Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2365

filgotinib 100mg and 200mg film-coated tablets (Jyseleca®)

Gilead Sciences, Inc

6 August 2021

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 NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

filgotinib (Jyseleca®) is accepted for restricted use within NHSScotland.

Indication under review: filgotinib is indicated 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). Filgotinib may be used as monotherapy or in combination with methotrexate (MTX).

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 and in patients with severe disease inadequately controlled by a TNF antagonist in whom rituximab is not appropriate.

In two phase III studies, filgotinib compared with placebo (both in combination with methotrexate), significantly improved signs and symptoms of rheumatoid arthritis in patients with an inadequate response to conventional or biologic DMARDs. Filgotinib was non-inferior to a biologic DMARD in patients who had an inadequate response to methotrexate.

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

Filgotinib is indicated 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). Filgotinib may be used as monotherapy or in combination with methotrexate (MTX).[1, 2]

Dosing Information

The recommended dose of filgotinib is 200mg taken orally once daily with or without food. A starting dose of 100 mg once daily is recommended for patients aged 75 years and older as clinical experience is limited, and for patients with moderate or severe renal impairment.

Treatment with filgotinib should be initiated by a physician experienced in the treatment of rheumatoid arthritis.

Refer to Summary of product characteristics (SPC) for further detail.[1, 2]

Product availability date

September 2020

Summary of evidence on comparative efficacy

Filgotinib is an adenosine triphosphate (ATP)-competitive and reversible inhibitor of the janus kinase enzyme (JAK) family. JAKs are intracellular enzymes that transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane and are important in mediating inflammatory cytokine signals, myelopoiesis, erythropoiesis, immune homeostasis and lymphopoiesis.[1, 2]

The submitting company has requested that SMC considers the submission in line with the licensed indication following the failure of intensive therapy with a combination of conventional DMARDs.

The key evidence supporting the efficacy and safety of filgotinib for the indication under review comes from two randomised, double-blind phase III studies, FINCH 1 and 2. Both studies recruited adults with a diagnosis of rheumatoid arthritis (RA) who had active moderate-to-severe disease (≥6 swollen joints and ≥6 tender joints) despite continuous treatment with oral methotrexate in FINCH 1 or with one or two conventional DMARDs (cDMARDs) and an inadequate response or intolerance to one or more prior biologic DMARDs (bDMARDs) in FINCH 2. Eligible patients also had serum C-Reactive Protein (CRP) ≥6 mg/L or in FINCH 1 ≥3 documented joint erosions on radiographs of the hands, wrists or feet by central reading, or ≥1 documented joint erosion on these radiographs if the rheumatoid factor (RF) or anti- cyclic citrullinated peptide (CCP) antibodies (Ab) were positive. [3-5]

In FINCH 1, patients were randomised in a 3:3:2:3 ratio to receive for up to 52 weeks filgotinib 200mg orally once daily (n=450), filgotinib 100mg orally once daily (n=450), adalimumab 40mg subcutaneous injection every 2 weeks (n=300), or placebo (n=450), all with stable weekly background methotrexate. Randomisation was stratified according to geographic region (group A to E as defined in protocol), prior exposure to bDMARD (Yes or No), and presence of RF or anti-CCP Ab at screening (Yes or No). At week 24, all patients assigned to placebo were re-randomised 1:1 to either filgotinib 100mg or 200mg in a blinded fashion and continued in the study through week 52.[3, 4]

In FINCH 2, patients were randomised equally to receive for up to 24 weeks orally once daily filgotinib 200mg (n=141), filgotinib 100mg (n=141), or placebo (n=141), with a stable dose of permitted cDMARD(s). Randomisation was stratified according to geographic region (group A to E as defined in protocol), prior exposure to number of bDMARDs (<3 or ≥3 bDMARDs) and seropositivity (presence of RF or anti-CCP Ab at screening). In both studies, there was a rescue possibility to standard of care at week 14 (in case improvement from baseline in swollen joint count and tender joint count was <20%).[4, 5]

In FINCH 1 and 2, the primary outcome was the proportion of patients who achieved an American College of Rheumatology 20% improvement response (ACR20) at week 12. Efficacy analyses were performed in the full analysis set (FAS), which includes all randomised patients who received at least one dose of study medicine.[3, 5]

