Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2463

tofacitinib 5mg film-coated tablets (Xeljanz®)

Pfizer Limited

05 August 2022

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

tofacitinib (Xeljanz®) is accepted for use within NHSScotland.

Indication under review: for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy.

In a phase III and phase II study, tofacitinib compared with placebo, significantly improved symptoms of AS in adults with active disease inadequately controlled with nonsteroidal anti-inflammatory drugs.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

For the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy.[1]

Dosing information

The recommended dose of tofacitinib is 5mg administered orally twice daily with or without food.

Available data suggest that clinical improvement in AS is observed within 16 weeks of initiation of treatment with tofacitinib. Continued therapy should be carefully reconsidered in a patient exhibiting no clinical improvement within this timeframe.

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which tofacitinib is indicated. For further information including advice on dose interruption, adjustment and discontinuation, and interactions see Summary of product characteristics (SPC).[1]

Product availability date

16 February 2022

Summary of evidence on comparative efficacy

Tofacitinib is a selective inhibitor of the Janus Kinase (JAK) family and preferentially inhibits cytokines, which use JAK1 and/or JAK3 to signal. Inhibition of JAK1 and JAK3 attenuates signalling of interleukins and type I and type II interferons, which modulates the immune and inflammatory response.[1]

Evidence for the indication under review is from A3921120, a multicentre, randomised, double-blind, phase III study with supportive evidence from A3921119, a multicentre, randomised, double-blind, dose-ranging, phase II study. Both studies evaluated the efficacy and safety of tofacitinib compared with placebo in adult patients (≥18 years) with a diagnosis of AS based on the modified New York Criteria for Ankylosing Spondylitis (1984) documented with a radiograph of the sacroiliac joints (AP Pelvis). Patients had active disease at screening and baseline, defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4, back pain score (BASDAI Question 2) of ≥4 and an inadequate response to ≥2 nonsteroidal anti-inflammatory drugs (NSAID) or intolerance to NSAIDs. In study A3921120, 77% of the study population were biologic disease-modifying antirheumatic drugs (DMARD)-naïve and 23% had an inadequate response or intolerance to ≤2 tumour necrosis factor (TNF)-alpha inhibitors or had prior biologic DMARD (TNF-alpha inhibitor or non-TNF-alpha inhibitor) use without an inadequate response. In study A3921119, patients were excluded if they had received prior biologic DMARD treatment including TNF-alpha inhibitor.[2-4]

In study A3921120, patients were randomised equally to receive oral tofacitinib 5mg twice daily (n=134) or placebo (n=136) during the 16-week double-blind treatment period. This was followed by a 32-week open-label treatment period (weeks 16 to 48) during which all patients received oral tofacitinib 5mg twice daily. Randomisation was stratified according to previous biologic DMARD use: (1) biologic DMARD-naïve and (2) TNF-alpha inhibitor inadequate response or prior biologic DMARD with adequate response. In study A3921119, patients were randomised equally to receive twice daily oral tofacitinib 2mg (n=52), 5mg (n=52), 10mg (n=52) or placebo (n=51) for 12 weeks followed by a 4-week off-treatment follow-up period. The tofacitinib 2mg and 10mg twice daily groups will not be discussed further as they are not licensed doses for this indication. In both studies, patients could continue to receive the following background therapies provided the dose was stable at baseline and they continued throughout the treatment period: NSAIDs, methotrexate (≤25mg per week in A3921120 and ≤20mg per week in A3921119), sulfasalazine (≤3 grams per day) and oral corticosteroids (≤10mg per day of prednisone or equivalent). Rescue medicine with paracetamol (≤2.6 grams per day) with or without opioids (equivalent of ≤30mg per day of orally administered morphine) was permitted for no more than 10 consecutive days if there was an increase in pain. Patients who required rescue medication for more than 10 consecutive days were discontinued from the study due to lack of efficacy. In addition, patients were not permitted to receive rescue paracetamol or opioids within 24 hours prior to a study visit.[2-5]

The primary outcome was Assessment of SpondyloArthritis international Society (ASAS)20 response measured at week 16 in A3921120 and week 12 in A3921119. An ASAS20 response was defined as at least a 20% and ≥1 unit improvement from baseline in at least 3 out of 4 domains (the patient global assessment of disease, spinal pain, function, and inflammation) on a scale of 0 to 10, and no worsening of ≥20% and ≥1 unit in the remaining domain. Efficacy analyses were conducted in the full analysis set (FAS), which included all patients who were randomised and received at least one dose of study treatment. A hierarchical strategy was applied to a range of secondary outcomes in A3921120 with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Study A3921119 did not have a hierarchical testing strategy and therefore results for secondary outcomes are considered descriptive and p-values are not reported.[2-4]

