SMC Scottish Medicines Consortium
NHS SCOTLAND
Advising on new medicines for Scotland
www.scottishmedicines.org.uk
Delta House • 50 West Nile Street • Glasgow • G1 2NP • Tel 0141 225 6999 • Chairman: Dr Alan G MacDonald

tofacitinib citrate 5mg film-coated tablets (Xeljanz®) SMC No 1298/18

Pfizer UK Limited

12 January 2018

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

tofacitinib citrate (Xeljanz®) is accepted for restricted use within NHS Scotland.

Indication under review: In combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Tofacitinib can be given as monotherapy in case of intolerance to methotrexate or when treatment with methotrexate is inappropriate.

SMC restriction: In patients with severe disease (a disease activity score [DAS28] greater than 5.1) that has not responded to intensive therapy with a combination of conventional DMARDs. In patients with severe disease inadequately controlled by a tumour necrosis factor (TNF) antagonist, it may be used in patients ineligible to receive rituximab.

In a phase III / IV study in patients with rheumatoid arthritis with an inadequate response to conventional DMARDs, non-inferiority of tofacitinib was demonstrated when compared with a tumour necrosis factor alpha (TNF) inhibitor (both in combination with methotrexate) in relation to proportion of patients achieving an American College of Rheumatology response of at least 50% (ACR50). A phase III study in patients with rheumatoid arthritis with an inadequate response to TNF inhibitors demonstrated that tofacitinib plus methotrexate significantly improved signs and symptoms of RA when compared with placebo plus methotrexate.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of tofacitinib. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Published 12 February 2018

Indication

In combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Tofacitinib can be given as monotherapy in case of intolerance to methotrexate or when treatment with methotrexate is inappropriate.[1]

Dosing Information

5mg administered orally twice daily.

Tofacitinib treatment should be interrupted if a patient develops a serious infection until the infection is controlled. Interruption of dosing may be needed for management of dose-related laboratory abnormalities including lymphopenia, neutropenia and anaemia. It is recommended not to initiate dosing in patients with an absolute lymphocyte count less than 750 cells/mm^3.

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of RA.

Further details are included in the summary of product characteristics (SPC).[1]

Product availability date

April 2017

Summary of evidence on comparative efficacy

Tofacitinib is the second Janus Kinase (JAK) inhibitor to be licensed in the UK. JAK inhibitors are a novel therapy for RA and have a different mode of action to biologic DMARDs. Tofacitinib modulates the immune and inflammatory response by selectively inhibiting JAK enzymes, JAK1 JAK2 and JAK3, (and to a lesser extent tyrosine kinase 2) which inhibits signalling by cytokine receptors. Inhibition of JAK1 and JAK3 reduces signalling of interleukins and type I and II interferons.[1]

The submitting company has requested that SMC considers tofacitinib when positioned for use in patients with severe disease (a disease activity score [DAS28] greater than 5.1) that has not responded to intensive therapy with a combination of conventional DMARDs. In patients with severe disease inadequately controlled by a tumour necrosis factor (TNF) antagonist, it may be used in patients ineligible to receive rituximab. Evidence of efficacy comes from the ORAL studies, in particular, ORAL Strategy, ORAL Standard and ORAL Step.

ORAL Strategy was an international, double-blind phase III / IV non-inferiority, randomised study in adult patients (≥18 years) with active RA despite receiving methotrexate therapy (n=1,146). Patients who met the 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria for RA, with active disease despite receiving methotrexate, were recruited between 11 September 2014 and 28 December 2015. Active RA was defined as having four or more tender or painful joints on movement and four or more swollen joints at baseline. All patients were required to have been receiving methotrexate for at least four months with a stable dose of between 15mg and 25mg for at least six weeks before

randomisation. Patients were also required to have a C-reactive protein level of 3mg/L or greater and class I to III functional capacity (ACR 1991). Included patients had to have stopped taking all conventional DMARDs (apart from methotrexate) for at least four weeks or five half-lives (whichever was longer) prior to randomisation. Patients who had previously had an inadequate response or adverse event related to a biologic DMARD were required to have stopped the biologic DMARD for a specified length of time prior to randomisation. Approximately 10% of patients included in the study had previously received a biologic DMARD. Prior use of adalimumab was not permitted. [2]

Patients were randomised equally to receive tofacitinib 5mg twice daily orally (n=384), tofacitinib 5mg twice daily orally plus methotrexate (n=376) or adalimumab 40mg subcutaneously every two weeks plus methotrexate (n=386). Methotrexate was continued at the patients' usual dose. Patients could continue to receive stable non-steroidal anti-inflammatory drugs (NSAIDs), analgesics and corticosteroids up to 10mg prednisolone or equivalent per day.[2]

The study was completed by 82% (315/386) of patients in the tofacitinib group, 81% (303/378) patients in the tofacitinib plus methotrexate group and 80% (312/388) of patients in the adalimumab plus methotrexate group. The primary outcome of proportion of patients achieving an ACR response of at least 50% (ACR50) at six months was 38% (147/384) in the tofacitinib group, 46% (173/376) in the tofacitinib plus methotrexate group and 44% (169/386) in the adalimumab plus methotrexate group. The difference between the proportion of patients with an ACR50 response in the tofacitinib plus methotrexate group compared with adalimumab plus methotrexate was 2% (98.34% confidence interval [CI] -6 to 11) and therefore non-inferiority was demonstrated as the lower limit of the CI was greater than the pre-specified level of -13%. Non-inferiority was not demonstrated for tofacitinib monotherapy compared with tofacitinib plus methotrexate where the difference was -8% (98.34 CI: -16 to 1) or tofacitinib monotherapy compared with adalimumab plus methotrexate, difference of -6% (98.34% CI: -14 to 3). At 12 months, the proportion of patients achieving ACR50 was 39% (151/384) in the tofacitinib monotherapy group, 48% (179/376) in the tofacitinib plus methotrexate group and 46% (177/386) in the adalimumab plus methotrexate group.[2]