This outcome, as well as the hierarchically tested secondary outcomes, achieved statistical significance in favour of both filgotinib 200mg and 100mg versus placebo. In FINCH 1, the only hierarchically tested outcome comparing filgotinib with adalimumab was Disease Activity Score 28 joints with C-Reactive Protein (DAS28-CRP) ≤3.2 at week 12. Non-inferiority of filgotinib to adalimumab was demonstrated for the 200mg dose but not for 100mg dose. Results for primary and selected secondary outcomes are detailed in Table 1.[3-5]

Table 1: Primary and selected secondary outcomes of FINCH 1 and 2 studies (Full Analysis Set).[3-5]

	FINCH 1 (Methotrexate inadequate response)				**FINCH 2 (bDMARD inadequate response or intolerance)**		
Week	**Filgotinib 200mg (n=475)**	**Filgotinib 100mg (n=480)**	**Adalimumab (n=325)**	**Placebo (n=475)**	**Filgotinib 200mg (n=147)**	**Filgotinib 100mg (n=153)**	**Placebo (n=148)**
Proportion of patients who achieved ACR20, %							
12	77[a]	70[a]	70	50	66[a]	58[a]	31
Change from baseline in HAQ-DI, mean							
12	−0.69[a]	−0.56[a]	-0.61	−0.42	-0.55[a]	-0.48[a]	-0.23
Proportion of patients who achieved DAS28-CRP <2.6, %							
24	48[a]	35[a]	36	16	-	-	-
Proportion of patients who achieved DAS28-CRP ≤3.2, %							
12	50[a,b]	39[a]	43	23	41[a]	37[a]	16

Change from baseline in mTSS, mean							
24	0.13[a]	0.17[a]	0.16	0.37	-	-	-

Abbreviations: ACR20 = American College of Rheumatology ≥20% improvement; CRP = C-Reactive Protein, DAS28 = Disease Activity Score 28 joints, HAQ-DI = Health Assessment Questionnaire-Disability Index; mTSS = van der Heijde modified total Sharp score.

[a] p< 0.001 filgotinib versus placebo

[b] p< 0.001 filgotinib versus adalimumab (non-inferiority)

In FINCH 1, 52-week data were also available for filgotinib (200mg and 100mg) and adalimumab. The EMA concluded based on the data that the absolute number of ACR20 responders in all groups increased from week 12 to week 24 and did not decrease from week 24 to week 52. [3]

The submitting company presented a post hoc subgroup efficacy analysis for the moderate RA population in FINCH 1 (as defined by DAS28-CRP score 3.2 to 5.1 inclusive at baseline), to allow separate analysis of patients with moderate disease activity (with inadequate response to cDMARDs and naïve to bDMARD and JAK inhibitors) in the economic model. In these patients, results for the proportion of patients who achieved ACR20 at week 12,DAS28-CRP <2.6 at week 24 and DAS28-CRP ≤3.2 at week 12 with filgotinib 200mg, filgotinib 100mg, adalimumab and placebo, were consistent with the results in the FAS, favouring filgotinib over placebo. A post hoc subgroup analysis for the severe RA population in FINCH 1 (as defined by DAS28-CRP score >5.1 at baseline) was also presented; results were consistent with the FAS results favouring filgotinib over placebo.

Health Related Quality of Life (HRQoL) was assessed using the 36-Item Short Form Survey (SF-36), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and the EuroQol five dimension Questionnaire (EQ-5D), in addition to the Health Assessment Questionnaire-Disability Index (HAQ-DI, results reported in Table 1 above). Work Productivity and Activity Impairment-RA (WPAI-RA) was also assessed. [3, 5] Numerically better responses with the reported outcomes of SF-36 and FACIT-F were seen with filgotinib 200mg and 100mg compared with placebo at week 12.[4]

Two Bayesian network meta-analyses (NMAs) were conducted in patients with moderate to severe RA to compare filgotinib (200mg and 100mg) against a number of comparators including adalimumab, etanercept, abatacept, tocilizumab, subcutaneous tocilizumab, tofacitinib, baricitinib, rituximab, certolizumab pegol, upadacitinib, sarilumab, all in combination with cDMARDs. One analysis was conducted in patients who had an intolerance or inadequate response to cDMARDs including methotrexate (cDMARDs-IR) and included 50 studies. The other analysis was conducted in patients who had an intolerance or inadequate response to bDMARDs (bDMARDs-IR) and included 10 studies. In both analyses, the majority of treatments were compared indirectly via a common comparator (cDMARD) and the reported outcomes were ACR response at 12 and 24 weeks and European League Against Rheumatism (EULAR) response at 24 weeks. The submitting company concluded that filgotinib could be considered broadly similar to other treatments across both populations.

