National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Tofacitinib for treating juvenile idiopathic arthritis ID2718

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 (BSR), endorsed by the Royal College of Physicians (RCP)	It is highly appropriate that this topic is dealt with, as Tofacitinib is a new medication for the treatment of juvenile arthritis, is given orally rather than by injection, and been examined in an international randomised double-blind, placebo-controlled withdrawal trial.	Thank you for your comment. No change to scope.
	Pfizer	Yes. Children and young people and their carers' and clinicians would welcome a new treatment option targeting different cytokines. Treatment failure with the currently available biologic therapies is common. There is also an unmet need for orally administered advanced treatment as biologic therapies are injected either subcutaneously or intravenously which can be challenging to administer for children and their carers. Xeljanz is an oral JAK inhibitor, which could address this unmet need.	Thank you for your comment. No change to scope.

Section	Consultee/ Commentator	Comments [sic]	Action
	Psoriasis and Psoriatic Arthritis Alliance (PAPAA)	Yes [it would be appropriate to refer this topic to NICE for appraisal]	Thank you for your comment. No change to scope.
Wording	BSR (endorsed by RCP)	Yes [the wording of the remit reflects the issue(s) of clinical and cost effectiveness about this technology that NICE should consider]	Thank you for your comment. No change to scope.
	Pfizer	Yes [the wording of the remit reflects the issue(s) of clinical and cost effectiveness about this technology that NICE should consider]	Thank you for your comment. No change to scope.
	PAPAA	Yes [the wording of the remit reflects the issue(s) of clinical and cost effectiveness about this technology that NICE should consider]	Thank you for your comment. No change to scope.
Timing Issues	BSR (endorsed by RCP)	Any additional options for treatment of JIA are highly welcomed, in particular treatment options that do not require an injection (intravenous or subcutaneous). Children really struggle with regular injections and the development of needle phobia. As soon as trial results are available, this is urgent. Tofacitinib acts in a mechanistically different way therefore offering a step change in management of JIA.	Thank you for your comments. NICE aims to provide draft guidance to the NHS within 90 days from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No changes needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Pfizer	This is the first oral targeted synthetic disease modifying anti-rheumatic drug (tsDMARD) in submission for treatment of JIA and should be appraised in line with regulatory timelines to allow prompt access for children and young people.	Thank you for your comments. NICE aims to provide draft guidance to the NHS within 90 days from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No changes needed.
	PAPAA	More urgent for this younger group than perhaps it might be for an adult population, due to fewer treatment options after therapy failure.	Thank you for your comment. No change to scope.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	BSR (endorsed by RCP)	Accurate and complete. One change under psoriatic arthritis: “diagnosed when there is arthritis in association with psoriasis” rather than “diagnosed when there is joint pain associated with psoriasis”	Thank you for your comment. The scope has been updated.
	Pfizer	We suggest adding UK specific data to describe the frequency of JIA subtypes from the Childhood Arthritis Prospective Study (*Davies et al. Treatment prescribing patterns in patients with juvenile idiopathic arthritis (JIA): Analysis from the UK Childhood Arthritis Prospective Study (CAPS).* Seminars in Arthritis and Rheumatism. Vol 46. Issue 2. October 2016. p190-	Thank you for your comment. The percentages for the different subtypes of JIA have been updated.

