Justification

Gemeinsamer Bundesausschuss

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Filgotinib (Rheumatoide Arthritis)

of 15 April 2021

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1st Approved therapeutic indications,

2nd Medical benefit,

3rd Additional medical benefit in relation to the appropriate comparator therapy,

4th Number of patients and patient groups for whom there is a therapeutically significant additional benefit,

5th Treatment costs for statutory health insurance funds,

6th Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the market of the combination of active ingredient filgotinib in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 October 2020. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 15 October 2020.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 January 2021 on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of filgotinib compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5,

Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of filgotinib.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of filgotinib (Jyseleca) in accordance with the product information

Jyseleca is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an inadequate response to or are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Jyseleca can be used as monotherapy or in combination with methotrexate (MTX).

Therapeutic indication of the resolution (resolution of 15/04/2021):

see therapeutic indication according to marketing authorisation

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with moderate to severe active rheumatoid arthritis who do not have poor prognostic factors[2] and who have had an inadequate response to, or were intolerant to, previous treatment with a disease-modifying anti-rheumatic drugs (classical DMARDs, including methotrexate (MTX))

- Alternative classical DMARDs, if suitable (MTX, leflunomide, sulfasalazine) as mono- or combination therapy

b) Adult patients with moderate to severe active rheumatoid arthritis for whom initial therapy with biotechnology DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated

- bDMARDs or tsDMARDs (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib or upadacitinib) in combination with MTX; if necessary as monotherapy taking into account the respective authorisation status in case of MTX intolerance or unsuitability

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

[2] Poor prognostic factors:
- Detection of autoantibodies (e.g. rheumatoid factors, high levels of antibodies against citrullinated peptide antigens)
- High disease activity (detected by DAS or DAS28 score, swollen joints, acute phase reaction parameters such as C-reactive protein, erythrocyte sedimentation rate)
- Early occurrence of joint erosions

c) Adult patients with moderate to severe active rheumatoid arthritis who have had an inadequate response to, or have not tolerated, previous treatment with one or more bDMARDs and/or tsDMARDs

- Change of bDMARD or tsDMARD therapy (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib or upadacitinib, in combination with MTX; if necessary as , taking into account the respective marketing authorisation status in the case of MTX intolerance or unsuitability; or in patients with severe rheumatoid arthritis, rituximab, taking into account the marketing authorisation status) depending on the previous therapy.

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1.

A variety of approved medicinal products are available for the treatment of rheumatoid arthritis. These include medicinal products belonging to the following classes of active ingredients and the following active ingredients:

- Non-steroidal anti-inflammatory drugs (NSAIDs/NSARs), whereby these are used purely symptomatically
- Steroidal anti-inflammatory drugs (glucocorticoids), e.g. prednisolone, methylprednisolone
- Classical synthetic disease-modifying anti-rheumatic drugs ("basic therapeutics", cDMARDs), e.g. MTX, leflunomide, sulfasalazine
- Other active ingredients: D-penicillamine, parenteral gold, ciclosporin and azathioprine
- Biological disease-modifying anti-rheumatic drugs ("biologics", bDMARDs): TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, infliximab and golimumab), abatacept, anakinra, rituximab, tocilizumab, sarilumab
- targeted synthetic DMARDs ("tsDMARDs"): the JAK inhibitors baricitinib, tofacitinib and upadacitinib

According to the marketing authorisation, some active ingredients are only used for severe forms of rheumatoid arthritis, e.g. rituximab, ciclosporin or azathioprine. These active ingredients are therefore only considered for a proportion of patients and do not represent an appropriate comparator therapy for a large proportion of the patient population covered by the therapeutic indication.

on 2.

For the treatment of rheumatoid arthritis, no non-medical measures can be considered as the sole appropriate comparative therapy.

on 3.