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

Summary of evidence on comparative safety

In the pooled analysis of phase II and III RA studies, the frequency of adverse events (AEs) during the first 3 months was 47% (658/1403) in patients treated with filgotinib 200mg, 44% (442/995) in patients treated with filgotinib 100mg, 40% (130/325) in patients treated with adalimumab and 44% (522/1197) in patients treated in the control groups (methotrexate, other cDMARD or placebo) and these were considered treatment-related in 20%, 18%, 14% and 17% respectively.[4]

In FINCH 1, safety data were available for filgotinib 200mg and 100mg versus adalimumab, all in combination with methotrexate, through to week 52. In the filgotinib 200mg (n=475), filgotinib 100mg (n=480) and adalimumab (n=325) groups respectively, 74%, 73% versus 74% reported any AE; 7.4%, 8.3% versus 6.8% reported a serious AE; 5.5%, 3.1% versus 5.5% reported an AE leading to therapy discontinuation; 43%, 40% versus 40% reported infection; 2.7%, 2.7% versus 3.1% reported serious infection; 0%, 0.4% versus 0.3% reported major adverse cardiac event; 0.2%, 0% versus 0% reported gastrointestinal perforation; 0.6%, 0.6% versus 0.6% reported malignancy; and 0.2%, 0% versus 0.3% reported venous thromboembolism. By week 52, the most frequently reported AEs (>7% of patients in any group) were nasopharyngitis (9.1%, 10% versus 7.4%) and upper respiratory tract infection (8.6%, 10% versus 6.5%).[3]

The major safety concern given the immunosuppressive effect of filgotinib is the risk for infections, and there is concern of an increased risk for venous thromboembolism for all JAK inhibitors. With filgotinib, there is also concern on the potential clinical consequences (currently being investigated in human males studies, MANTA and MANTA-Ray) of preclinical findings on the substantial decrease of fertility, impaired spermatogenesis and histopathological effects on male reproductive organs. Warnings were included in the SPC aimed at limiting the use of filgotinib to female patients and male patients without intent of fathering a child. Important uncertainties relate to unfavourable effects of long latency and low frequency (such as malignancies, major adverse cardiovascular events). Longer-term safety data are awaited.[4]

Overall, the EMA considered that the safety profile of filgotinib was acceptable in view of the information included in the SPC and risk management plan.[4]

Summary of clinical effectiveness issues

Rheumatoid arthritis (RA) is a chronic progressive autoimmune disease affecting approximately 1% of the population and is characterised by joint inflammation in the synovial tissue. Women are affected more frequently than men. It is not curable and a significant number of patients experience pain, swelling, stiffness, destruction of joints, decline in function and premature mortality. It may also be associated with extra-articular involvements in the skin, eyes, salivary glands and lung.[4]

All patients with moderate to severe disease activity should receive DMARDs, adjusted to achieve remission or a low disease activity score. Treatment is typically initiated with a cDMARD, most

commonly methotrexate.[6,7] For patients with severe disease not adequately controlled by a combination of cDMARDs, Healthcare Improvement Scotland (HIS) has endorsed National Institute of Health and Care Excellence (NICE) technology assessment TA375 that recommends the following bDMARDs (in combination with methotrexate) as treatment options: adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept. Adalimumab, etanercept, certolizumab pegol and tocilizumab can also be used as monotherapy for people who cannot take methotrexate. For patients with severe disease not adequately controlled by cDMARDs and a tumour necrosis factor (TNF)-antagonist (including adalimumab, etanercept and infliximab), HIS has endorsed NICE TA195, which recommends rituximab and, for rituximab-ineligible patients, the following bDMARDs (in combination with methotrexate) as treatment options: adalimumab, etanercept, infliximab and abatacept. Subcutaneous tocilizumab (SMC 982/14), in combination with methotrexate or as monotherapy, was then recommended by SMC in adult patients who have either responded inadequately to, or who were intolerant to previous therapy with one or more DMARDs or TNF inhibitors, and is restricted to use in accordance with current eligibility and continuation rules for biologic therapies in RA. More recently JAK inhibitors (baricitinib [SMC 1265/17], tofacitinib [SMC 1298/18] and upadacitinib [SMC2315]) and humanised anti-interleukin-6 (IL-6) receptor antibody, sarilumab (1314/18), have been made available to patients in Scotland; they can be used in patients with severe disease that has not responded to intensive therapy with a combination of cDMARDs and additionally in patients with severe disease inadequately controlled by a TNF antagonist who are ineligible to receive rituximab.