Health Assessment Questionnaire-Disability Index (HAQ-DI) response at six months, which was defined as an improvement from baseline of ≥0.22, was achieved by 66% (254/384) of patients in the tofacitinib monotherapy group, 70% (264/376) of patients in the tofacitinib plus methotrexate group and 67% (260/386) of patients in the adalimumab plus methotrexate group. At 12 months, the percentage of patients achieving a response was 63% (241/384) in the tofacitinib monotherapy group, 64% (241/376) in the tofacitinib plus methotrexate group and 64% (247/386) in the adalimumab plus methotrexate group. Further secondary endpoints, assessed at six months, identified numerically similar response rates in the tofacitinib plus methotrexate group and the adalimumab plus methotrexate group as summarised in table 1. These outcomes were not tested for superiority or non-inferiority. [2]

Table 1: Secondary outcomes at six months (percentage of patients achieving the outcome) for the ORAL Strategy study[2]

	Tofacitinib monotherapy (n=384)	Tofacitinib plus methotrexate (n=376)	Adalimumab plus methotrexate (n=386)
ACR response			
ACR20	65%	73%	71%
ACR70	18%	25%	21%
Outcomes indicating low disease activity			
SDAI ≤11	43%	50%	47%
CDAI ≤10	42%	49%	46%
DAS28-4(ESR) <3.2	21%	27%	27%
DAS28-4(CRP) <3.2	41%	46%	47%
Outcomes indicating remission			
SDAI ≤3.3	10%	13%	13%
CDAI ≤2.8	10%	14%	13%
DAS28-4(ESR) <2.6	10%	12%	12%
DAS28-4(CRP) <2.6	21%	31%	28%
ACR-EULAR Boolean criteria	7%	8%	9%

ACR20 = the proportion of patients attaining an ACR response of at least 20%. ACR70 = the proportion of patients attaining an ACR response of at least 70%. SDAI = Simplified Disease Activity Index. CDAI=Clinical Disease Activity Index. DAS28-4(ESR) = Disease Activity Score in 28 joints, (erythrocyte sedimentation rate). DAS28-4(CRP) = Disease Activity Score in 28 joints, (C-reactive protein). EULAR=European League Against Rheumatism.

ORAL Standard was an international, randomised, double-blind, phase III study in adult patients (≥18 years) with active RA who had an inadequate response to methotrexate (n=717). This study excluded patients with a lack of response to TNF inhibitor biologic treatment; 9.2% of included patients had previously been treated with a TNF inhibitor or other biologic DMARD. Patients were recruited in a ratio of 4:4:4:1:1 to tofacitinib 5mg twice daily, tofacitinib 10mg twice daily (unlicensed dose), adalimumab 40mg fortnightly, placebo for three or six months followed by tofacitinib 5mg twice daily or placebo for three or six months followed by tofacitinib 10mg twice daily. All patients received methotrexate. The study duration was 12 months and aimed to compare the efficacy of tofacitinib with placebo. There were three primary efficacy endpoints.[3] Results are reported here for the licensed dose of tofacitinib. The proportion of patients who achieved ACR20 at six months was 51% (101/196) in the tofacitinib 5mg plus methotrexate group and 47% (94/199) in the adalimumab plus methotrexate group compared with 28% (30/106) in the placebo plus methotrexate group. The difference when compared with placebo plus methotrexate was 23% and 19% in the tofacitinib 5mg plus methotrexate and adalimumab plus methotrexate groups respectively which was statistically significant favouring the active groups ($p<0.001$ for all comparisons).[3, 4] The mean change from baseline in HAQ-DI at three months was -0.55 points in the tofacitinib 5mg plus methotrexate group (n=188) and -0.49 points in the adalimumab plus methotrexate group (n=190) compared with -0.24 in the placebo plus methotrexate group (n=90).[3, 4] The difference when compared with placebo plus methotrexate was -0.31 and -0.25 for the tofacitinib 5mg plus methotrexate and adalimumab plus methotrexate groups respectively which was statistically significant favouring the active groups ($p<0.0001$ for all comparisons).[4] The proportion of patients with DAS28-4(ESR) <2.6 at six months was 6.2% (11/177) in the tofacitinib 5mg plus methotrexate group and 6.7% (12/178) in the adalimumab group plus methotrexate compared with 1.1% (1/92) in the plus methotrexate placebo group.[3] The differences when compared with placebo plus methotrexate were statistically significant favouring tofacitinib 5mg plus methotrexate and adalimumab plus methotrexate ($p=0.0051$ and $p=0.0154$).[4]

Patients receiving placebo initially in ORAL Standard were switched to tofacitinib, either at month three if they did not achieve ACR20 or month six for all remaining patients. The primary efficacy endpoints of ACR20 response and DAS28-4(ESR) were assessed at month six although patients classed as non-responders (by not achieving ACR20) at three months were considered to be non-responders for the duration of the study. ORAL Standard compared tofacitinib 5mg plus methotrexate with adalimumab plus methotrexate as a secondary outcome to investigate non-inferiority but the study was not designed or powered to formally test this comparison. Numerically, these results favoured tofacitinib 5mg plus methotrexate for the primary endpoints of ACR20 response and DAS28-4(ESR) <2.6 at six months but HAQ-DI LSM change results at three months favoured adalimumab plus methotrexate. Secondary endpoints of proportion of patients achieving ACR50/70, HAQ-DI improvement from baseline ≥0.22 and DAS28 <3.2 numerically favoured tofacitinib 5mg plus methotrexate and proportion of patients achieving DAS28 <2.6 numerically favoured adalimumab plus methotrexate.[4]

