factor inhibitor (TNFi) biologics whose efficacy can diminish over time, and as an oral therapy, baricitinib could have a substantial impact on patients who may experience painful injection related reactions, and potentially discontinue currently available TNFi biologics.	**Comment from Technology Appraisals** Thank you for your comments. The partial review will only cover the treatments included in the original appraisal of TA375. NICE will issue an updated scope prior to the development of this part review appraisal. This will cover the population, interventions and comparators intended to be included in this partial review. A proposal for a review of any final TA guidance can be made, in line with NICE processes (see section 6 of the Guide to the processes of technology appraisal). This proposal should show that the committee's preferred ICER in that appraisal will be reduced to £20,000 to £30,000 per QALY gained for people with moderate active disease (that is, the range that is considered a cost-effective use of NHS resources) by including updated data for that intervention.

Respondent: Merck Sharp & Dohme (MSD) **Response to proposal:** No comment MSD would not like to participate in the partial review of TA375. However, MSD would appreciate to be included as a commentator, in order to remain abreast of the development of the appraisal and its outcomes.	**Comment from Technology Appraisals** Thank you, your comments have been noted. As per our usual process we will invite all companies to participate in the appraisal. It is at the discretion of the company if they wish to return a confidentiality and undertaking form at that point.

Respondent: National Rheumatoid Arthritis Society (NRAS) **Response to proposal:** Agree We agree that a partial review of TA375 for patients with moderate disease only should be planned into the appraisal work programme as the price reductions, not only in the biosimilars but also in the originator biologic therapies will change the existing, negative recommendations in TA375 for patients with moderate disease. We were aware that ScHARR re-ran the moderate ICER at a 50% discount which reduced ICER to £31,500 and given that many of the prices have since been discounted beyond 50%, feel confident that without in any way stratifying the moderate patients, we should be comfortably under the £30K threshold needed to grant these patients access to more effective medicines to control their disease.	**Comment from Technology Appraisals** Thank you, your comments have been noted. No action required.

Respondent: Pfizer **Response to proposal:** Agree Pfizer welcomes NICE's proposal for the partial review of TA375, we wish to raise some remarks with regards to the proposed pragmatic approach to the update. The review seems to be clearly driven by the price reduction of the treatments included in the original appraisal only, without considering important NICE recommended treatment options available to patients in England and Wales since its publication in 2016. This price reduction of the treatments will then populate the 2016 economic model, owned by the School of Health and Related Research, Sheffield (ScHARR). The economic model produced by ScHARR has a number of limitations and we would urge NICE to reconsider its use to inform this important review. More importantly the clinical and economic evidence based that informed the original TA375 appraisal in in 2013, is out-dated, and it is highly likely that more up-to-date estimates are now available that will enable the Committee to address the key uncertainties raised in the final decision made in 2016. Pfizer would like to highlight two points for NICE to consider during the consultation process: 1. Exclusion of important NICE recommended treatment options that have become available since TA375 publication; 2. Appropriateness of the ScHARR model for assessing the cost-effectiveness of the different treatment options due to its limitations;	**Comment from Technology Appraisals** Thank you for your comments. The partial review will only cover the treatments included in the original appraisal of TA375. NICE will review the cost-effectiveness model and its assumptions during the appraisal. A proposal for a review of any final TA guidance can be made, in line with NICE processes (see section 6 of the Guide to the processes of technology appraisal). This proposal should show that the committee's preferred ICER in that appraisal will be reduced to £20,000 to £30,000 per QALY gained for people with moderate active disease (that is, the range that is considered a cost-effective use of NHS resources) by including updated data for that intervention.

Respondent: Roche **Response to proposal:** Agree Roche support the Guidance Executive's recommendation for a partial review of TA375, as outlined in the published Proposal Paper. Specifically, we support the proposal to review the guidance for these therapies in the treatment of moderate rheumatoid arthritis. Roche would also welcome consideration of the data available for specific subgroups of moderate rheumatoid arthritis patients. Such subgroups of patients could include, but are not limited to, patients who are unable to receive methotrexate, are anaemic, obese, diabetic, have mental health disorders or bone mineral density disorders.	**Comment from Technology Appraisals** Thank you, your comments have been noted. NICE will issue an updated scope prior to the development of this appraisal. This will include relevant subgroups.

Respondent: Sandoz **Response to proposal:** Agree EULAR recommendations include use of biologics in early / moderate RA and do not just restrict to severe RA and interestingly other European countries allow use of biologic DMARDs earlier in the treatment of RA patients. The availability of cost- effective biosimilars, falling under the threshold that was set by the originator product, make it imperative that the original threshold be re-evaluated as the original considerations of benefit vs value are no longer relevant. Cost savings of 50-80% for first line use biologics such as Etanercept, Adalimumab, and Infliximab, and even second line options such as Rituximab, which are core therapies in the treatment and management of RA, point strongly to a case for lowering the threshold and as a result widening patient access, which showcases the NHS putting the savings to good use for patient benefit.	**Comment from Technology Appraisals** Thank you, your comments have been noted. No action required.

Respondent: UCB **Response to proposal:** Agree This update will potentially allow patients with moderate disease to access treatment that will substantially improve their quality of life.	**Comment from Technology Appraisals** Thank you, your comments have been noted. No action required.