There are four resolutions of the G-BA in the indication area rheumatoid arthritis, for baricitinib dated 21 September 2017, for tofacitinib dated 19 October 2017 and 1 November 2018 respectively, for sarilumab dated 15 February 2018 and for upadacitinib dated 16 July 2020. Furthermore, a final report by the Institute for Quality and Efficiency in Health Care (IQWiG) of 28 June 2013 is available on a comparative benefit assessment of biotechnologically produced medicinal products in the second-line therapy of rheumatoid arthritis on the active ingredients rituximab, abatacept, etanercept, infliximab, adalimumab, certolizumab pegol, golimumab, anakinra and tocilizumab. Furthermore, a final report by the Institute for Quality and Efficiency in Health Care (IQWiG) dated 23 July 2019, on bioengineered active ingredients for rheumatoid arthritis is available. In addition, the therapy notes according to Section 92, paragraph 2, sentence 7 SGB V in conjunction with Section 17 Pharmaceuticals Directive (AM-RL) on the economic prescription of medicinal product for the active ingredient leflunomide are to be taken into account.

on 4.

The generally recognised state of medical knowledge was illustrated by a search for guidelines as well as systematic reviews of clinical studies in the present indication.

The approved therapeutic indication and the thereby described marketing authorisation population of the medicinal product to be assessed are decisive for the determination of the appropriate comparative therapy.
Due to different therapeutic situations, the population in the present therapeutic indication is to be subdivided into

a) Patients who do not have poor prognostic factors[2] and who have had an inadequate response to, or have not tolerated, previous treatment with a disease-modifying anti-rheumatic drug (classical DMARDs, including methotrexate),
b) Patients for whom initial therapy with biotechnologically produced DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated, and
c) Patients who have had an inadequate response or intolerance to previous treatment with one or more bDMARDs and/or tsDMARDs.

According to current scientific knowledge, MTX is considered the drug of choice in first-line therapy and is also established in combination therapy.

Due to their strong antiphlogistic quality of action, the glucocorticoids group of active ingredients is usually used for a limited time as high-dose therapy or orally in low doses as "bridge therapy" at the beginning of treatment until the response of the basic therapy. They also represent an important therapy option in malignant disease progression, but cannot replace a basic therapy.

About a)

In second-line therapy (patient group A), patients are first differentiated according to the presence or absence of poor prognostic factors. If no poor prognostic factors are present and patients have responded inadequately to or have not tolerated previous therapy with a classical DMARD (cDMARD), the current guideline from the European League Against Rheumatism[3] (EULAR) as well as the S2-e guideline of the DGRh from 2018 recommends[4] the use of an alternative classical DMARD, if suitable (MTX, leflunomide, sulfasalazine) as monotherapy or combination therapy. Parenteral gold has no relevant value in this treatment situation compared to the available alternatives. Thus, parenteral gold is neither mentioned in the current guidelines nor is parenteral gold currently available on the German market. D-penicillamine is also neither mentioned nor recommended in the current guidelines. In addition, other active ingredients such as ciclosporin and azathioprine play a subordinate role in this therapy situation due to their poorer risk-benefit ratio and are not included in the appropriate comparative therapy. In individual cases, patient population A may also include patients with unfavourable prognostic factors who have responded inadequately to initial treatment with a cDMARD or who have not tolerated this treatment but who, in medical care practice, on the basis of individual criteria, may first be considered for a second classical DMARD before initial bDMARD therapy is started.

about b)

After failure or intolerance of treatment with a classical disease-modifying anti-rheumatic drug, the use of a biologic or tsDMARD is recommended if poor prognostic factors are present. For patients who have already responded inadequately to several cDMARDs or have not tolerated them, the use of a biologic is also recommended. Thus, the first use of a bDMARD or tsDMARD is equally suitable as an appropriate comparative therapy for these two patient groups, although they differ with regard to their previous therapy and the previous course of the disease. A grouping of patients is considered justified, since the presence of negative prognostic markers and the number of previous therapies in this therapeutic situation no longer have predictive value for the course of therapy. Thus, the patient group of patients for whom initial therapy with bDMARDs or tsDMARDs (patient group b) includes both patients with unfavourable prognostic factors[2] who have responded inadequately to or failed to tolerate previous treatment with one disease-modifying anti-rheumatic drug (classical DMARDs, including MTX) and patients who have responded inadequately to or failed to tolerate previous treatment with multiple disease-modifying ant rheumatic drugs (classical DMARDs, including MTX).

The use of the interleukin (IL)-1 receptor antagonist anakinra is not recommended due to weaker efficacy compared to other biologics based on the IQWiG final report from 2019. Means of choice after failure of classical DMARDs are bDMARDs or tsDMARDs, including TNF-alpha

[3] Smolen JS, et al. Ann Rheum Dis. 2020 Jun;79(6):685-699.