In study A3921120, tofacitinib was associated with a statistically significant improvement in ASAS20 response at 16 weeks compared with placebo. This was supported by improvements in secondary outcomes measuring disease activity, function, pain and quality of life. Many of these were included in the hierarchical testing strategy and were statistically significant. In study A3921119, tofacitinib was associated with a significant improvement in ASAS20 response compared with placebo at 12 weeks. This was supported by improvements in secondary outcomes.[2-4] The results have been detailed in Table 1.

Table 1: Primary and secondary outcomes from Study A3921120 and A3921119 in the FAS.[2-4]

	Study A3921120 16-week outcomes		Study A3921119 12-week outcomes	
	Tofacitinib 5mg (n=133)	**Placebo (n=136)**	**Tofacitinib 5mg (n=52)**	**Placebo (n=51)**
Primary outcome: ASAS20 response				
Response, %	56%	29%	63%	40%
Difference versus placebo, (95% CI)	27% (16 to 38), p<0.001		23% (8.4 to 38), p<0.001[C]	
Selected secondary outcomes				
ASAS40 response	41%[A]	12%	46%	20%
ASDAS CFB, LSM	-1.4[A]	-0.4	-1.4	-0.7
ASDAS inactive disease rate	6.8%[B]	0%	14%	7.8%
ASAS partial remission rate	15%[B]	2.9%	19%	12%
BASDAI50 response	43%[B]	18%	42%	24%
BASDAI CFB, LSM	-2.6[B]	-1.1	-2.9	-1.9
BASMI CFB, LSM	-0.6[A]	-0.1	-0.4	-0.2
BASFI CFB, LSM	-2.1[A]	-0.8	-2.4	-1.4
Total back pain CFB, LSM	-2.6[A]	-1.0	-3.2	-2.0
SPARCC spine score CFB, LSM	-	-	-5.5	-0.1
ASQoL CFB, LSM	-4.0[A]	-2.0	-4.8	-2.5
SF-36v2 PCS score CFB, LSM	6.7[A]	3.1	6.5	2.7

ASAS: Assessment of SpondyloArthritis international Society; ASDAS: Ankylosing Spondylitis Disease Activity Score; ASQoL: Ankylosing Spondylitis Quality of Life; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CFB: change from baseline; CI: confidence interval; CRP: C-reactive protein; FAS: full analysis set; LSM: least squares mean; SF-36v2 PCS: Short Form-36 Health Survey version 2 Physical Component Summary; SPARCC: SPondyloArthritis Research Consortium of Canada. [A]p-values <0.001 for tofacitinib versus placebo when adjusted for multiplicity. [B]Not controlled for multiplicity. [C]Analysed using a Bayesian Emax model to characterise the dose-response relationship.

In study A3921120, an improvement in ASAS20 and ASAS40 response rates were observed from week 2 and week 4 respectively for the tofacitinib group. Efficacy outcomes were generally sustained over time up to week 48 including ASAS20 and ASAS40 response rates (65% and 50% respectively in patients originally randomised to tofacitinib) and other secondary outcomes. For patients in the placebo group who switched to open-label tofacitinib 5mg twice daily after week 16, ASAS20 and ASAS40 responses improved from week 16 to 24 and then remained stable until week 48 (60% and 45% respectively).[2, 3] In study A3921119, an improvement in ASAS responses and most secondary outcomes was observed from week 4.[4]

In study A3921120, prespecified subgroup analyses were generally consistent with the FAS and favoured tofacitinib for the proportion of patients that achieved an ASAS20 and ASAS40 response. This included the subgroups based on prior treatment history. For biologic DMARD-naïve patients (n=207), 62% versus 33% achieved an ASAS20 response and 45% versus 14% achieved an ASAS40 response at week 16 in the tofacitinib and placebo groups respectively. For patients with prior biologic DMARD use or inadequate responders to TNF-alpha inhibitors (n=62), an ASAS20 response was achieved by 39% versus 16% and an ASAS40 response was achieved by 26% versus 6.5% in each group at week 16.[2, 3, 6]