Section	Consultee/ Commentator	Comments [sic]	Action
		195. *https://doi.org/10.1016/j.semarthrit.2016.06.001).* The study presents the following percentages for the different subtypes of JIA, which are consistent with the figures currently reported in the scope, but they are from a UK database, therefore they reflect the local population systemic JIA 6%, persistent oligoarthritis 51%, extended oligoarthritis 2%, polyarticular-onset RF negative 19%, polyarticular-onset RF positive 3%, psoriatic arthritis 6%, enthesitis-related 6%, undifferentiated arthritis 7%. Note there is a difference in the figures for prevalence of the disease, NHS England estimates 12,000 people affected rather than 10,000. (NHS England. Clinical Commissioning Policy Statement: Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis (JIA) E03X04). The National Rheumatoid Arthritis Society (NRAS) also refers to the same number (https://www.nras.org.uk/what-is-jia-).	The prevalence has also been updated.
	PAPAA	Looks complete	Thank you for your comment. No change to scope.
The technology/ intervention	BSR (endorsed by RCP)	Yes [the description of the technology is accurate]	Thank you for your comment. No change to scope.
	Pfizer	In paragraph 1: Please amend the description of the technology to explain the mode of action of tofacitinib specifically rather than janus kinase enzymes and their role. There are 4 JAK isoforms and a JAK inhibitor may have different selectivity for the isoforms. Therefore, we suggest the following amendment to sentence 1 and 2; *Tofacitinib is a potent, selective Janus Kinase (JAK) inhibitor classed as a targeted synthetic small molecule disease-modifying antirheumatic drug (tsDMARD). Its mode of action results in modulation of the immune response in the joints by interrupting the inflammatory process. It inhibits signalling by heterodimeric cytokine*	Thank you for your comments. Regarding the description of the technology, this section is intended to provide a brief description. No change to scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		receptors that associate with JAK3 and/or JAK1 with functional selectivity over cytokine receptors that signal via pairs of JAK2. In paragraph 2: Concomitant medication with MTX and oral corticosteroids or NSAIDs was permitted as a continuation of stable existing baseline treatment, but not all patients were treated with these agents. Therefore we suggest the following amendment to the wording; *It has been studied in a phase 3 double blind, randomised controlled withdrawal clinical trial compared with placebo in children aged 2 to 17 who have JIA (including extended oligoarthritis, polyarthritis, psoriatic arthritis, enthesitis-related arthritis and systemic JIA with active arthritis but without active systemic features). Patients in the trial who have extended oligoarthritis, polyarthritis and systemic JIA with active arthritis but without active systemic features must be intolerant to, or their disease must have responded inadequately to, 1 or more DMARD. The disease of patients in the trial who have psoriatic arthritis or enthesitis-related arthritis must have responded inadequately to NSAIDs. Stable doses of NSAIDs and/or MTX and/or oral glucocorticoids were permitted.* In the paragraphs where other licensed indications of tofacitinib are listed, please amend the indication for RA to include monotherapy. Tofacitinib can be given as monotherapy without methotrexate (MTX), in case of intolerance to MTX or where treatment with MTX is inappropriate. Therefore, please amend the bullet point to say; *Tofacitinib has a UK marketing authorisation in combination with methotrexate for treating moderate to severe active rheumatoid arthritis in adult patients whose disease has responded inadequately to, or who are intolerant to one or more DMARDs. Tofacitinib can be given as monotherapy in case of intolerance to MTX or where treatment with MTX is inappropriate.* Please also add all licensed UK indications for tofacitinib by adding the third indication of tofacitinib; ulcerative colitis.	The description of the trial has been updated. The description of tofacitinib's UK marketing authorisation for rheumatoid arthritis has been updated to state that tofacitinib can be given as a monotherapy in case of intolerance to methotrexate or when treatment with methotrexate is inappropriate. The marketing authorisation in ulcerative colitis was excluded as it is not a relevant indication for this appraisal. However, the scope has been updated to clarify that the 2 indications listed are rheumatic diseases

Section	Consultee/ Commentator	Comments [sic]	Action
		Tofacitinib has UK marketing authorisation for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.	specifically and therefore of interest.
	PAPAA	Yes [the description of the technology is accurate]	Thank you for your comment. No change to scope.
Population	BSR (endorsed by RCP)	Population is appropriate	Thank you for your comment. No change to scope.
	Pfizer	The population is defined appropriately.	Thank you for your comment. No change to scope.
	PAPAA	Yes [the population is defined appropriately]	Thank you for your comment. No change to scope.
Comparators	BSR (endorsed by RCP)	The comparators are accurate. There are no patients who receive 'best supportive care alone' i.e. all patients will receive one or more DMARDs (could include sulphasalazine/ azathioprine/leflunomide) and are likely to have had a biologic. It is very unlikely that any patient would be ineligible for all currently available biologic DMARDs. As per 'Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis (JIA)' clinical commissioning statement (January 2015), other biologic therapies are used in particular situations, for example Infliximab (especially uveitis associated with JIA), anakinra (in systemic JIA) and rituximab (in RF	Thank you for your comments. Best supportive care has been removed from the scope. Infliximab, anakinra and rituximab have been added to the scope to be inclusive.

Section	Consultee/ Commentator	Comments [sic]	Action
		positive polyarticular JIA). These could also form part of the comparator arm for completeness.	
	Pfizer	The relevant comparators for tofacitinib in people with polyarticular course JIA are Abatacept, Adalimumab, Etanercept and Tocilizumab. Methotrexate or best supportive care are not relevant comparators for the following reasons; • For polyarticular course JIA, the licensed indications generally add the advanced treatment (biologic DMARD) to MTX if there has been an inadequate response, unless the patient is intolerant to MTX in which case some biologics are used as monotherapy. The current UK clinical practice for treating enthesitis-related arthritis is to initiate biologic therapy (etanercept or adalimumab) after the failure of conventional therapy (NSAIDs, steroids). • In the previous appraisal for polyarticular juvenile idiopathic arthritis, the assessment group did not present analyses comparing the biologic DMARDs with BSC, because of lack of available data. They stated, patients who cannot tolerate a DMARD, such as methotrexate, would likely be offered a biologic DMARD rather than receiving BSC therefore this comparison is not necessarily clinically relevant. This position has not changed as no new evidence became available since the publication of the previous guidance. Therefore, please consider deleting best supportive care or methotrexate as comparators in the scope.	Thank you for your comments. NHS England's Suggested Treatment Flow-chart for JIA states that all patients with JIA (other than oligo-articular JIA) should start treatment with methotrexate as their first-line DMARD. Methotrexate is therefore a relevant comparator and remains in scope. Best supportive care has been removed from the scope.
	PAPAA	Yes [these are the standard treatments currently used in the NHS with which the technology should be compared]	Thank you for your comment. No change to scope.