ORAL Step was an international, double-blind, phase III study in adult patients (≥18 years) with moderate to severe RA who had inadequate response to TNF inhibitors (n=399). Patients with a diagnosis of active, moderate to severe RA assessed as per the ACR 1987 revised criteria were recruited between October 2009 and March 2011. Active RA was defined as six or more tender or sore joints (of 68 joint count), six or more swollen joints (of 66 joint count) and either erythrocyte sedimentation rate (ESR) >28mm/h (Westergren method) or C-reactive protein (CRP) >66.67nmol/L (7mg/L). Patients were required to have had inadequate response or intolerance to at least one TNF inhibitor. Methotrexate had to be taken orally or parenterally for at least four months prior to the first study dose and have been at a stable weekly dose of between 7.5mg and 25mg (20mg in the Republic of Ireland) for at least six weeks prior to the first study dose.[4, 5]

Patients were randomised in a 2:2:1:1 ratio to receive oral tofacitinib 5mg twice daily (n=133), tofacitinib 10mg twice daily (n=134), placebo for three months then tofacitinib 5mg twice daily (n=66) or placebo for three months then tofacitinib 10mg twice daily (n=66). All patients received a stable dose of methotrexate. Patients were allowed to continue on anti-malarial therapy, stable for eight weeks prior to the first dose of study medication. Other DMARDs were not allowed and had to be discontinued prior to the first dose of study medication including a washout period. Patients were permitted to continue NSAIDs, certain cyclooxygenase-2 inhibitors or glucocorticoids (≤10mg prednisolone or equivalent) as long as the dose had been stable for at least four weeks prior to the first study dose and patients were required to continue at that dose up to the third month of the study.[4, 5]

The study duration was six months and there were three primary efficacy endpoints which were assessed at three months. These were the ACR20 response rate, mean change from baseline in physical function measured by HAQ-DI and proportion of patients with DAS28-4(ESR) <2.6, assessed in a step-wise manner.[4, 5]

Results are only reported here for the licensed dose of tofacitinib. ACR20 response rate at three months was 42% (55/132) in the tofacitinib 5mg plus methotrexate group and 24% (32/131) in the combined placebo plus methotrexate groups. There was a statistically significant difference of 17% (95% CI: 6.1 to 28) between the tofacitinib 5mg plus methotrexate group and placebo plus methotrexate group favouring tofacitinib (p=0.0024). The least squares mean (LSM) changes from baseline in HAQ-DI at three months were -0.43 in the tofacitinib 5mg plus methotrexate group and -0.18 in the combined placebo plus methotrexate groups. There was a statistically significant difference of -0.25 (95% CI: -0.36 to -0.15) between the tofacitinib 5mg plus methotrexate group and the placebo plus methotrexate group favouring tofacitinib (p<0.0001). [4, 5] The proportion of patients achieving DAS28-4(ESR) <2.6 at three months was 6.7% (8/119) in

the tofacitinib 5mg plus methotrexate group and 1.7% (2/120) in the combined placebo plus methotrexate groups. The difference of 5.1% (95% CI 0 to 10.10) between tofacitinib 5mg plus methotrexate and placebo plus methotrexate was statistically significant favouring tofacitinib (p=0.0496). [5]

Secondary outcomes were measured at all visits up to six months. A statistically significant improvement in ACR50 and ACR70 response rate at three months was observed in the tofacitinib 5mg plus methotrexate group versus placebo plus methotrexate. Statistically significant improvements in the proportion of patients achieving an increase in HAQ-DI ≥0.5 units, LSM change from baseline in patient assessment of pain related to arthritis and functional assessment of chronic illness therapy-fatigue (FACIT-F) were also observed at three months in the tofacitinib 5mg plus methotrexate group versus placebo plus methotrexate. [5] These secondary outcomes are shown in table 2.

Table 2: Secondary outcomes at three months for the ORAL Step study[5]

	Tofacitinib 5mg twice daily plus methotrexate	**Placebo plus methotrexate**
ACR50 response rate	26%* (35/132)	8.4% (11/131)
ACR70 response rate	14%* (18/132)	1.5% (2/131)
Increase in HAQ-DI ≥0.5 units	36%** (47/131)	21% (27/131)
LSM change from baseline in patient assessment of pain related to arthritis	-27 units* (n=114)	-8.3 units (n=115)
Improvement in FACIT-F from baseline	6.3* (n=117)	1.1 (n=114)

* p<0.0001 ** p p<0.0053

ORAL Sequel and A3921041 were open-label studies assessing the long term safety and efficacy of tofacitinib. Patients were recruited who had previously participated in tofacitinib trials (phase I to III). Study A3921041 was completed in December 2013 and only included Japanese patients. ORAL Sequel is an on-going study. A published abstract of data from a pooled analysis included 4,967 patients and data for up to eight years are available. Patients received tofacitinib 5mg or 10mg twice daily either as monotherapy or with additional DMARDs. Secondary endpoints assessed clinical efficacy including ACR20/50/70 response rates, DAS28-4(ESR), HAQ-DI, and clinical disease activity index (CDAI). The authors concluded that results from month one were maintained at 90 months although only 168 patients were included in the results presented for month 90 compared with 4,776 at month one.[6]