Health-Related Quality of Life (HRQoL) was assessed using the Ankylosing Spondylitis Quality of life (ASQoL), Short Form-36 Health Survey (SF-36) version 2, EuroQoL Health State Profile – 5 domains – 3 levels (EQ-5D-3L), EQ-visual analogue scale (VAS), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Work Productivity and Activity Impairment (WPAI) Questionnaire: Spondyloarthritis and AS HealthCare Resource Utilisation Questionnaire (AS-HCRU). Results for ASQoL and SF-36 PCS have been detailed in Table 1. Overall, results at week 12 and 16 for the other outcomes generally favoured tofacitinib compared with placebo.[2-4]

In the absence of direct evidence with an active comparator, the submitting company presented Bayesian network meta-analyses (NMAs) comparing tofacitinib (data from two studies) versus adalimumab (data from four studies) in adult patients with AS who have responded inadequately to conventional therapy. On request, the submitting company also provided an NMA comparing tofacitinib (data from two studies) with secukinumab (data from three studies). Separate analyses were conducted in a biologic-naïve and mixed population (both patients with and without prior biologic treatment) as well as a biologic-experienced population (for secukinumab only). Efficacy, HRQoL and safety outcomes included ASAS20 and ASAS40 response, BASDAI50 response and change from baseline in BASDAI, BASFI, BASMI, ASQoL, SF-36v2, discontinuation events, AE-related discontinuation and serious AEs. The submitting company concluded that the NMAs demonstrated that tofacitinib has similar efficacy, safety and HRQoL as adalimumab and secukinumab across all outcomes that could be assessed in mixed, biologic-naïve and biologic-experienced patients. The results of the NMAs informed the company's decision to perform a cost-minimisation analysis to assess cost-effectiveness.

Summary of evidence on comparative safety

An integrated safety analysis was conducted using data from the placebo-controlled treatment period of A3921120 (16 weeks) and A3921119 (12 weeks). Any treatment-emergent adverse event (AE) was reported by 55% (101/185) of patients in the tofacitinib 5mg twice daily group and 49% (92/187) in the placebo group and these were considered serious in 1.6% versus 1.1%. The proportion with AEs that led to dose reductions or temporary treatment discontinuation due to an AE was 6.5% versus 3.2%. The most frequent treatment-emergent AEs by system organ class of any grade in the tofacitinib group versus the placebo group were: infections and infestations (28% versus 23%), gastrointestinal disorders (13% versus 15%), investigations (11% versus 4.3%), and musculoskeletal and connective tissue disorders (8.1% versus 11%).[3]

In the A3921120 study, using data from the double-blind and open-label phases up to week 48, any treatment-emergent AE was reported by 77% of patients in the tofacitinib 5mg twice daily group and 68% of patients originally randomised to the placebo group. In each group respectively, 5.3% versus 1.5% of patients experienced a serious AE, 14% versus 9.6% had a dose reduction or temporarily stopped study treatment and 6.0% versus 2.2% discontinued treatment due to an AE. The most frequently reported treatment-emergent AEs of any grade during the double-blind and open-label phases up to week 48, with an incidence >5% in the tofacitinib group versus the original placebo group were: upper respiratory tract infection (16% versus 13%), nasopharyngitis (8.3% versus 12%), diarrhoea (7.5% versus 5.9%), arthralgia (1.5% versus 6.6%), alanine aminotransferase (ALT) increased (6.0% versus 1.5%), protein urine present (6.0% versus 2.9%), headache (3.8% versus 5.1%) and upper abdominal pain (1.5% versus 5.1%).[2]

The incidence rate for most AEs of special interest (such as malignancies, major adverse cardiovascular events and opportunistic infections) for patients treated with tofacitinib for AS was lower compared with other licensed indications, however, this is likely due to lower exposure during these clinical studies. The regulator considered it acceptable that the long-term safety profile of tofacitinib in patients with AS is similar to that for rheumatoid arthritis and psoriatic arthritis. See the SPC for further safety information.[1, 3]