In FINCH 1 and 2, the primary outcomes as well as all key secondary outcomes achieved statistical significance in favour of filgotinib over placebo (both in combination with one or two cDMARDs including methotrexate). The primary outcome (ACR20) is not consistent with the 2018 EMA guideline on clinical investigation of medicinal products for RA (which came into effect after the studies started)[8]; however, the preferred outcomes of low disease activity (DAS28-CRP ≤3.2) and remission (DAS28-CRP <2.6), which reflect a target disease state, were included as key secondary outcomes. In FINCH 1, filgotinib 200mg was found to be non-inferior to adalimumab based on low disease activity. Overall, the EMA concluded that filgotinib has a clinically relevant effect in inducing clinical response as measured by ACR20 and in inducing remission or low disease activity in patients with active RA both as second and third line treatment, relevant to the licensed indication. The EMA also concluded that available data support maintenance of effect of filgotinib for up to one year.[4]

Limited data are available for the use of filgotinib as monotherapy in this indication, after inadequate response or intolerance to at least one DMARD. The EMA noted that, together with extrapolation from FINCH 3 (a phase III study in patient naïve to methotrexate), which provided first line monotherapy data, supportive monotherapy data came from the phase II studies, DARWIN 2 and 3, which showed benefits with filgotinib 200mg versus placebo and maintenance of effect of filgotinib monotherapy second line.[4]

The submitting company presented a post hoc exploratory analysis in moderate RA patients from FINCH 1 to inform the economic model in this population. However, FINCH 1 was not powered for this analysis and the results are uncertain.

There is a lack of long-term efficacy and safety data for treatment with filgotinib, including in patients in >75 year olds. In addition, clinical data (from studies MANTA and MANTA-Ray) are awaited to address the potentially irreversible risk on male fertility, which was raised based on pre-clinical findings and considered of concern by the EMA. Warnings were included in the SPC with the aim of limiting the use of filgotinib to female patients and male patients without intent of fathering a child.[4]

FINCH 1 provided data comparing filgotinib with adalimumab in patients on a stable background of methotrexate and who have had an inadequate response to methotrexate. However, there are no direct comparative data with all the other available RA treatments. Thus, the submitting company performed NMAs comparing filgotinib (100mg and 200mg) with active comparators. There were a number of limitations that affected the validity of the NMA's results. The population in the NMA included a mixed population of patients with moderate and severe RA. Several studies were at an unclear risk of bias. Clinical heterogeneity exists across the included studies, with variability in the treatment posology, baseline characteristics and a number of studies were conducted on Asian populations, all of which may introduce uncertainty. An NMA for filgotinib monotherapy was not feasible and only combination therapies were included. The EMA preferred outcomes of low disease activity and remission were not compared in these NMAs, nor were HRQoL and safety outcomes. Despite these limitations, the submitting company's conclusion of comparable efficacy seem reasonable.

Clinical experts consulted by SMC considered that the place in therapy for filgotinib would be as an alternative JAK inhibitor.

Summary of comparative health economic evidence

The submitting company provided two separate analyses: a cost-utility analysis (CUA) assessing filgotinib versus best supportive care (BSC) in patients with moderately active RA, and a cost-minimisation analysis (CMA) assessing filgotinib versus approved treatments (bDMARD and JAK inhibitors) in patients with severely active RA. Both analyses required that patients had experienced treatment failure with two different conventional DMARDs (cDMARD). BSC was defined as low dose cDMARDs (which may have been previously used) and corticosteroids. The bDMARD and JAK inhibitor therapies included in the analysis were as follows: adalimumab, rituximab, sarilumab, tocilizumab, abatacept, etanercept, baricitinib, and tofacitinib. Results were presented as a series of sub-groups according to disease severity (moderately or severely active), line of treatment (first line or after failure of first line), and tolerance to guideline-recommended treatments (eligible/ineligible for methotrexate or rituximab).

A *de novo* economic model was created in the form of a discrete event simulation model; this model type generates a cohort of patients with relevant baseline characteristics and tracks these patients over time capturing any key clinical events without the need for explicit health states. The model structure was based on patients' EULAR response and their disease activity (moderate or severe). A 6-month cycle length was used with a lifetime time horizon (maximum age: 100 years) and an NHSScotland and social work perspective was utilised.