Summary of evidence on comparative safety

In the ORAL Strategy study, the percentage of patients who experienced a treatment related adverse event was 26% (101/384) in the tofacitinib group, 30% (111/376) in the tofacitinib plus methotrexate group and 35% (133/386) in the adalimumab plus methotrexate group. Serious adverse events were reported in 9.1% (35/384), 7.2% (27/376) and 6.2% (24/386) of patients in the tofacitinib monotherapy, tofacitinib plus methotrexate and adalimumab plus methotrexate groups respectively. Discontinuation due to adverse events occurred in 6.0% (23/384) of patients in the tofacitinib group, 6.9% (26/376) of the tofacitinib plus methotrexate group and 10% (37/386) of the adalimumab plus methotrexate group.[2]

The most frequently occurring investigator-reported adverse events in the tofacitinib monotherapy, tofacitinib plus methotrexate and adalimumab plus methotrexate groups

respectively were upper respiratory tract infection affecting 6.5% (25/384), 10% (37/376) and 7.5% (29/386), raised alanine aminotransferase 2.1% (8/384), 6.1% (23/376) and 6.7% (26/386), nasopharyngitis 5.7% (22/384), 4.1% (16/376), 4.7% (18/386), urinary tract infections 2.9% (11/384), 4.0% (15/376) and 4.1% (16/386) and nausea 2.9% (11/384), 3.5% (13/376) and 4.1% (16/386).[2]

Serious infections occurred in 1.6% (6/384) of patients in the tofacitinib group, 2.6% (10/376) of the tofacitinib plus methotrexate group and 1.6% (6/386) of the adalimumab plus methotrexate group. Herpes zoster occurred in 1.0% (4/384) of patients in the tofacitinib group and 2.1% (8/376) of patients in the tofacitinib plus methotrexate group and by 1.6% (6/386) of patients in the adalimumab plus methotrexate groups. In the tofacitinib plus methotrexate group there were two reported cases of tuberculosis.[2]

There were two deaths during the study which were both in the tofacitinib plus methotrexate group. One patient's death was considered likely to have been due to urinary sepsis and the other patient had a confirmed diagnosis of H1N1 influenza and died from septic shock and cardiopulmonary arrest.[2]

Long-term safety of tofacitinib was assessed in open-label studies ORAL Sequel and A3921041. A published abstract of data from a pooled analysis included 4,967 patients and data for up to eight years is available. The primary outcome was safety and the most common adverse events reported were nasopharyngitis (19%), upper respiratory tract infection (17%), bronchitis (12%) and urinary tract infection (12%). The most common classes of adverse events were infections and infestations (69%) and musculoskeletal / connective tissue disorders (39%).[6]

The SPC states that tofacitinib should not be started in patients with active infections, including localised infections as serious infections have been reported in patients with RA receiving tofacitinib.[1] Non-infection related adverse events noted in the SPC include malignancy, interstitial lung disease, gastrointestinal perforations, hepatic safety and laboratory abnormalities. Caution is required due to potential drug interactions. Dose reduction to 5mg once daily is recommended in patients with moderate hepatic impairment or severe renal impairment.[1, 4]

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

Summary of clinical effectiveness issues

RA is a common autoimmune disease affecting approximately 1% of the population and is characterised by joint inflammation and swelling. Women are affected more frequently than men. It is not curable and a significant number of patients experience pain, stiffness, destruction of joints, decline in function and premature mortality.[4, 8]

The first-line choice of DMARD is usually methotrexate or sulfasalazine. In patients with an inadequate response to DMARD therapy a combination is recommended rather than further monotherapy with a different medication. The Scottish Intercollegiate Guidelines Network (SIGN) guideline states that TNF inhibitors are not recommended in patients who have not been previously treated with methotrexate or other DMARDs.[8] The National Institute for Health and Care Excellence (NICE) technology appraisal (TA) 375, recommends adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept in patients with severe disease not adequately controlled by conventional DMARDs, either in combination with

methotrexate or, within marketing authorisation, as monotherapy when methotrexate is not suitable. In patients who have inadequately controlled disease despite receiving conventional DMARDs and at least one TNF inhibitor, NICE TA195 recommends rituximab with methotrexate. In patients who are not suitable for rituximab the recommended options are adalimumab, etanercept, infliximab and abatacept, in combination with methotrexate or adalimumab and etanercept monotherapy in patients who cannot receive methotrexate.[9, 10] NICE TA375 and TA195 have been endorsed by Healthcare Improvement Scotland (HIS). SMC guidance published after these recommendations include tocilizumab, subcutaneous formulation (SMC number: 982/14) and baricitinib (SMC number: 1265/17). Subcutaneous tocilizumab in combination with methotrexate, is recommended in adult patients who have either responded inadequately to, or who were intolerant to previous therapy with one or more DMARDs or TNF inhibitors, in accordance with current eligibility and continuation rules for biologic therapies in rheumatoid arthritis. In these patients, tocilizumab can be given as monotherapy where methotrexate is inappropriate.[11] Baricitinib, a selective JAK inhibitor, is accepted for restricted use in Scotland in patients with severe disease (DAS28 >5.1) that has not responded to intensive therapy with a combination of conventional DMARDs. In patients with severe disease inadequately controlled by a TNF inhibitor, it may be used in patients ineligible to receive rituximab.[12] Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely in the subset of patients with an inadequate response to conventional and biologic DMARDs.