Summary of clinical effectiveness issues

Ankylosing spondylitis is a chronic inflammatory rheumatic disease that predominantly affects the spine and sacroiliac joints, with or without extra-spinal manifestations (including peripheral arthritis, inflammatory eye conditions, psoriasis and inflammatory bowel disease). AS (also known as radiographic axial spondyloarthritis) is characterised by the presence of structural changes in the sacroiliac joints on plain radiography. Chronic back pain is the predominant symptom, however, stiffness, fatigue and progressive morbidity can also occur which affect quality of life.[3, 7, 8] Guidelines recommend NSAIDs as first-line pharmacological treatment for pain associated with AS. TNF-alpha inhibitors are recommended for patients with severe active AS whose disease has responded inadequately to, or who cannot tolerate, NSAIDs. TNF-alpha inhibitor options include adalimumab, certolizumab pegol, etanercept, golimumab and infliximab. Treatment with an alternative TNF-alpha inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or whose disease has stopped responding after an initial response. Interleukin-17A (IL-17A) inhibitors may also be considered if TNF-alpha inhibitor treatment fails.[8, 9] Secukinumab and ixekizumab are IL-17A inhibitors licensed for the treatment of active AS which has responded inadequately to conventional therapy, however, only secukinumab has been accepted for use by SMC (SMC 1159/16 and SMC2440). Upadacitinib is an alternative JAK inhibitor also licensed for the treatment of AS that has failed to respond to conventional therapy.[10]

Treatment with tofacitinib 5mg twice daily demonstrated a 27% improvement in ASAS20 response and a 28% improvement ASAS40 response at week 16 compared with placebo in the phase III study A3921120. The results were statistically significant and considered clinically relevant by the

regulator.[3] A higher response was observed in patients who were biologic DMARD-naïve, which was clinically expected. Secondary outcomes measuring signs and symptoms, inflammation and quality of life were supportive. The efficacy of tofacitinib was generally maintained up to week 48. The primary and key secondary outcome results from the phase II study A3921119 were also supportive.

There were some limitations with the evidence presented. The primary outcome in studies A3921120 and A3921119 was ASAS20 response; European Medicines Agency (EMA) guidelines note that a higher magnitude of clinical response is expected for biological medicinal products or products from a new therapeutic class. Therefore, ASAS40 response would have been the preferred primary outcome that was assessed. Some important outcomes, for example BASDAI50 response, have not been included in the hierarchical testing procedure in study A3921120 and therefore these results are descriptive only. Study A3921120 provides evidence for tofacitinib in AS up to 48 weeks; however, this is relatively short to assess longer-term efficacy and safety. Placebo-controlled data is available up to 16 weeks, which limits the ability to interpret relative efficacy and safety beyond this treatment period. There is no evidence to assess whether treatment with tofacitinib should continue long-term following resolution of inflammation or if a dose reduction or change in dose interval following resolution should be considered. Study A3921120 did not include secondary outcomes that monitor structural changes to the spine or sacroiliac joints. These were included in study A3921119 and supported a benefit of effect in favour of tofacitinib. The regulator noted that outcomes measuring low disease activity or partial remission showed limited effect size when aimed at inactive disease or partial remission, and therefore could not be regarded as conclusive.[2, 3, 8, 11]

Evidence for tofacitinib in biologic-experienced patients with AS is limited as study A3921119 included biologic DMARD-naïve patients only and in study A3921120 only 23% (62/269) had an inadequate response to TNF-alpha inhibitors or had received prior biologic DMARDs. Subgroup analysis for the primary outcome indicated a benefit in favour of tofacitinib regardless of prior biologic DMARD experience however, A3921120 was not powered to detect differences between subgroups and the sample size is small, therefore results should be interpreted with caution. In studies A3921120 and A3921119, patients were permitted to continue treatment with NSAIDs (use was 80% in A3921120 and 92% in A3921119), oral corticosteroids (<10% in both studies) and conventional DMARDs (approximately 30% in both studies). The studies did not analyse the efficacy of combinations of concomitant treatment, which may differ from clinical practice in Scotland and could affect the generalisability of study results. There were no study sites in the UK, which may also affect the generalisability of results [2-4]