Section	Consultee/ Commentator	Comments [sic]	Action
Outcomes	BSR (endorsed by RCP)	Yes [the outcome measures will capture the most important health-related benefits (and harms) of the technology]	Thank you for your comment. No change to scope.
	Pfizer	The list of outcomes is appropriate.	Thank you for your comment. No change to scope.
	PAPAA	Yes [the outcome measures will capture the most important health-related benefits (and harms) of the technology]	Thank you for your comment. No change to scope.
Economic analysis	BSR (endorsed by RCP)	The economic assessment should be long enough to capture all possible benefits. This is difficult as ideally the time-line is several years. Long term, the child in flare may miss schooling, affecting education and consequent ability to contribute to the adult workforce. Joint destruction takes place usually over several years and joint replacement may occur in early adult life, at great expense to the NHS. Capturing these later issues requires prolonged follow-up and the data may not currently be available. Proxy measures of gaining remission / remaining in remission for 1-2 years may be adequate. Quality of life should include the difficulties children have with injections / needle phobia versus taking tablets/medication.	Thank you for your comment. No change to scope.
	Pfizer	[redacted]	Thank you for your comment. No change to scope.

Section	Consultee/ Commentator	Comments [sic]	Action
	PAPAA	No comment	No change to scope.
Equality and Diversity	BSR (endorsed by RCP)	No impact of the scope on equality	Thank you for your comment. No change to scope.
	Pfizer	No comments. We do not anticipate the recommendation of tofacitinib would lead to any equality concerns.	Thank you for your comment. No change to scope.
	PAPAA	None	No change to scope.
Other considerations	BSR (endorsed by RCP)	Impact of untreated disease on family members (emotional, siblings, financial). Other JAK inhibitors are currently under investigation for treatment of JIA (e.g. Baricitinib)	Thank you for your comment. The health effects of the technology on carers can be considered in NICE's reference case, when relevant. No change to scope.
	Pfizer	No comment.	No change to scope.
	PAPAA	None	No change to scope.
Innovation	BSR (endorsed by RCP)	Yes, it acts in a mechanistically different way to available treatments. Therefore, it is likely to benefit a proportion of JIA patients who were previously resistant to currently-available treatment. All biologic agents for treatment of JIA are administered by injection (subcutaneous or intravenous infusion). Tofacitinib would be the first novel treatment which can be administered orally (available as liquid or tablet). This could have a	Thank you for your comment. The extent to which the technology may be innovative and impact on the child's quality of life will be

Section	Consultee/ Commentator	Comments [sic]	Action
		substantial impact on a child's quality of life as it avoids the pain of needles and requirement to attend hospital for an infusion. Ruperto, N., Brunner, H.I., Zuber, Z. et al. Pharmacokinetic and safety profile of tofacitinib in children with polyarticular course juvenile idiopathic arthritis: results of a phase 1, open-label, multicenter study. Pediatr Rheumatol 15, 86 (2017). https://doi.org/10.1186/s12969-017-0212-y Ruperto N, Synoverska O, Ting T on behalf of PRINTO/PRCSG, et al. OP0291 TOFACITINIB FOR THE TREATMENT OF POLYARTICULAR COURSE JUVENILE IDIOPATHIC ARTHRITIS: RESULTS OF A PHASE 3, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED WITHDRAWAL STUDY. Annals of the Rheumatic Diseases 2020;79:180-181. https://ard.bmj.com/content/79/Suppl_1/180.2 Brunner H, et al. Tofacitinib for the Treatment of Polyarticular Course Juvenile Idiopathic Arthritis: Results of a Phase 3 Randomized, Double-blind, Placebo-controlled Withdrawal Study [abstract]. Arthritis Rheumatol. 2019; 71 (suppl 10). https://acrabstracts.org/abstract/tofacitinib-for-the-treatment-of-polyarticular-course-juvenile-idiopathic-arthritis-results-of-a-phase-3-randomized-double-blind-placebo-controlled-withdrawal-study	considered in the appraisal of the technology. No change to scope.
	Pfizer	Tofacitinib if approved for polyarticular course JIA will be the first orally administered advanced therapy i.e. targeted synthetic DMARD. Tofacitinib will allow for convenient storage and administration either as a tablet formulation or as an oral solution for children and young people with JIA compared to current biologic treatment options. Pfizer believes that this will lead to significant benefit for patients' and their families' quality of life and will reduce the burden of the disease on their life.	Thank you for your comment. The extent to which the technology may be innovative and its impact on patient's and families' quality of life will be considered in