For the moderate population, relative efficacy was estimated using head-to-head data from the FINCH 1 moderate sub-group (including patients with one or more cDMARDs failures). These data informed efficacy for both for filgotinib 200mg and placebo/methotrexate in the moderate population.[3] The company stated that these are the most appropriate data available because this study included all relevant comparators (with the placebo plus methotrexate arm of the study used as a proxy for BSC). At the end of the 6-month initial treatment phase a patient's HAQ-DI score is assumed to reduce dependent upon the initial treatment effect (i.e. whether achieving a moderate or good EULAR response). Patients with no response do not experience a reduction in HAQ-DI (i.e. their HAQ-DI trajectory is assumed to be constant). The reduction applied was derived using data from the British Society of Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA).[9] After the initial 6-month treatment phase the change in HAQ-DI score is dependent on the treatment received (bDMARD or cDMARD/BSC). HAQ-DI is assumed to change immediately at the end of each 6-month period. Treatment with a bDMARD results in a HAQ-DI trajectory based on those reported in the 36-month BSRBR dataset and is dependent on the initial response of the patient (moderate or good response) and their baseline characteristics. A patient's HAQ-DI is assumed to remain stable after the first 36 months of treatment. Treatment with a cDMARD results in a HAQ-DI trajectory estimated from the 15-year ERAS cohort data described by Norton et al. [10] These estimates combined with patient baseline characteristics defined the long-term HAQ-DI trajectory for individual patients. Each patient followed an average trajectory based on their probabilities of being in each class, for 15 years following treatment with a cDMARD, after which HAQ-DI is assumed to remain stable. The patients receiving BSC are assumed to experience the same HAQ-DI trajectory as patients receiving cDMARDs. Age- and sex-specific all-cause survival was derived from Scottish life-tables 2017-2019; Gompertz parametric curves were fitted to the raw data and adjusted within the model dependent on the starting age of the individual patient. Survival was adjusted by hazard ratios as a function of baseline HAQ-DI.

For the severe populations, the clinical evidence regarding the relative efficacy of filgotinib versus comparators was estimated from a series of Bayesian NMAs conducted by the company. This is used by the company to support the assumption of comparable efficacy and safety across treatments required to validate the use of a CMA in this population.

A patient's utility at each time-point is a function of their age, sex, HAQ-DI score and VAS pain score, which was subject to change over the model time horizon. HAQ-DI score trajectories were mapped to EQ-5D, based on the mapping algorithm in RA published by Hernandez-Alva et al.[11] This mapping algorithm estimates patients' VAS pain score using their current HAQ-DI score. The probability of belonging to each of the four latent classes (i.e. disability trajectory following treatment) was estimated based on each patient's simulated HAQ-DI score and VAS pain score,

using coefficients reported in Hernandez et al. Finally, utility was estimated based on patient's HAQ-DI score, pain, age and sex, using coefficients reported in Hernandez et al, and weighted by the probabilities of belonging to each class. Utility decrements associated with adverse events were also included and their incidence varied by class of medicine.

Medicine acquisition, administration and monitoring costs were estimated for all treatments. The cost of hospital care and background resource use by HAQ-DI score were included and taken from previously published HTAs. Adverse event costs for all treatments were also included in the economic analysis.

A Patient Access Scheme (PAS) was proposed by the submitting 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. PAS discounts are also in place for the following comparators: tocilizumab, sarilumab, abatacept, baricitinib, and tofacitinib. These were included in the results used for decision-making by the SMC by using estimates of the comparator PAS prices. SMC is unable to present these results due to commercial confidentiality and competition law issues.

The main economic results, including the PAS for filgotinib, for each of the moderate populations analysed are shown in Tables 2 below. A selection of key scenario analyses are presented in Table 3.

Table 2: Two cDMARD failure, methotrexate ineligible, moderate RA: FIL 200mg monotherapy versus BSC (with PAS)

Population	ICER (£/QALY)
1a: Moderate RA patients after two cDMARD failures (methotrexate ineligible)	12,572
1b: Moderate RA patients after two cDMARD failures (methotrexate eligible)	15,519

Abbreviations: BSC: best supportive care, QALY: quality adjusted life year, ICER: incremental cost-effectiveness ratio

The scenario analysis results presented in Table 3 appear to suggest that the model is relatively robust to changes in structural assumptions; however, there are concerns with the reliability of the clinical effectiveness data (i.e. treatment response and time to disease progression) that are not sufficiently captured in the scenarios below.