The submitting company has requested that SMC considers tofacitinib when positioned for use in patients with severe disease (a disease activity score [DAS28] greater than 5.1) that has not responded to intensive therapy with a combination of conventional DMARDs. In patients with severe disease inadequately controlled by a tumour necrosis factor (TNF) antagonist, it may be used in patients ineligible to receive rituximab. There were no subgroup analyses of patients who had severe RA in the key studies. The mean DAS28-4(ESR) at baseline in all groups for the studies described above was greater than six which may indicate that a significant proportion of patients had severe disease. A pooled analysis (abstract) of ORAL studies: Step, Standard, Scan, Sync, Solo and Start identified that according to DAS28, 91% of included patients had severe disease.[13]

In ORAL Strategy, the key study for the population of patients who had previously had an inadequate response to conventional DMARDs, non-inferiority of tofacitinib plus methotrexate compared with adalimumab plus methotrexate was demonstrated for the primary outcome of proportion of patients achieving ACR50 at six months. Non-inferiority was not demonstrated for tofacitinib monotherapy compared with tofacitinib plus methotrexate or compared with adalimumab plus methotrexate. Secondary endpoints including indicators of remission / low disease activity (LDA) as recommended by the European Medicines Agency (EMA) guideline DAS28-4(ESR), DAS28-4(CRP), ACR-EULAR Boolean criteria and also SDAI and CDAI identified numerically similar response rates in the tofacitinib plus methotrexate group and the adalimumab plus methotrexate group. [2] The key study for the population of patients who previously had an inadequate response to biologic DMARDs, ORAL Step, identified a statistically significant difference favouring tofacitinib 5mg plus methotrexate compared with placebo plus methotrexate in the three primary endpoints ACR20 response rate, LSM change from baseline in HAQ-DI and proportion of patients DAS28-4(ESR). [4, 5] There are a lack of data for prevention of structural progression with tofacitinib in combination with methotrexate. Radiographic progression assessed in ORAL Scan identified a numerical benefit in the tofacitinib 5mg plus methotrexate group compared with placebo plus methotrexate but this did not achieve statistical significance. [14] The EMA concluded that tofacitinib 5mg twice daily has been shown to give efficacy benefit on

signs, symptoms and physical function in all treatment line settings which is clinically relevant, either as monotherapy or in combination with methotrexate.[4]

The primary endpoint of ACR50 response in the ORAL Strategy study measured a direct health outcome. The EMA has produced an updated draft guideline on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis. This guideline states that in patients with early arthritis / first-line treatment, remission and maintenance of remission would be an appropriate primary endpoint and in more advanced patients who have failed on standard treatment with multiple DMARDs, LDA may be a more realistic and relevant primary endpoint. The EULAR criteria defines LDA as DAS28 <3.2 and remission as DAS28 <2.6, remission can also be defined according to the EULAR-ACR Boolean or Index-based criteria. Time to onset of LDA / remission and sustainability of this should also be assessed. It does not recommend ACR scores as a primary endpoint as these 'represent a relative change from baseline, these do not necessarily reflect treatment targets of remission or an established level of LDA'. ACR scores are however recommended as secondary endpoints.[15]

The three co-primary endpoints, assessed after three months, in the ORAL Step study were statistically significant in favour of tofacitinib plus methotrexate versus placebo plus methotrexate. This population of patients had failed on TNF inhibitors and are therefore are likely to be in a later stage of disease with fewer remaining options for treatment. Although the EMA considers that ACR20 'lacks stringency' as a primary endpoint, it concluded that it was very ambitious to include DAS28-4(ESR) <2.6 response rate (indicating remission) in this patient population, particularly after only three months of treatment. It also stated that the secondary endpoints of ACR50/70 response rates support the clinical relevance of the DAS28-4(ESR) <2.6 response.[4] ORAL Strategy and Standard studies included comparative results for tofacitinib 5mg plus methotrexate and adalimumab 40mg plus methotrexate as secondary outcomes which indicated similar proportions of patients achieving DAS28-4(ESR) in these groups although these studies were not designed or powered to show statistical significance for these comparisons.

The EMA suggests that disease activity should be assessed at baseline, month one, three and six. In maintenance studies, disease activity should also be assessed after 12 months of treatment. [15] Primary outcomes for all of the studies described above were either from month three or month six. Long-term data are available for efficacy endpoints however data at month 90 were only presented for 3.5% of patients that were included at month one. [6]

Two network meta-analyses (NMA) were presented to provide indirect comparative data versus biologic DMARDs used in the economic analysis. The first was conducted in patients with moderate to severe RA not adequately controlled by conventional DMARDs. The second was conducted in patients who had an inadequate response to biologic DMARDs. The outcomes reported for both networks were EULAR response criteria at month 6 (presented as odds ratios) and change in HAQ-DI from baseline at month 6 (presented as mean treatment differences). Results were reported for biologic DMARDs in combination with a conventional DMARD versus tofacitinib plus conventional DMARD (and as monotherapy in some cases).

Tofacitinib (plus conventional DMARD) had comparable efficacy to most biologic DMARDs (plus conventional DMARD) used in NHS Scotland in terms of the odds ratio of having a good or at least a moderate EULAR response, in both the inadequate response to conventional DMARD and inadequate response to biologic DMARD populations. Comparable efficacy for tofacitinib (plus conventional DMARD) to biologic DMARDs (with and without conventional DMARD) was also demonstrated for change in HAQ-DI from baseline, in both populations. Rankograms and SUCRA statistics were provided for these outcomes.

Post-hoc analyses of the ORAL Strategy study were provided for EULAR response and change in HAQ-DI from baseline for tofacitinib plus methotrexate versus adalimumab plus methotrexate in patients who had not responded adequately to conventional DMARDs. These suggested similar results in both groups.