Section	Consultee/ Commentator	Comments [sic]	Action
			the appraisal of the technology. No change to scope.
	PAPAA	No	No change to scope.
Questions for consultation	BSR (endorsed by RCP)	*Have all relevant comparators for tofacitinib been included in the scope? In particular:* • *Which treatments are considered to be established clinical practice in the NHS for JIA?* A: See above. Infliximab, Anakinra and Rituximab are also established treatments for JIA. • *Is best supportive care a relevant comparator for tofacitinib? If so, how should best supportive care be defined?* A: See above. It is very unlikely that a patient with JIA would be ineligible for all the biologic DMARDs. If a patient was not able to have any DMARDs or biologic DMARDs, best supportive care would be appropriate analgesia and the temporary use of glucocorticoids (systemic or by intra-articular injection) at the discretion of the treating physician and in consultation with the patients and carer(s). *Are the outcomes listed appropriate?* A: Yes *Is the population listed in the scope appropriate?* A: Yes *Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom tofacitinib is expected to be more*	Thank you for your comments. Infliximab, anakinra and rituximab have been added to the scope to be inclusive. Best supportive care has been removed from the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		clinically effective and cost effective, or other groups that should be examined separately? A: Yes, the subgroups are appropriate and no further subgroups to consider. The systemic onset JIA with active systemic features subgroup is currently subject to a clinical trial. *Where do you consider tofacitinib will fit into the existing NICE pathway, Musculoskeletal conditions?* A: In the JIA treatment pathway as a second line treatment in the event of failure of, or intolerance to, methotrexate. *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)?* A: See above. Different mechanism of action compared with current therapies, therefore offers potential benefit to patients resistant to other treatments. *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?* A: Oral medication therefore: less needle phobia, fewer admissions to hospital, less NHS resource use (vs. injection/infusion) *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.* A: References above. Clinical trial results available in abstract form but likely to be published in full in the near future.	

Section	Consultee/ Commentator	Comments [sic]	Action
		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. • *Would it be appropriate to use the cost comparison methodology for this topic?* A: Yes • *Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?* A: Clinical efficacy likely to be similar. Full results of the clinical trial awaiting publication. Resource use potentially less – no need for hospital admission for intravenous infusion or for training/delivery/collection related to subcutaneous injections given at home. • *Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?* A: Trial primary outcome was percentage of participants with disease flare in the double-blind, randomised, placebo-controlled phase. Disease flare is a clinically relevant outcome. • *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?* A: Ongoing trials of Tofacitinib in systemic JIA with systemic features, and Baricitinib in systemic JIA, polyarticular-course JIA and JIA-associated uveitis. These are not expected to be reporting results within the next year.	
	Pfizer	Please see responses to the specific questions on population, comparators, outcomes, economic analysis etc. above and responses to the outstanding questions below.	Thank you for your comment. The extent to which the technology

Section	Consultee/ Commentator	Comments [sic]	Action
		Where do you consider tofacitinib will fit into the existing NICE pathway, Musculoskeletal conditions? Pfizer considers tofacitinib [redacted] *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.* The currently available advanced treatment options for people with JIA are all administered as subcutaneous or intravenous injection. Tofacitinib is going to be the first targeted synthetic DMARD that is administered orally, either as a solution or tablet formulation and therefore has the potential to improve treatment convenience for patients. Whilst needle phobia affects 10% of the population it is even more pronounced in children. Over a third of children treated with MTX injections for JIA reported fear of injections (Orenius et al. SAGE Open Nursing Journal, 2018). Besides, pain associated with administering injections may be more pronounced in children also. Evidence for JIA is limited but adult RA patients, when assuming treatments are equally efficacious, rank route of administration as a key attribute. Oral route was preferred by 49.1% compared to SC 29% and IV 21.9% (Alten et al. Patient Preference and Adherence 2016). *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.* No barriers to adoption of tofacitinib into clinical practice are expected. *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.*	may be innovative and its impact on patient's and families' quality of life will be considered in the appraisal of the technology. No change to scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		[redacted]	
Additional comments on the draft scope	Pfizer	In the section on 'Related NICE recommendations and NICE Pathways' Pfizer recommends including the appraisal on tofacitinib for ulcerative colitis [Tofacitinib for moderately to severely active ulcerative colitis (TA547)].	Thank you for your comment. The NICE appraisal of tofacitinib for moderately to severely active ulcerative colitis was excluded as it is not a relevant indication for this appraisal. No change to scope.

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

AbbVie, Amgen