Table 3: Scenario analyses for moderate RA populations (with PAS)

Scenario	Description	ICER (£/QALY)	
		Population 1a	Population 1b
0	*Base case*	12,572	15,519
1	Alternate treatment sequence upon progression to severe disease (ETN as first-line treatment)	12,304	15,148
2	Alternate effectiveness in moderate disease: EULAR responses from the FINCH 1 trial for the subset of the moderate	12,720	15,718

	population after treatment with 2 cDMARDs		
3	Utility mapping from Malottki et al	8,264	10,167
4	Alternate HAQ-DI trajectory for cDMARD/BSC patients from Norton et al	4,239	7,460
5	Different model for progression from moderate to severe disease: linear mixed model with random intercept and slope	11,622	14,785

Abbreviations: BSC: best supportive care, cDMARDs: conventional disease-modifying anti-rheumatic drugs, ETN: etanercept; EULAR: European League Against Rheumatism, HAQ-DI: Health Assessment Questionnaire – Disability Index, PAS: Patient Access Scheme QALY: quality adjusted life year, ICER: incremental cost-effectiveness ratio

The main economic results using list prices for all treatments for each of the severe populations analysed are shown in Tables 4-9 below.

2a. Severe RA patients in first line advanced therapy treatment (methotrexate ineligible)

Table 4: cDMARD-IR, methotrexate ineligible, severe RA: FIL 200mg monotherapy (list prices)

First-line treatment	Cost breakdown (£)					Total costs (£)	Incremental costs/savings (£)
	Drug acquisition	Administration	Monitoring	Hospitalisation	Adverse events		
Filgotinib	104,383	559	27,263	11,450	98	143,753	-
Adalimumab	95,089	883	27,263	11,450	98	134,784	-8,970
Etanercept	95,624	1,207	27,263	11,450	98	135,643	-8,111
Baricitinib	104,383	559	27,263	11,450	98	143,753	0.00
Tocilizumab SC	110,196	1,207	27,263	11,450	98	150,214	6,461

Abbreviations: SC: subcutaneous
A negative figure denotes cost savings for filgotinib

2b. Severe RA patients in first line advanced therapy treatment (methotrexate eligible)

Table 5: cDMARD-IR, methotrexate eligible, rituximab eligible, severe RA: Filgotinib 200mg in combination with methotrexate (list prices)

First-line treatment	Cost breakdown (£)					Total costs (£)	Incremental costs/savings (£)
	Drug acquisition	Administration	Monitoring	Hospitalisation	Adverse events		
Filgotinib + Methotrexate	88,938	2,353	27,697	10,588	130	129,706	-
Adalimumab + Methotrexate	79,644	2,677	27,697	10,588	130	120,737	-8,970
Etanercept + Methotrexate	80,179	3,001	27,697	10,588	130	121,596	-8,111
Baricitinib + Methotrexate	88,938	2,353	27,697	10,588	130	129,706	0.00

A negative figure denotes cost savings for filgotinib

3a. Severe RA patients after failure of first line advanced therapy treatment (methotrexate ineligible, rituximab ineligible)

Table 6: bDMARD-IR, methotrexate ineligible, rituximab ineligible, severe RA: versus filgotinib 200mg monotherapy (list prices)

First-line treatment	Cost breakdown (£)					Total costs (£)	Incremental costs/savings (£)
	Drug acquisition	Administration	Monitoring	Hospitalisation	Adverse events		
Filgotinib	51,731	0.00	25,028	11,702	55	88,516	-
Tofacitinib	45,197	0.00	25,028	11,702	55	81,981	-6,535
Baricitinib	51,731	0.00	25,028	11,702	55	88,516	0.00
Abatacept	74,584	678	25,028	11,702	55	112,047	23,531

A negative figure denotes cost savings for filgotinib

3b. Severe RA patients after failure of first line advanced therapy treatment (methotrexate eligible, rituximab ineligible)

Table 7: bDMARD-IR, methotrexate eligible, rituximab ineligible, severe RA: Filgotinib 200mg in combination with methotrexate (list prices)

First-line treatment	Cost breakdown (£)					Total costs (£)	Incremental costs/savings (£)
	Drug acquisition	Administration	Monitoring	Hospitalisation	Adverse events		
Filgotinib + Methotrexate	51,793	0.00	25,028	11,702	55	88,578	-
Baricitinib + Methotrexate	51,793	0.00	25,028	11,702	55	88,578	0.00
Sarilumab + Methotrexate	57,828	339	25,028	11,702	55	94,951	6,374
Tocilizumab SC + Methotrexate	57,877	678	25,028	11,702	55	95,339	6,762
Abatacept + Methotrexate	74,646	678	25,028	11,702	55	112,109	23,531