[4] Fiehn C, Holle J, Iking-Konert C, Leipe J, Weseloh C, Frerix M, et al. Therapy of rheumatoid arthritis with disease-modifying drugs; S2e guideline [online]. AWMF register number 060-004. Berlin (GER): Association of the Scientific Medical Societies (AWMF); 2018.

inhibitors in combination with MTX, the CTLA-4 analogue abatacept, the IL-6 inhibitors tocilizumab and sarilumab, the JAK inhibitors tofacitinib and baricitinib, both in the recommendations of the EULAR[3], as well as in other included guidelines (including, among others, the S2-e guideline of the DGRhfrom 2018[4]). In the early benefit assessment according to §35a SGB V, no inferiority or equivalence was determined for tofacitinib or baricitinib compared to the TNF-α inhibitor adalimumab, and an additional benefit was declared for sarilumab and upadacitinib compared to the TNF-α inhibitor adalimumab.

The subordination of the TNF-α inhibitor infliximab to the other active ingredient in its class due to an increased side effect profile, which was previously seen on the basis of the IQWiG final report on bDMARDs from 2013, is no longer seen on the basis of the current, aggregated evidence. Against this background and due to the fact that also in the current guidelines[3, 4] no recommendations are derived within the class of bDMARDs that would justify a priority or subordination of individual active ingredients at the present time, infliximab is included as a further TNF-α inhibitor in the appropriate comparative therapy.
Thus, the G-BA comes to the conclusion that in the overall view, in addition to the TNF-α inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), other bDMARDs and tsDMARDs are equally suitable as appropriate comparative therapy. tsDMARDs are equally suitable, including abatacept, the IL-6 inhibitors tocilizumab and sarilumab as well as the JAK inhibitors baricitinib, tofacitinib and upadacitinib - in each case in combination with MTX.
Consequently, bDMARDs or tsDMARDs (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib or upadacitinib, in combination with MTX (if applicable, as monotherapy taking into account the respective approval status in case of MTX intolerance or unsuitability) are determined as equally appropriate comparative therapies for patients for whom first-time therapy with biotechnologically produced DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated, as monotherapy, taking into account the respective approval status in the case of MTX intolerance or unsuitability)) as equally appropriate comparative therapies. bDMARDs or tsDMARDs should generally be used in combination with MTX, as this improves efficacy and, in the case of bDMARDs, reduces the formation of neutralising "anti-drug antibodies". Only for patients who cannot tolerate MTX or who have an MTX contraindication, monotherapy with a bDMARD or tsDMARD can be considered as an appropriate comparator therapy. The data situation for monotherapy with the anti-IL-6 receptor antibody tocilizumab in MTX intolerance is not currently assessed as sufficient, also in view of the safety profile of tocilizumab, to consider the TNF-α inhibitors adalimumab, etanercept and certolizumab pegol or tsDMARDs tofacitinib or baricitinib or upadacitinib or the bDMARD sarilumab as less appropriate alternatives in this situation (patient population b1), so that also in this case all approved bDMARDs or tsDMARDs can be considered as equally appropriate comparator therapy. Abatacept, golimumab and infliximab are only approved in combination with MTX.

about c)
For the therapy situation "after failure of at least one bDMARD or tsDMARD therapy", the active ingredient tocilizumab, abatacept and rituximab (in combination with MTX) are explicitly approved (after failure of a TNF-α inhibitor therapy) However, the marketing authorisation of TNF-α inhibitors does not exclude their use even after failure of a previous TNF-α inhibitor therapy (in a "later line of therapy"), provided that the application requirement, failure of DMARDs, is met. Thus, in the therapy situation "after failure of at least one bDMARD or

tsDMARD therapy", various TNF-alpha inhibitors, the CTLA-4 analogue Abatacept, IL inhibitors, JAK inhibitors and for severe rheumatoid arthritis also Rituximab are approved.