There were some weaknesses associated with the NMAs including heterogeneity across included studies with respect to baseline characteristics, baseline disease severity, variation in primary outcome, treatments given to control groups and background DMARD. Some studies in the NMA for inadequate response to conventional DMARDs included patients who had previously received biologic DMARDs. The NMAs did not include any outcomes for radiographic disease progression or safety, and EULAR outcomes for tofacitinib were derived from patient level data in a number of studies.

Tofacitinib would provide another treatment option for patients with severe RA and is the second JAK inhibitor to be licensed in the UK. Clinical experts consulted by SMC considered that tofacitinib is a therapeutic advancement as JAK inhibitors are a new class of medication. They considered that the place in therapy would be in patients who do not have an adequate response to, or who are intolerant of, conventional and biologic DMARDs. It is available as an oral preparation which may have advantages for the patient and the service as it could replace biologic DMARDs which are currently available as injectable preparations. Blood tests are required initially, after four to eight weeks of treatment and three monthly thereafter which may impact on the patient and the service.

Summary of comparative health economic evidence

The submitting company presented a range of economic analyses of tofacitinib for patients with severe RA in combination with methotrexate and as monotherapy for six subgroups of patients that were identified according to whether patients have had an inadequate response to conventional DMARDs or to biologic DMARDs , and whether patients were tolerating rituximab and/or methotrexate. All comparisons were underpinned by cost-utility analyses (CUA) and cost-minimisation analyses (CMA). Given the results of the NMAs presented by the submitting company, the CMA appears the most relevant base case approach to assess the cost-effectiveness of tofacitinib and therefore only results of the CMA are presented below.

Table 3: Patient subgroups, comparators and treatment sequences considered in the submission

Subgroup		Direct comparator	Subsequent treatment sequence
Inadequate response to conventional DMARDs subgroup (CMA and CUA)			
1	Methotrexate tolerant	Abatacept + methotrexate Adalimumab + methotrexate Certolizumab pegol + methotrexate Golimumab + methotrexate Tocilizumab + methotrexate Biosimilar etanercept + methotrexate Biosimilar infliximab + methotrexate	Post-biologic therapy (PBT)
2	Methotrexate intolerant	Tocilizumab Biosimilar etanercept Adalimumab	PBT
Inadequate response to biologic DMARDs subgroup (CUA)			

3	Rituximab tolerant (after rituximab)	Tocilizumab + methotrexate Tocilizumab + methotrexate	Methotrexate, PBT Tofacitinib + methotrexate, methotrexate alone, PBT
4	Rituximab intolerant	Abatacept + methotrexate Tocilizumab + methotrexate Golimumab + methotrexate Biosimilar etanercept + methotrexate	Tocilizumab/golimumab + methotrexate, methotrexate, PBT
5a	Rituximab tolerant (alongside rituximab)	Rituximab + methotrexate *Abatacept* + methotrexate *Golimumab* + methotrexate *Biosimilar etanercept* + methotrexate	Tocilizumab + methotrexate, methotrexate, PBT
6	Methotrexate intolerant	Biosimilar etanercept *Tocilizumab*	Sulfasalazine, PBT
Inadequate response to biologic DMARDs subgroup (CMA)			
5b	Rituximab tolerant (alongside rituximab)	Abatacept + methotrexate Adalimumab + methotrexate Certolizumab pegol + methotrexate Golimumab + methotrexate Tocilizumab + methotrexate Biosimilar etanercept + methotrexate Biosimilar infliximab + methotrexate Rituximab + methotrexate	PBT

A patient-level discrete event simulation model was presented which was broadly based on the model used in the recent NICE MTA (TA375). This model used treatment sequences to reflect the pathways patients may follow in clinical practice. Patients entering the model started their treatment and were assigned an initial EULAR response depending on their baseline clinical characteristics. The stopping rule required that patients had at least moderate response to continue treatment. Patients who did not respond to treatment switched to the subsequent regimen in the sequence. The subsequent therapies were identical between tofacitinib and comparator sequences if possible. This process of switching to subsequent treatments in the sequence was repeated until a patient moved to receive palliative care. Patients were also assigned a probability of treatment discontinuation that was calculated depending on their characteristics. A rate of disease progression as measured by changing HAQ-DI scores was incorporated into the model and utility values were also calculated using information on HAQ-DI. The CMA were derived from the CUA by equalising the effect of comparators and tofacitinib, i.e. applying the odds ratios for EULAR responses to one for all comparators, and by excluding sequencing of medicines.

The analysis included drug acquisition and administration costs, costs associated with monitoring, background medical resource use depending on HAQ-DI band and adverse events.

A patient access scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland.

PAS discounts are also in place for abatacept, certolizumab pegol, golimumab, tocilizumab, and rituximab and these were included in the results used for decision-making by SMC by using estimates of the comparator PAS prices.

In the patient subgroups who have not responded adequately to conventional DMARDs, tofacitinib in combination with methotrexate or as monotherapy was a cost-saving treatment option when

compared to some but not all biologic DMARDs. The results, at list prices, not are presented in tables 4 and 5 below.