A negative figure denotes cost savings for filgotinib

4. Severe RA patients after failure of first line advanced therapy (methotrexate eligible, rituximab eligible)

Table 8: bDMARD-IR, methotrexate eligible, rituximab eligible, severe RA: Filgotinib 200mg in combination with methotrexate (list prices)

First-line treatment	Cost breakdown (£)					Total costs (£)	Incremental costs/savings (£)
	Drug acquisition	Administration	Monitoring	Hospitalisation	Adverse events		
Filgotinib + Methotrexate	80,742	404	25,522	10,158	97	116,924	-
Rituximab + Methotrexate	62,531	3,482	25,522	10,158	97	101,789	-15,134

A negative figure denotes cost savings for filgotinib

5. Severe RA patients after failure of rituximab in combination with methotrexate

Table 9: bDMARD-IR, methotrexate eligible, rituximab IR, severe RA: Filgotinib 200mg in combination with methotrexate (list prices)

First-line treatment	Cost breakdown (£)					Total costs (£)	Incremental costs/savings (£)
	Drug acquisition	Administration	Monitoring	Hospitalisation	Adverse events		
Filgotinib + Methotrexate	51,793	0.00	25,027	11,702	55	88,578	-
Sarilumab + Methotrexate	57,828	339	25,027	11,702	55	94,951	6,374
Tocilizumab SC + Methotrexate	57,877	678	25,027	11,702	55	95,339	6,762

A negative figure denotes cost savings for filgotinib

The analysis was subject to the following limitations:

- The relative effectiveness data for the moderate population were based on a post hoc analysis of the FINCH 1 study. This study was not powered for this purpose, which increases the uncertainty in the economic results for this population.
- The rate of progression from moderate to severe disease activity was based on patient level data from the FINCH 1 study over 52 weeks. This timeframe is unlikely to be sufficient to achieve an accurate estimate of disease progression and therefore increases the uncertainty associated with the CUA results.
- The key clinical studies used to inform the effectiveness of filgotinib (FINCH 1 and 2) did not include all relevant comparators. The company was therefore required to conduct a series of NMAs to estimate the effectiveness of filgotinib versus potential comparators for the severe population. These NMAs included data from patients with moderate and severe disease, which creates concerns about the use of these results to underpin an assumption of comparable efficacy and safety in the severe population. However the company explained that it is not possible to identify patients' disease severity from the available data.

Despite the limitations outlined above, the economic case for the use of filgotinib in patients with severe disease was demonstrated.

Due to limitations with the clinical evidence underpinning the analysis for patients with moderate disease, the economic case for this group was not demonstrated.

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 (NRAS), which is a registered charity.

- NRAS has received 9% pharmaceutical company funding in the past two years, with none from the submitting company.

- RA is an incurable, painful disease. Physical and emotional well-being, relationships, and sexuality are all impacted by the condition. As three out of four people are of working age when diagnosed, many worry about losing their job because of their condition. Witnessing loved-ones suffer from severe pain and fatigue can be very distressing.

- Treatment responses can vary, even for the same person over time. Many have to take a combination of medicines to control the symptoms of their disease. Even with the addition of these treatments, however, some find that their symptoms are not controlled.

- Filgotinib would provide an additional therapeutic option. It can be used in different places in the current pathway and, as an oral medicine, would likely be preferred over treatments that are injected or require an infusion. Filgotinib may enable more people with moderate RA, in particular, to reach remission. The opportunity for reduced pain and fatigue, together with potential remission, could also reduce the care burden for family members and carers.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline 123 Management of early RA 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). For DAD28, scores of >5.1, >3.2 to ≤5.1 or ≤3.2 indicate the presence of high, moderate or low disease activity, respectively. A score of <2.6 indicates remission. Use of TNF antagonists (including adalimumab, certolizumab, etanercept, infliximab) for the treatment of severe, active and progressive RA in adults not previously treated

with methotrexate or other DMARDs is not recommended. [12] This guideline predates the availability of the various therapies including the JAK inhibitors, baricitinib, tofacitinib and upadacitinib.

