National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Upadacitinib for treating moderate to severe rheumatoid arthritis ID1400

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: 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.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	British Society for Rheumatology	The objective is appropriate but Note that this drug does not have marketing authorisation yet	Comment noted. No action required.
	Abbvie	AbbVie consider it appropriate to refer this topic to NICE for appraisal	Comment noted. No action required.
Wording	Abbvie	AbbVie consider the wording of the remit of this appraisal to be appropriate	Comment noted. No action required.
Timing Issues	Abbvie	AbbVie consider it appropriate that a recommendation should be made as close to marketing authorisation as is possible within the NICE appraisal programme	Comment noted. The aim of the STA process is to provide guidance close to the MA being granted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	British Society for Rheumatology	Fine, could include DAS 28 remission (<2.6)	Comment noted. The background information has been updated to include the DAS28 definition of disease remission.
	Abbvie	AbbVie recommends adding that the aim of management in early disease is also to reduce stiffness and fatigue. Please note that NICE clinical guideline 79 has now been updated and replaced with NICE guideline 100 [NG100]. The recommendations in NG100 state the following for adults with newly diagnosed active rheumatoid arthritis (RA): • Offer first-line treatment with conventional disease-modifying anti-rheumatic drug (cDMARD) monotherapy using oral methotrexate, leflunomide or sulfasalazine as soon as possible and ideally within 3 months of onset of persistent symptoms Additional cDMARDs (oral methotrexate, leflunomide, sulfasalazine or hydroxychloroquine) should be offered in combination in a step-up strategy when the treatment target (remission or low disease activity) has not been achieved despite dose escalation.	Comment noted. The background information has been updated to include information from NICE clinical guideline 100.
	MSD	Information is accurate	Comment noted. No action required.
	Pfizer	The NICE clinical guideline 79 ('Rheumatoid arthritis in adults: management') referred to in the background have been updated and replaced by NICE guideline NG100. With that, paragraph three and	Comment noted. The background information has been updated to include

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		four of the background section are outdated and will require revising to appropriately reflect the NG100.	information from NICE clinical guideline 100.
The technology/ intervention	Abbvie	AbbVie request the description of the technology is changed to the following: Upadacitinib (brand name unknown, AbbVie) is a reversible, second generation selective Janus-kinase (JAK) 1 inhibitor.	Comment noted. The description of the technology aims to describe the biological target without providing full detail of pharmacological action.
Population	British Society for Rheumatology	Yes- although would be useful to know exclusions e.g. age limits etc.	Comment noted. The technology will be appraised within its marketing authorisation. Any optimised recommendations can be considered by the Appraisal Committee based on the evidence presented to it.
	Roche	Roche recommend NICE considers whether an analysis of subgroups by RF/anti-CCP status would be worthwhile, to help stratify patients	Comment noted. The subgroups included in the scope are not exhaustive. The company can submit relevant subgroup analyses in their submission which will be considered by the Appraisal Committee.
Comparators	Pfizer	The current description of comparators is incomplete as the distinctive population people for whom methotrexate is contraindicated and have had inadequate response to at least one TNF is missing. This	Comment noted. The comparators table separates out treatments being given as