Since the marketing authorisation of TNF-α inhibitors, IL inhibitors, and JAK inhibitors, a growing body of proof has been found supporting the efficacy of these active ingredients after failure of a first bDMARD or tsDMARD. The aggregated evidence is overall more limited compared to the therapy situation in patient group b, but some recommendations from German[4] and European guidelines[3] as well as results from early benefit assessments according to §35a SGB V are available for this treatment situation "after failure of at least one bDMARD or tsDMARD therapy". Thus, in the overall view, depending on the previous therapy of a patient in the above-mentioned therapy stage, both the change to a TNF-alpha inhibitor (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) and to a therapy with a different mode of action from TNF-α inhibition (CTLA-4 analogue, IL-6 inhibitor or JAK inhibitor), in each case in combination with MTX, is considered appropriate. Rituximab is also suitable and appropriate for patients with severe active rheumatoid arthritis who respond inadequately to other DMARDs including one or more TNF-alpha inhibitors. For anakinra, please refer to the comments under patient population B.

Analogous to patient group b, according to the respective guidelines, bDMARDs or tsDMARDs should always be used in combination with MTX, as this improves efficacy and reduces the formation of neutralising "anti-drug antibodies" in the case of bDMARDs. Only for patients who cannot tolerate MTX or who have an MTX contraindication, monotherapy with a bDMARD or tsDMARD can be considered.

In summary, for patients who have had an inadequate response or intolerance to previous treatment with one or more bDMARDs and/or tsDMARDs, depending on the previous therapy, a change of bDMARD or tsDMARD therapy, taking into account the agents abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib or upadacitinib in patients with severe rheumatoid arthritis rituximab, in each case in combination with MTX or, where appropriate as monotherapy, taking into account the respective approval status in the case of MTX intolerance or unsuitability. Depending on the previous therapy, a change of the active principle should be considered. A further differentiation of the patient population C (e.g. also with regard to failure on two vs more than two bDMARDs/tsDMARDs) is not made at this time due to the lack of uniform therapy recommendations.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment order.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of filgotinib is assessed as follows:

a) Adult patients with moderate to severe active rheumatoid arthritis who do not have unfavourable prognostic factors and who have had an inadequate response to, or failure of, previous treatment with a disease-modifying anti-rheumatic drug (DMARD)[2] and who have had an inadequate response or intolerance to previous treatment with a disease-modifying anti-rheumatic drug (classical DMARDs, including methotrexate (MTX))

For adult patients with moderate to severe active rheumatoid arthritis who do not have any unfavourable prognostic factors[2] and who have had an inadequate response to or have not tolerated previous treatment with a disease-modifying anti-rheumatic drug (classical DMARDs,

including methotrexate (MTX)), the additional benefit of filgotinib (as monotherapy or in combination with MTX) compared with the appropriate comparator therapy is not proven.

Justification for patient population a1:

No data were submitted with the dossier for the assessment of the additional benefit of therapy with filgotinib as monotherapy compared with the appropriate comparator therapy.

Justification for patient population a2:

No data were submitted with the dossier for the assessment of the additional benefit of therapy with filgotinib in combination with MTX compared with the appropriate comparator therapy.

b) Adult patients with moderate to severe active rheumatoid arthritis for whom initial therapy with biotechnology DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated

For adult patients with moderate to severe active rheumatoid arthritis for whom a first therapy with biotechnologically produced DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated, the additional benefit for filgotinib as monotherapy compared to the appropriate comparator therapy is not proven, while for filgotinib in combination with MTX compared to the appropriate comparator therapy adalimumab + MTX a hint for a minor additional benefit is derived.

Justification for patient population b1:

In the dossier, no data were presented in the relevant patient population b1 for the assessment of the additional benefit of therapy with filgotinib as monotherapy compared with the appropriate comparator therapy.

Justification for patient population b2:

The benefit assessment is based on the Phase III FINCH1 study submitted by the pharmaceutical company. This is a randomised, double-blind study comparing filgotinib in two doses with adalimumab and placebo, each in combination with MTX.

The study included a total of 1,759 adult patients with moderate to severe active rheumatoid arthritis who had an inadequate response to MTX. Included patients were randomised in a 3:3:2:3 ratio to the four treatment arms: filgotinib 200 mg + MTX (N = 477), filgotinib 100 mg + MTX (N = 480), adalimumab + MTX (N = 325), and placebo + MTX (N = 477). In addition to pre-treatment with bDMARD (yes/no) and the presence of rheumatoid factor or anti-CCP antibodies, stratification was performed according to geographic region. The planned double-blind, randomised treatment phase was 52 weeks. After the end of the study, patients in the filgotinib study arms were able to continue their therapy in an open-label, long-term extension study.