The National Institute for Health and Care Excellence (NICE) updated its guideline NG100 in July 2018, which refers to MTA advice for the use of biologics (TA375 and TA195). In patients that have had inadequate response to cDMARDs, the following treatments have been recommended (with restrictions): sarilumab, adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, abatacept, tofacitinib, and baricitinib. In patients with inadequate response or intolerance to biological DMARDs, and rituximab is suitable, NICE recommend rituximab plus methotrexate. When rituximab is not suitable, the following treatments are available: sarilumab, adalimumab, etanercept, infliximab, abatacept, golimumab, certolizumab pegol, tocilizumab, tofacitinib, and baricitinib.[13]

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update makes the following recommendations:

- Phase I, in patients who are naive to any DMARD therapy: methotrexate first-line (or alternative cDMARD [including leflunomide, sulfasalazine] if methotrexate contraindicated);
- Phase II, in patients who had an insufficient response (IR) to initial course(s) of cDMARDs: if poor prognostic factors present = methotrexate plus bDMARD (TNF inhibitor: adalimumab, certolizumab, etanercept, golimumab, infliximab; interleukin 6 receptor inhibitors: sarilumab, tocilizumab; costimulation modulator: abatacept; anti-B cell: rituximab) or JAK inhibitor. If poor prognostic factors absent = change to or add a second cDMARD;
- Phase III, in patients who had an IR to a first bDMARD or JAK inhibitor: change the bDMARD or JAK inhibitor.[7]

Additional information: comparators

Methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, upadacitinib, baricitinib, tofacitinib, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, sarilumab, tocilizumab, subcutaneous tocilizumab, abatacept and rituximab.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Filgotinib	**100 or 200mg orally once daily**	**10,472**

Costs from BNF online on 4 June 2021. Costs do not take patient access schemes into consideration.

Additional information: budget impact

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.

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

References

1. Gilead Sciences I. Filgotinb (Jyseleca® 200 mg) Summary of product characteristics. 2020 [cited; Available from: http://www.medicines.org.uk/emc/product/11810/smpc.
2. Gilead Sciences I. Filgotinb (Jyseleca® 100 mg) Summary of product characteristics. 2020 [cited; Available from: http://www.medicines.org.uk/emc/product/11809/smpc.
3. Combe B, Kivitz A, Tanaka Y, Van Der Heijde D, Simon JA, Baraf HSB*, et al.* Filgotinib versus placebo or adalimumab in patients with rheumatoid arthritis and inadequate response to methotrexate: a phase III randomised clinical trial. Annals of the Rheumatic Diseases. 2021;(no pagination).
4. European Medicines Agency (EMA). European Public Assessment Report. Filgotinib (Jyseleca®). 23/07/2020, EMEA H-C-005113. www.ema.europa.eu
5. Genovese MC, Kalunian K, Gottenberg JE, Mozaffarian N, Bartok B, Matzkies F*, et al.* Effect of Filgotinib vs Placebo on Clinical Response in Patients with Moderate to Severe Rheumatoid Arthritis Refractory to Disease-Modifying Antirheumatic Drug Therapy: The FINCH 2 Randomized Clinical Trial. JAMA - Journal of the American Medical Association. 2019;322(4):315-25.
6. SIGN. Management of early rheumatoid arthritis. 2011 [cited 13 Oct 2020]; Available from: https://www.sign.ac.uk/media/1061/sign123.pdf.
7. Smolen JS, Landewe RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A*, et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;79(6):685-99.
8. European Medicines Agency (EMA). Guideline on clinical investigation of medicinal products for the treatment of rheumatoid arthritis. 14 December 2017. CPMP/EWP/556/95 Rev. 2. www.ema.europa.eu.
9. Kearsley-Fleet L, Davies R, De Cock D, Watson KD, Lunt M, Buch MH*, et al.* Biologic refractory disease in rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Ann Rheum Dis. 2018;77(10):1405-12.
10. Norton S, Fu B, Scott DL, Deighton C, Symmons DP, Wailoo AJ*, et al.* Health Assessment Questionnaire disability progression in early rheumatoid arthritis: systematic review and analysis of two inception cohorts. Semin Arthritis Rheum. 2014;44(2):131-44. Epub 2014/06/14.
11. Hernández Alava M, Wailoo A, Wolfe F, Michaud K. The relationship between EQ-5D, HAQ and pain in patients with rheumatoid arthritis. Rheumatology (Oxford). 2013;52(5):944-50. Epub 2013/01/23.
12. Scottish Intercollegiate Guidelines N. Guideline 123: Management of early rheumatoid arthritis. 2011 [cited; Available from: https://www.sign.ac.uk/media/1061/sign123.pdf. .
13. National Institute for H, Care E. Rheumatoid arthritis in adults: management. NICE guideline [NG100]. 2018 [cited; Available from: https://www.nice.org.uk/guidance/ng100/resources/rheumatoid-arthritis-in-adults-management-pdf-66141531233989. Accessed 15 January 2021].

This assessment is based on data submitted by the applicant company up to and including 16 July 2021.

**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*

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.