Table 4: CMA results for patients who have an inadequate response to conventional DMARDs and receiving combination therapy, at list prices

Strategy	**ABT+ MTX**	**ADA+ MTX**	**CZP+ MTX**	**ETNb+ MTX**	**GOL+ MTX**	**INFb+ MTX**	**TOC+ MTX**	**TOF+ MTX**
Total cost	**£85,352**	**£71,109**	**£72,093**	**£68,448**	**£70,920**	**£65,837**	**£71,933**	**£70,270**
Treatment costs	£62,860	£48,604	£49,589	£45,961	£48,421	£43,331	£49,429	£47,768
Monitoring costs	£13,946	£13,946	£13,946	£13,947	£13,946	£13,947	£13,946	£13,946
Medical resource use	£7,693	£7,707	£7,708	£7,689	£7,701	£7,707	£7,705	£7,703
Adverse event costs	£852	£852	£851	£852	£852	£852	£853	£852

Abbreviations: ABT – abatacept, ADA – adalimumab, CZP – certolizumab pegol, ETNb – biosimilar etanercept, GOL – golimumab, IFNb – biosimilar infliximab, MTX – methotrexate, TOC – tocilizumab, TOF – tofacitinib

Table 5: CMA results for patients who have an inadequate response to conventional DMARDs and receiving monotherapy, at list prices

Strategy	**TOC**	**TOF**	**ETNb**	**ADA**
Total cost	**£72,062**	**£69,926**	**£68,484**	**£71,186**
Treatment costs	£49,572	£47,450	£46,005	£48,697
Monitoring costs	£13,922	£13,923	£13,923	£13,923
Medical resource use	£7,716	£7,700	£7,705	£7,715
Adverse event costs	£852	£852	£852	£851

Abbreviations: TOC – tocilizumab, TOF – tofacitinib, ETNb – biosimilar etanercept, ADA – adalimumab

In the subgroup of patients who have not had sufficient response to biologic DMARDs, tofacitinib in combination with methotrexate was a cost-saving treatment option compared to some but not all biologic DMARDs. The exact figures, not reflecting PAS discounts, are presented in table 6.

Table 6: CMA results for patients who have an inadequate response to biologic DMARDs, tolerant to rituximab and receiving combination therapy, at list prices

Strategy	**ABT+ MTX**	**ADA+ MTX**	**CZP+ MTX**	**ETNb+ MTX**	**GOL+ MTX**	**INFb+ MTX**	**TOC+ MTX**	**TOF+ MTX**	**RTX+ MTX**
Total cost	**£77,138**	**£62,583**	**£60,193**	**£59,858**	**£61,765**	**£60,905**	**£67,092**	**£61,541**	**£48,496**
Treatment costs	£55,258	£40,717	£38,337	£37,974	£39,900	£39,025	£45,219	£39,708	£26,648
Monitoring costs	£12,968	£12,969	£12,969	£12,968	£12,969	£12,969	£12,969	£12,969	£12,969
Medical resource use	£8,396	£8,381	£8,373	£8,400	£8,381	£8,395	£8,388	£8,350	£8,364
Adverse event costs	£515	£515	£516	£515	£515	£515	£515	£515	£515

Abbreviations: ABT – abatacept, ADA – adalimumab, CZP – certolizumab pegol, ETNb – biosimilar etanercept, GOL – golimumab, IFNb – biosimilar infliximab, MTX – methotrexate, TOC – tocilizumab, TOF – tofacitinib, RTX - rituximab

The results presented in the tables above do not take account of the PAS discounts for abatacept, certolizumab pegol, golimumab, tocilizumab and rituximab or the PAS for tofacitinib. SMC is unable to present the results provided by the company which used estimates of the PAS prices due to commercial confidentiality and competition law issues.

The main limitations include:

- On the basis that the overall findings from the NMAs are that of no substantial differences in effectiveness in the inadequate response to conventional DMARDs and inadequate response to biologic DMARDs subgroups between tofacitinib and comparators, the focus on the CMAs seems reasonable rather than using the CUAs, as these may have used non-significant findings to drive any QALY gains.

It was however noted that the NMAs had limitations that are described in more detail above.

Despite these issues, the economic case was considered demonstrated.

*Other data were also assessed but remain commercially 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 Rheumatoid Arthritis Society, which is a registered charity.

- The National Rheumatoid Arthritis Society has received 15% pharmaceutical company funding in the past two years, including from the submitting company.

- Being diagnosed with an incurable, painful disease like RA can be extremely distressing, as it is life-changing. RA impacts on every area of life and has effects on emotional and physical well-being. It can be very distressing for the partner of someone with RA to witness their loved-one in severe pain and suffering the debilitating effects of fatigue, so this disease does very much impact on the whole family. As three quarters of people are diagnosed when of working age, anxiety over job-loss due to their disease is a significant factor.

- The combination of conventional DMARD and biologic/biosimilar DMARDs currently available provide a range of options for people living with RA. However, there remains unmet need due to the heterogeneity of RA. Carers often have to help patients with their biologic therapy and with an oral medicine like tofacitinib, the patient becomes more independent in taking their medication.

- Tofacitinib is one of a new class of therapy. It will add to the therapeutic options available to clinicians and patients. As an oral medication it may be preferred by some patients over having to have a regular infusion or inject themselves.

Additional information: guidelines and protocols

Many of the guidelines predate the availability of JAK inhibitors such as tofacitinib and recommendations are limited to conventional DMARDs and biologic DMARDs.