Before initiating treatment, patients had to have received continuous treatment with MTX for ≥ 12 weeks at a stable dose within the 4 weeks prior to the first dose of study medication. This dosage was continued as adjunctive treatment during the study. Therapy adjustments were also made at predefined time points if certain criteria for treatment response were not met. At

week 14, patients with <20% improvement in the number of swollen and pressure painful joints compared to baseline should discontinue study treatment. They were followed up according to local standard of care and the investigator's decision, and study visits and examinations were to continue according to protocol until the end of the study. The same measures applied to patients who achieved <20% improvement in the number of swollen and pressure painful joints at two consecutive visits from week 30 compared with treatment initiation. No information is available on the therapy with which the patients were further treated after discontinuation of the study medication.

The primary endpoint of the study was defined as the proportion of patients with a 20% improvement in ACR criteria (ACR 20) at week 12 compared to placebo. In addition, patient-relevant endpoints on morbidity, health-related quality of life and adverse events (AEs) were collected.

For the present benefit assessment, only the study arms adalimumab + MTX and filgotinib 200 mg + MTX are relevant, as these are the approved doses for filgotinib. This does not include the treatment of patients with moderate or severe renal impairment, for whom a dosage of 100 mg filgotinib has been approved. The latter is also intended as the starting dose for patients > 75 years of age, in accordance with the information provided in the product information. Thus, a portion of the study population was not dosed with filgotinib compliant with marketing authorisation. In addition, the study included a combination of filgotinib with MTX and other csDMARDs. Regardless of this, the benefit assessment is based on the total population of the FINCH1 study.

Evaluations for week 12, week 24 and week 52 were presented in the dossier. At week 52, 83.8% of patients were still treated with filgotinib 200 mg + MTX and 81.8% with adalimumab + MTX, so that the present benefit assessment is based on the final analysis at week 52.

Extent and probability of the additional benefit

Mortality

For all-cause mortality, there were no statistically significant differences between the two treatment groups at week 52 in the FINCH1 trial.

Morbidity

Morbidity is assessed by the pharmaceutical company using remission, low disease activity, disease-specific symptoms, patient-reported disease activity, physical functional status and health status.

Remission (CDAI ≤ 2.8; SDAI ≤ 3.3; Boolean definition according to ACR/EULAR)

Remission - assessed by the Clinical Disease Activity Index (CDAI) - is considered patient-relevant. The CDAI is a clinical construct composed of information on pressure painful and swollen joints and disease activity reported by both the patient and the examiner on a VAS. Inflammatory parameters such as CRP or ESR are not included in the calculation of the CDAI. Therefore, the collection of effects via the CDAI versus constructs that include inflammatory

parameters is considered more appropriate, especially for active ingredients with a direct influence on inflammatory parameters.

Remission is operationalised by the achievement of a CDAI ≤ 2.8. At week 52, statistically significantly more patients achieved remission with filgotinib + MTX compared to treatment with adalimumab + MTX. However, this effect is not confirmed in terms of statistical significance in the sensitivity analyses using alternative replacement strategies.

In addition, the endpoint remission was assessed in the study using the Simplified Disease Activity Index (SDAI) and the Boolean definition according to ACR/EULAR. For clinical remission operationalised by the SDAI ≤ 3.3, there is no statistically significant advantage or disadvantage for filgotinib + MTX over adalimumab + MTX at week 52. In contrast, the Boolean definition shows a statistically significant difference to the advantage of filgotinib + MTX.

Overall, for the endpoint remission, operationalisation via the Boolean definition according to ACR-EULAR at week 52 confirms the statistically significant advantage of filgotinib + MTX over adalimumab + MTX present for operationalisation as CDAI ≤ 2.8. There are also effects of comparable magnitude and direction across all operationalisations. In the overall view, therefore, an advantage for filgotinib + MTX over adalimumab + MTX is derived for the endpoint disease remission.