A3921120 and A3921119 were placebo-controlled studies, therefore there is no direct evidence comparing tofacitinib with TNF-alpha inhibitors or secukinumab, which are alternative treatments that may be used in patients with AS who have failed conventional therapy. The submitting company provided supportive indirect evidence to the regulator which indicated similar ASAS20 and ASAS40 response rates between tofacitinib 5mg twice daily and adalimumab, certolizumab, etanercept, golimumab, infliximab, ixekizumab and secukinumab.[3] To support this submission, NMAs were conducted comparing tofacitinib with adalimumab and secukinumab. The networks

were sparse, credible intervals were wide for some outcomes and there was clinical and methodological heterogeneity, which increases uncertainty in the results. Comparisons with secukinumab were not possible for some outcomes (including BASDAI50, BASMI and BASFI) due to limited available data. Outcomes in the NMA were assessed at 12 or 16 weeks therefore, longer-term comparable efficacy is uncertain. There was a lack of comparison with other TNF-alpha inhibitors which may be used in clinical practice as the submitting company considered that adalimumab was the most commonly used in clinical practice and that TNF-alpha inhibitors have a class effect. There is also no indirect data comparing tofacitinib versus adalimumab in a biologic-experienced population. Despite these uncertainties, the company's conclusion of similar efficacy with adalimumab and secukinumab seems plausible.

Clinical experts consulted by SMC considered that tofacitinib is a therapeutic advancement as it provides an additional biologic treatment option from a new medicine class for patients with AS who have failed conventional therapy. They indicated that its place in therapy is likely to be following an inadequate response or intolerance to TNF-alpha inhibitors and/or IL-17A inhibitors, or when these treatments are contraindicated. Tofacitinib is administered orally, which may be particularly advantageous for needle phobic patients. Prescription and blood monitoring are likely to be conducted in secondary care however service implications are likely to be minimal.

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis of tofacitinib within its full marketing authorisation. Comparisons were provided against adalimumab and secukinumab.

All clinical and patient outcomes were assumed to be equivalent between the three treatments, based upon the results of the indirect treatment comparison.

Medicines costs included the costs of medicines acquisition, administration (as a one-off cost at first administration) and monitoring. Costs were then presented on an annual basis, for year 1 and subsequent years. Annual medicines costs were calculated based upon the doses and dosing frequencies stipulated in the SPC for the three medicines, with separate analyses presented for secukinumab 150mg and secukinumab 300mg. A small difference was assumed in terms of monitoring costs for year 1, with an assumption of additional lipid monitoring requirements for tofacitinib versus the two comparators (which were assumed to have equal monitoring costs).

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price. A PAS discount is in place for secukinumab and this was included in the results used for decision-making by using estimates of the comparator PAS price.

The results are shown below in Table 2. The results presented do not take account of the PAS for secukinumab or the PAS for tofacitinib but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for secukinumab due to commercial confidentiality and competition law issues.

Table 1: Base case results: list price for all medicines

Treatment	Tofacitinib	Adalimumab biosimilar	Secukinumab 150 mg	Secukinumab 300 mg
Initiation year				
Acquisition cost	£8,995	£8,259	£10,229	£17,411
Administration cost	£0	£42	£42	£42
Monitoring cost	£630	£628	£628	£628
Total	£9,625	£8,929	£10,899	£18,081
Difference (tofacitinib versus comparator)	-	£696	-£1,273	-£8,456
Subsequent years				
Acquisition cost	£8,995	£8,259	£7,944	£15,888
Administration cost	£0	£0	£0	£0
Monitoring cost	£340	£340	£340	£340
Total	£9,336	£8,600	£8,284	£16,228
Difference (tofacitinib versus comparator)	-	£736	£1,051	-£6,893

The analysis was very straightforward and conservative in its approach.
The main limitation resulted from a potential inconsistency in the approach to applying dosing frequency of secukinumab versus the licensed indication. The submitting company stated that it was assumed that secukinumab will be dosed q4w, after the 5-week induction phase. However, the SPC states that secukinumab should be administered once-monthly. Whilst seemingly trivial, this difference results in nearly an additional month's dose being applied in the first year (16.79 doses versus 16 if administered monthly) and over one additional dose applied in subsequent years (13.04 versus 12 if administered monthly). By assuming dosing is more frequent than the licence, the annual costs of secukinumab were overestimated to a limited extent.

A related limitation is the assumption that the two secukinumab doses represent separate comparators. In reality, patients may escalate and de-escalate between the two over a treatment course, and as such the average dose will lie somewhere between the two doses. Given the cost differential between the doses, the likely split will have an impact on the degree of additional costs or cost savings associated with tofacitinib.

Despite these limitations, the economic case was considered to have been made.