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		population was identified in both baricitinib and tofacitinib technologiy appraisals (TA466 and TA480) and explored in comparative and cost-effectiveness by the ERG in both baricitinib and tofacitinib technology appraisals (TA466 and TA480). Please include the following comparators within the distinct population; For severe active rheumatoid arthritis that has not responded adequately to therapy with DMARDs including at least one TNF inhibitor where methotrexate is not appropriate due to intolerance or contraindication: • Adalimumab, baricitinib, etanercept, certolizumab pegol, tocilizumab, tofacitinib or sarilumab (each as monotherapy)	monotherapy or in combination with methotrexate and this should be read in conjunction with the background section of the scope.
	Abbvie	AbbVie propose the following changes to the population and comparators in the scope: For severe active rheumatoid arthritis that has not responded adequately to therapy with conventional DMARDs only **and who tolerate methotrexate and it is not contraindicated**: • Biological DMARDs in combination with methotrexate (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept, **baricitinib, tofacitinib** or sarilumab) For severe active rheumatoid arthritis that has not responded adequately to therapy with conventional DMARDs only **and who do not tolerate methotrexate or it is contraindicated**: • Adalimumab, etanercept, certolizumab pegol, tocilizumab, baricitinib, tofacitinib or sarilumab (each as monotherapy)	Comment noted. The comparator section of the scope has been updated to include tocilizumab and sarilumab for those whose disease does not respond adequately to rituximab in combination with methotrexate. However, the comparators table already separates out treatments being given as monotherapy or in combination with methotrexate and this should be read in conjunction with the background section of the scope.

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		For severe active rheumatoid arthritis that has not responded adequately to therapy with biological DMARDs either in combination with methotrexate or as monotherapy and who tolerate methotrexate and it is not contraindicated: • **Rituximab in combination with methotrexate** When rituximab is contraindicated or withdrawn due to adverse events **and who tolerate methotrexate and it is not contraindicated**: • Adalimumab, etanercept, infliximab, abatacept tocilizumab, certolizumab pegol, golimumab, **baricitinib, tofacitinib**, or sarilumab, each in combination with methotrexate When rituximab is contraindicated or withdrawn due to adverse events **and who do not tolerate methotrexate or it is contraindicated:** • Adalimumab, etanercept, certolizumab pegol, **tofacitinib, baricitinib** or sarilumab (each as monotherapy) **For severe active rheumatoid arthritis that has not responded adequately to therapy with rituximab and methotrexate:** • **Tocilizumab, sarilumab in combination with methotrexate**	
Outcomes	Abbvie	AbbVie suggest that extra articular manifestations of disease is removed as this is not an outcome of interest in rheumatoid arthritis	Comment noted. Extra-articular manifestation was considered as a relevant outcome in previous appraisals, therefore for consistency no changes to the scope required.

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Economic analysis	British Society for Rheumatology	QALY is the usual measure	Comment noted. No action required.
Equality and Diversity	British Society for Rheumatology	Need to bear in mind the difficulty sometimes of assessing outcome measures in people with communication difficulties	Comment noted. The committee will consider any equalities issues during the appraisal.
Other considerations	British Society for Rheumatology	Psychological effects of the medication	Comment noted. No action required.
Innovation	British Society for Rheumatology	This is not a step change, it is an addition to the current JAK inhibitors. The more that are available the more choice as patients can have idiosyncratic reactions to specific drugs. Also, the arrival of each new drug affects the price of those already on the market. There are unlikely to be any barriers for adoption other than local pathways.	Comment noted. No action required.
	Abbvie	Upadacitinib is the only JAK inhibitor to date to meet the two independent primary endpoints and all the ranked secondary endpoints across all the pivotal phase 3 studies evaluating its safety and efficacy. Substantial improvements in disease activity measures such as clinical remission and patient reported outcomes (PROs) including pain, fatigue and duration and severity of morning joint stiffness (which are important and difficult factors to achieve for patients with RA) were observed across all the phase 3 trials even	Comment noted. Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its

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		without methotrexate. The results of the pivotal trials highlight the effectiveness of upadacitinib as a monotherapy as well as a combination therapy and also considering the once daily oral formulation, this would represent a significant step change in the management of moderate and severe RA in clinical practice.	product in its submission. No action required.
Questions for consultation	Abbvie	**Have all relevant comparators for upadacitinib been included in the scope?** **Are the outcomes listed appropriate?** Please note AbbVie's proposed changes to relevant comparators based on the population of interest. **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?** All appropriate subgroups have been considered **Where do you consider upadacitinib will fit into the existing NICE pathway, Rheumatoid arthritis** AbbVie consider upadacitinib will be positioned for use as monotherapy or combination therapy in the following places in the existing NICE pathway:	Comments noted. See response to comments in the comparators section. Comment noted. No action required. Comment noted. No action required.