Low disease activity (CDAI ≤ 10; SDAI ≤ 11)

Low disease activity - assessed by the Clinical Disease Activity Index (CDAI) - represents a patient-relevant endpoint. The CDAI is a clinical construct composed of information on pressure painful and swollen joints and disease activity reported by both the patient and the examiner on a VAS. Low disease activity by achieving a CDAI ≤ 10 represents a patient-relevant therapeutic goal. Analogous to the endpoint remission, inflammation parameters such as CRP or ESR are not included in the calculation of the CDAI.

For the endpoint "low disease activity" (CDAI ≤ 10), there is no statistically significant difference overall between the intervention arm filgotinib + MTX and the comparator arm adalimumab + MTX in the FINCH1 study at week 52.

In addition, the endpoint "low disease activity" was assessed by the SDAI. If the further operationalisation SDAI ≤ 11 is used as support, both operationalisations show statistically significant effects in favour of filgotinib + MTX compared with adalimumab + MTX at week 52 that are comparable in terms of their magnitude, so that in the overall view for the endpoint "low disease activity" an advantage is derived for filgotinib + MTX compared with adalimumab + MTX.

Pain (VAS improvement of ≥ 15 mm or points)

The symptom pain is recorded patient-reported by means of a visual analogue scale. This includes a scale from 0 mm (no pain) to 100 mm (most severe pain imaginable). Pain intensity assessed via the VAS is a patient-relevant endpoint.

For the endpoint, there is no statistically significant difference between filgotinib + MTX and adalimumab + MTX for an improvement of ≥ 15 mm or points at week 52 in the FINCH1 trial.

Patient-reported assessment of disease activity (VAS improvement by ≥ 15 mm or points)

Patient-reported disease activity is a patient-relevant endpoint for the benefit assessment. In this study, the assessment of disease activity was recorded in a patient-reported manner using a visual analogue scale. Patients were asked to rate the severity of their current impairment from their rheumatoid arthritis, with a score of 0 mm indicating "no impairment" and a score of 100 mm indicating "highest impairment."

For the endpoint, there is no statistically significant difference between filgotinib + MTX and adalimumab + MTX for an improvement of ≥ 15 mm or points at week 52 in the FINCH1 trial.

Physical functional status (improvement HAQ-DI by ≥ 0.45 points, improvement HAQ-DI by ≥ 0.22 points)

The patient questionnaire Health Assessment Questionnaire - Disability Index (HAQ-DI) measures physical functional status including activities of daily living. It consists of 8 domains (dressing/dressing, personal hygiene, getting up, eating, walking, hygiene, reaching objects, grasping and general daily activities). The items on these 8 domains are each answered on a 4-point Likert scale, with a score of 0 corresponding to "without difficulty" and a score of 3 corresponding to "unable to perform". The functional scales is calculated using the mean values of the individual domains.

According to IQWiG's current methodological approach (Methods 6.0, published on 05.11.20201), IQWiG considers a response threshold for responder analyses of at least 15% of the scale range of an instrument (for *post hoc* analyses of exactly 15% of the scale range) to be necessary for patient-reported endpoints in order to represent a noticeable change with sufficient certainty. The G-BA has already recognised a response threshold of ≥ 0.22 points as a clinically relevant change in HAQ-DI in the present indication. Therefore, against the background of the current methodological discussion, both the responder analysis with a response threshold of 15% (here ≥ 0.45 points) and the responder analysis with a response threshold of ≥ 0.22 points are used to assess the additional benefit. The methodological discussion on the further procedure in the G-BA has not yet been concluded.

For the patient-relevant physical functional status endpoint, the HAQ-DI at week 52 in the FINCH1 trial did not show a statistically significant difference between treatment groups for either an improvement of ≥ 0.22 points or an improvement of ≥ 0.45 points.

Fatigue (improvement FACIT-F by ≥ 7.8 points, improvement FACIT-F by ≥ 4 points)

The FACIT-Fatigue Scale is a validated self-report instrument designed to measure fatigue in patients with chronic illness. The instrument consists of 13 items that ask about the intensity of fatigue and the weakness and difficulty in performing daily activities due to fatigue within the last 7 days. Items are answered on a 5-point numerical scale (0 = not at all; 4 = very much).
For FACIT-Fatigue, the G-BA has recognised a response threshold of ≥ 4 points as a clinically relevant change in the present indication. Therefore, analogous to the procedure for the HAQ-DI, this responder analysis is also used in addition to the responder analysis with a response threshold of 15% of the scale range (here ≥ 7.8 points) in the present assessment.