Respondent: Sanofi **Response to proposal:** Agree An important aspect of such a review should not only be to recognise the changing commercial landscape driven by biosimilar pricing but also to reflect the evolving treatment paradigm. We are conscious that the TA375 was published before the NICE recommendation for Kevzara (sarilumab) in 2017 (TA485) and so does not include it however it is noteworthy that patients for whom a TNFi is unsuitable are specifically highlighted in TA485. We believe that it is crucial as part of the update to TA375 to include the recommendation found in TA485 that a move to an alternate mode of action should be recommended when patients are unsuitable for, or do not respond to, a biosimilar bDMARD, since improved patient outcomes have been demonstrated in clinical trials when moving to an non-TNF biologic therapy	**Comment from Technology Appraisals** Thank you for your comments. The partial review will only cover the treatments included in the original appraisal of TA375. NICE will issue an updated scope prior to the development of this appraisal. This will cover the population, interventions and comparator intended to be included in this partial review. The scope will also cover a brief background including the current treatment pathway for people with moderate disease.

Respondent: British Society for Rheumatology **Response to proposal:** Agree This proposal is welcome and would bring us into line with other European countries	**Comment from Technology Appraisals** Thank you, your comments have been noted. No action required.

http://www.lse.ac.uk/business-and-consultancy/consulting/assets/documents/a-common-disease-with-uncommon-treatment.pdf EULAR RA guidelines suggest treatment adjustment every 1-3 months to bring the DAS28 below 3.2 (moderate disease activity) using biologics after the failure of conventional DMARDs. https://ard.bmj.com/content/76/6/960 • This is also seen in the American guidelines https://onlinelibrary.wiley.com/doi/full/10.1002/art.39480 RA has work and societal costs with 1/4 to 1/3 stopping work within 1-2 years of their disease onset despite improvements in treatment https://academic.oup.com/rheumatology/article/39/12/1403/1784284 https://ard.bmj.com/content/61/4/335 Early treatment and treating to target are established pillars of RA treatment-being able to escalate treatment from cDMARDs to bDMARDs at moderate disease activity within 6 months could have implications on likelihood of remission (treat aggressively early to improve remission rates), ability to stay in employment within the first year, improving functional ability and quality of life (in non-financial terms). Given the research into tapering biologics once in remission, there is increased potential to get patients into remission on lower frequency (and lower cost) drugs and also drug free remission. Deighton et al and Kiely et al have shown that moderate disease will progress to high disease activity, and increased number of joint replacements. https://ard.bmj.com/content/75/12/2080 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4613151/ early costs of biologics could lead to reduced costs of later joint replacements	

There is data to show that anti TNF is equally as effective in moderate as to high disease activity- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2744336/ The cost of biosimilars is 1/3 to 1/2 of the originator and with increased competition as more arrive this will have also hopefully have dropped the ICER to £20000-30000 per QALY gained. Work regarding biologics waste has also reduced the costs of biologics in general. Work around patient education has reduced biologics waste. Early inflammatory arthritis clinics could have potentially reduced the need for escalation to biologics (generally 30-40% go into remission at 6 months in a well-run service) (the caveat to this is as more patients are referred in, more will be diagnosed and more go onto high cost drugs). Consider workforce implications of reducing the DAS28 threshold to 3.2.	

Respondent: Royal College of Physicians **Response to proposal:** Agree We would like to endorse the response submitted by the British Society for Rheumatology.	**Comment from Technology Appraisals** Thank you, your comments have been noted. No action required.

Respondent: Napp Pharmaceuticals **Response to proposal:** Agree	**Comment from Technology Appraisals** Thank you, your comments have been noted. No action required.

Since TA375 was published in 2016, cheaper biosimilar versions of adalimumab, etanercept and rituximab have become available. In addition, there have been changes to the confidential prices of all the treatments included in TA375 paid by the NHS (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept). There have been changes in 3 areas that are relevant to the management of patients with moderately active rheumatoid arthritis within the current guidance which may change the cost effectiveness and recommendations: 1. More evidence around the clinical effectiveness of biologics in moderate disease activity RA patients 2. When taking into account tender pricing, the cost of biologics (bDMARDs) is significantly lower due to the introduction of biosimilars 3. More research and evidence around identifying the sub population of moderate disease activity patients for whom biologics are cost effective The previous TA375 assessment has already highlighted the clinical effectiveness of bDMARDs in moderate patients. However, the Committee considered that for treating these patients, cDMARDs were an effective therapy and that the main clinical interest in using bDMARDs was after cDMARDs had failed. Importantly, there have been significant advancements in the respective research since the last assessment in 2016, further strengthening the use of bDMARDs in this population. Evidence from a United States registry indicates that biologics-naive patients with moderate to severe RA who were offered a bDMARD experienced greater improvements in disease activity, with a greater proportion of them achieving remission, compared to those with severe RA (Kavanaugh et al., 2017). The same authors found the progressive increase in biologic use to be accompanied by progressive decreases in Clinical Disease Activity Index (CDAI) and mean Health Assessment Questionnaire score (HAQ) in moderate/high disease activity patients (Kavanaugh et al., 2018).	

However, it is the price reductions that will probably have the most significant effect on changing the existing recommendations in TA 375 for patients with moderately active disease. The previous TA375 assessment had a range £28,500 to £51,000 / QALY based on an NHS list price for the biosimilar infliximab of £377.66/vial for patients with moderate to severe RA. The real price of biosimilar infliximab has been driven down over time through the tendering process so that the NHS is now paying significantly less than 3 years ago. Therefore, the price of infliximab (Remsima®) is now much lower than when the original appraisals took place in 2013-2015. [redacted] The NHS list price of infliximab biosimilar, Remsima is £377.66 per 100-mg vial (BNF 77, May 2019). Assuming a weight per person of 70 kg, vial wastage, and 3 initial doses in the first year followed by treatment every 8 weeks, the cost in the first year is £9063.84, and then £7930.86 per year. [redacted] Therefore, due to the recent price changes, we agree with the proposal to conduct a partial of TA375 which include patients with moderately active RA.	

Paper signed off by: Frances Sutcliffe, 09/07/2019

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