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline 123 Management of early rheumatoid arthritis in February 2011. All patients with moderate to severe disease activity should receive treatment with DMARDs, adjusted with the aim of achieving remission or a low disease activity score (DAS)/28-joint disease activity score (DAS28). Use of TNFα inhibitors for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended. However biologic DMARDs may be used, in combination with conventional DMARDs, if patients do not respond adequately to conventional DMARD therapy.[8]

The National Institute for Health and Care Excellence (NICE) updated its guideline CG79 in December 2015, which refers to multiple technology appraisal (MTA) advice for the use of biologics (TA375 and TA195). Similar to the SIGN guideline, these are recommended for use in combination with methotrexate for severe disease which has not responded adequately to conventional DMARD therapy. [9, 10, 16]

The European League Against Rheumatism (EULAR) guidelines published in 2013 are broadly similar to the SIGN and NICE guidance, but state that in patients for whom conventional DMARDs have failed to produce an adequate response biologic DMARDs should be used upon failure of conventional DMARDs, irrespective of disease severity.[17]

The Royal College of Physicians published a national clinical guideline for the management and treatment rheumatoid arthritis in adults in 2009.[6] It states that, in patients with established active disease despite conventional DMARDs, the addition of a biologic drug generally adds significant benefits for symptom control, function and quality of life, and that the combination of biologic drug plus methotrexate compared with methotrexate alone favours the combination. This approach is also reflected in the British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) guidelines for the management of rheumatoid arthritis in the first two years, and after the first two years, published in 2006 and 2009, respectively.[18, 19]

NICE published MTA guidance on biologics in rheumatoid arthritis in January 2016 (TA375)[9] and August 2010 (TA195).[10]

Additional information: comparators

Tofacitinib is likely to be used in place of other biologic medicines for RA and baricitinib.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
tofacitinib	5mg orally twice daily	8,970
abatacept	125mg SC once a week	15,725
tocilizumab	162mg SC once a week	11,870
baricitinib	2mg to 4mg orally once daily	10,472
tocilizumab	8mg/kg IV every four weeks	9,984
certolizumab pegol	400mg SC at weeks 0, 2, 4 then 200mg SC every two weeks	9,295 (10,368 in year 1)
etanercept biosimilar	50mg SC once a week or 25mg twice a week	9,295
adalimumab	40mg SC every two weeks	9,156
golimumab	50mg SC once a month	9,156
infliximab biosimilar	Initially 3mg/kg by IV infusion at weeks 0, 2, 6, then every eight weeks	6,786 (10,197 in year 1)

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 03 November 2017 except for infliximab (MIMS). Dose assumes weight of 70kg, where applicable. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration. IV = intravenous; SC = subcutaneous.

Additional information: budget impact

The submitting company estimated there would be 403 patients eligible for treatment with tofacitinib in all years to which confidential estimates of treatment uptake were applied.

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.

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

References

1. Electronic Medicines Compendium. XELJANZ 5 mg film-coated tablets. 2017 [cited 2017 Aug 3]; Available from: http://www.medicines.org.uk/emc/medicine/33167.
2. Fleischmann R, Mysler E, Hall S, Kivitz AJ, Moots RJ, Luo Z*, et al.* Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet (London, England). 2017.
3. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Garcia Meijide JA, Wagner S*, et al.* Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. The New England journal of medicine. 2012;367(6):508-19.
4. European Medicines Agency. Xeljanz : EPAR - Public assessment report. 2017 [cited 2017 Aug 3]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004214/WC500224913.pdf.
5. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B*, et al.* Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: A randomised phase 3 trial. The Lancet. 2013;381(9865):451-60.
6. Wollenhaupt J, Silverfield J, Bong Lee E, Terry K, Kwok K, Abramsky S*, et al.* Tofacitinib, an oral Janus kinase inhibitor, in the treatment of rheumatoid arthritis: Safety and efficacy in open-label, long-term extension studies over 8 years. Arthritis and Rheumatology. 2016;68:2056-8.
7. *Commercial in Confidence**
8. Scottish Intercollegiate Guidelines Network. Management of early rheumatoid arthritis (123). 2011.
9. National Institute of Health and Care Excellence. Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. 2016 [cited 2017 Aug 7]; Available from: https://www.nice.org.uk/guidance/ta375.
10. National Institute of Health and Care Excellence. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. 2010 [cited 2017 Aug 7]; Available from: https://www.nice.org.uk/guidance/ta195.
11. Scottish Medicines Consortium. tocilizumab (RoActemra®). 2014 [cited 2017 Aug 7]; Available from: http://www.scottishmedicines.org.uk/SMC_Advice/Advice/1020_14_tocilizumab_RoActemra/tocilizumab_RoActemra.
12. Scottish Medicines Consortium. baricitinib (Olumiant®). 2017.
13. S. Schwartzman PS, L. Takiya, M. Snyder, H. Fan, T. Lukic, J. Roberts, W. F. C. Rigby. Comparison of tofacitinib efficacy in patients with moderate versus severe rheumatoid arthritis: Pooled analysis of phase III studies. 2017.
14. van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C*, et al.* Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: Twelve-month data from a twenty-fourmonth phase III randomized radiographic study. Arthritis and Rheumatism. 2013;65(3):559-70.
15. European Medicines Agency. Guidance on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis (draft guideline 2015).
16. National Institute for Health and Care Excellence. Rheumatoid Arthritis in Adults Management. 2009.
17. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M*, et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Annals of the rheumatic diseases. 2014;73(3):492-509.

18. Luqmani R. British Society for Rheumatology and British Health Professionals in Rheumatology Guideline for the Management of Rheumatoid Arthritis (The first 2 years). Rheumatology. 2006.
19. Luqmani R, Hennell S, Estrach C, Basher D, Birrell F, Bosworth A*, et al.* British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of rheumatoid arthritis (after the first 2 years). Rheumatology (Oxford). 2009;48(4):436-9. Epub 2009/01/29.

This assessment is based on data submitted by the applicant company up to and including 15 December 2017.

**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:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

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 drug 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 NHS Scotland 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 NHS Scotland 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.