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		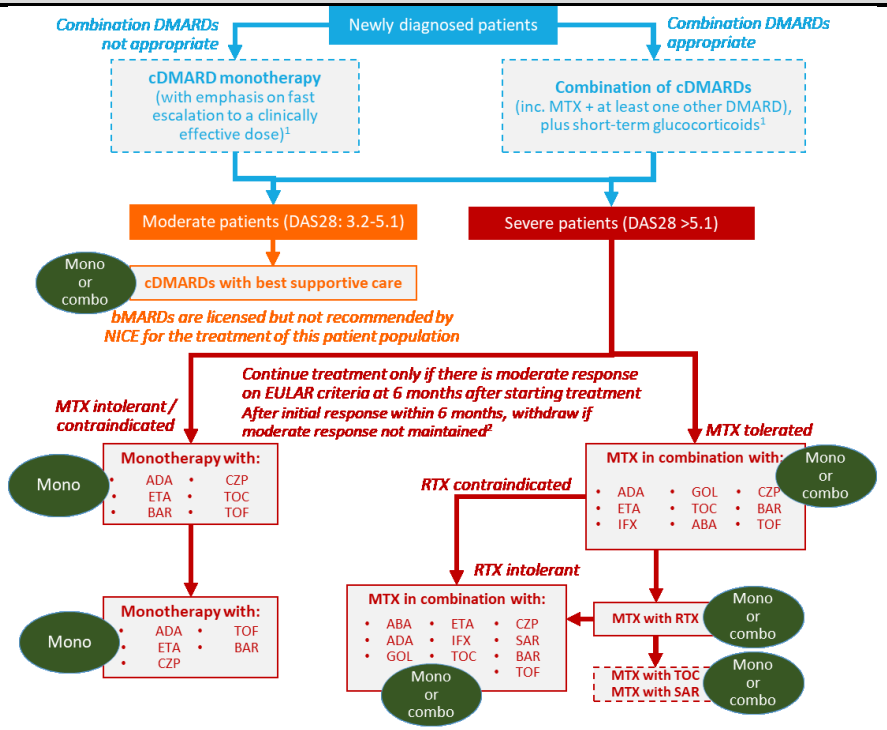 *Mono indicates use as upadacitinib monotherapy, combo indicated use of upadacitinib in combination with cDMARDs	
Additional comments on the draft scope	British Society for Rheumatology	It would be useful to be able to use JAK inhibitors and the other biologics in moderate disease activity (DAS28>3.2), the evidence is available for good outcomes. Single Technology appraisal seems appropriate.	Comment noted. No action required.

Comment 3: provisional matrix of consultees and commentators

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Provisional matrix	British Society for Rheumatology	Why is a specific religious group and a specific ethnic group on the consultee list?	Comment noted. Consultees and commentators are chosen based on their stated remits, both the Muslim Council of Britain and South Asian Health Foundation included medical policy in their remit.
	Pfizer	• In the spirit of equality, we would suggest inclusion of other ethnic groups alongside the Muslim Council of Britain, who may also benefit from inclusion as a consultee. We would like to encourage NICE to reach out to other relevant groups for their consideration as consultees. • Please consider inclusion of Academy of Medical Sciences as a Commentator	Comments noted. Consultees and commentators are chosen based on their stated remits, NICE considers updates to consultee lists on a regular basis. The stakeholder matrix has been updated to include the Academy of Medical sciences.
	Abbvie	Please note that Arthritis Research UK is now known as Versus Arthritis.	Comment noted. The stakeholder matrix has been updated.

The Royal College of Physicians endorse the comments made by British Society of Rheumatology

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Amgen
Eli Lilly
Sanofi Genzyme