*Other data were also assessed but remain confidential.**

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from the National Axial Spondyloarthritis Society (NASS), which is a registered charity.
- NASS has received 34% pharmaceutical company funding in the past two years, with none from the submitting company.
- Ankylosing spondylitis (also known as radiographic axial spondyloarthritis) is an inflammatory condition of the spine which often produces pain, stiffness, deformity and disability throughout adult life. It is a chronic progressive disease characterised by periods of fluctuating intensity, leading to slowly increasing spinal and peripheral joint damage. Often the pain and fatigue impacts negatively on people's ability to carry on with everyday life. Many have to stop working with financial implications. There are also impacts on mental health, relationships and social lives.
- Current treatment options are generally satisfactory for many patients. However, the patient group noted that a new medicine targeting a different enzyme could provide a useful alternative treatment to enable more people with ankylosing spondylitis to be able to exercise more easily and to live a fuller life.
- In a survey conducted by the patient group, patients described positive impacts that they thought tofacitinib may bring: 84% liked that it is in tablet form, 54% thought it would be easy to store and 43% liked that it had already been used in other conditions. Overall it was felt that there are a number of people who might benefit more such as those who: cannot tolerate NSAIDs, have not responded to other biologics, have a needle phobia, live in shared accommodation and do not have access to their own fridge and those who travel lots for work or want to go travelling.

Additional information: guidelines and protocols

The British Society of Rheumatology (BSR) and the British Health Professionals in Rheumatology (BHPR) published the "BSR and BHPR guideline for the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics" in 2017.[7] The guidance predates the availability of tofacitinib and therefore no specific recommendations are made, however the guidance makes the following relevant recommendations:

- Patients should be considered for anti-TNF therapy if they have active AS. Active disease is defined as a BASDAI and spinal pain VAS score ≥4 despite standard therapy.
- Extra-articular manifestations and patient choice should be considered when selecting an anti-TNF agent. In the absence of head-to-head studies, systematic reviews have shown no statistical difference in efficacy between infliximab, golimumab, etanercept and adalimumab in the treatment of AS (certolizumab data were not included in these comparative reviews, but its efficacy has been established in clinical trials). However, not all biologics are licensed for or

effective in the treatment of extra-articular disease, so treatment choice should take into account comorbidities and the preferred route and frequency of administration.

- Initial efficacy response should be assessed following 3 to 6 months of therapy and responders should then be reassessed every 6 months.
- Response is defined as a reduction in the BASDAI and spinal pain VAS of ≥2U from baseline.
- In the absence of an initial clinical response by 6 months, or failure to maintain response at two consecutive assessments, withdrawal of that anti-TNF agent should be considered.
- In the event of anti-TNF failure due to inefficacy or adverse events, an alternative anti-TNF agent should be offered if clinically appropriate.

The National Institute for Health and Care Excellence (NICE) "Spondyloarthritis in over 16s: diagnosis and management (NG65)" was updated in 2017.[9] The guidance recommends the use of adalimumab, certolizumab pegol, etanercept, golimumab and infliximab, within their marketing authorisations, as options for treating severe active AS in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs. The guideline also advises that the choice of treatment should be made after discussion between the clinician and the patient and recommends that if more than one treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen. The guidance recommends that people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or whose disease has stopped responding after an initial response, be treated with another TNF-alpha inhibitor.

The Assessment of SpondyloArthritis international Society (ASAS) in collaboration with the European League Against Rheumatism (EULAR) published guidance in 2006 (ASAS-EULAR) which was last updated in 2016.[8] The guideline predates the availability of tofacitinib and therefore no specific recommendations are made, however the guidance makes the following relevant recommendations:

- Patients suffering from pain and stiffness should use an NSAID as first-line treatment up to the maximum dose, taking risks and benefits into account. For patients who respond well to NSAIDs continuous use is preferred if symptomatic otherwise.
- Patients with purely axial disease should normally not be treated with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs); sulfasalazine may be considered in patients with peripheral arthritis.
- Biologic DMARDS should be considered in patients with persistently high disease activity despite conventional treatments; current practice is to start with TNF-alpha inhibitor therapy.
- If TNF-alpha inhibitor therapy fails, switching to another TNF-alpha inhibitor or an anti-IL-17 therapy should be considered.

Additional information: comparators

Adalimumab, certolizumab pegol, etanercept, golimumab, infliximab and secukinumab.

Additional information: list price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Tofacitinib	5mg orally twice daily	8,970

Costs from BNF online on 1 June 2022. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 3,038 patients eligible for treatment with tofacitinib in each year.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

These estimates do not take account of any patient access schemes applied to displaced medicines.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 15 July 2022.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via

the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.