For the patient-relevant fatigue endpoint, the FACIT-F at week 52 in the FINCH1 trial did not show a statistically significant difference between treatment groups for either an improvement of ≥ 4 points or an improvement of ≥ 7.8 points.

Health status (EQ-5D VAS improvement by ≥ 15 mm or points)

The health status is recorded patient-reported by means of a visual analogue scale on which the patient assesses his health status at the time of measurement. Here, 0 mm stands for the worst imaginable health status and 100 mm for the best imaginable health status. Since the pharmaceutical company also submitted analyses of the 15% scale range in addition to the analyses of the mean change in the EQ-5D VAS, the latter are used for the benefit assessment.

There is no statistically significant advantage or disadvantage for filgotinib + MTX compared to adalimumab + MTX in health status in the FINCH1 study at week 52.

Joint status (pressure painful joints, swollen joints)

For the "pressure painful joints" endpoint, a statistically significant difference to the benefit of filgotinib + MTX is shown at week 52 based on the mean differences in the FINCH1 study. The associated 95%-confidence interval (CI) of the mean change includes a difference of < 1 joint. Thus, it cannot be inferred that the effect is clinically relevant.

Also, for the "swollen joints" endpoint, a statistically significant difference to the advantage of filgotinib + MTX is shown at week 52 based on the mean differences in the FINCH1 study. The associated 95%-confidence interval (CI) of mean change includes a difference of < 1 joint, analogous to pressure-painful joints. Thus, analogous to the pressure painful joints, it cannot be deduced that the effect is clinically relevant in the swollen joints.

Quality of life

Health Survey Short Form 36 (SF-36) (improvement SF-36 by ≥ 5 points)

The Health Survey Short Form 36 (SF-36) is a generic instrument for measuring health-related quality of life, consisting of 8 domains and a total of 36 questions. The physical sum scale (PCS) and the mental sum scale (MCS) of the generic quality-of-life questionnaire SF-36 were used in the assessment.
According to IQWiG's current methodological approach (Methods 6.0, published on 05.11.20201), IQWiG considers a response threshold for responder analyses of at least 15% of the scale range of an instrument (for *post hoc* analyses of exactly 15% of the scale range) to be necessary for patient-reported endpoints in order to represent a noticeable change with sufficient certainty. For the SF-36, the G-BA has recognised a response threshold of ≥ 5 points as a clinically relevant change in previous benefit assessment procedures in the present indication. Analogous to the procedure for HAQ-DI and FACIT-F, this responder analysis is therefore also used in the present assessment.

There was no statistically significant difference between filgotinib + MTX and adalimumab + MTX in the FINCH1 study for either the physical sum score of the SF-36 or the psychological sum score for the proportion of patients with an improvement of ≥ 5 points at week 52.

The responder analyses additionally submitted by the pharmaceutical company on the basis of a relevance threshold of ≥ 15 points could not be considered in the present benefit assessment procedure for methodological reasons, as stated by IQWiG in the appendix to the benefit assessment of filgotinib. For the SF-36, a relevance threshold of approximately 10 points can generally be regarded as a sufficient approximation to the 15% scale range

according to the IQWiG methods paper. The methodological discussion on the further procedure in the G-BA has not yet been concluded.

Side effects

SAE, discontinuation due to AE

For the SAE endpoints and discontinuation due to AE, there were no statistically significant advantages or disadvantages of filgotinib + MTX compared to adalimumab + MTX in the FINCH1 study at week 52.

Infections, Serious infections

For the patient-relevant infections and serious infections endpoints, there is no statistically significant difference between filgotinib + MTX and adalimumab + MTX in the FINCH1 study at week 52.

Overall assessment/conclusion

For adult patients with moderate to severe active rheumatoid arthritis for whom initial therapy with biotechnologically produced DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated, analyses of the direct comparison study FINCH1 are available for the comparison of filgotinib + MTX with adalimumab + MTX at week 52.

In summary, there is no difference in mortality at week 52 between the treatment groups. In the morbidity category, statistically significant advantages for filgotinib + MTX over adalimumab + MTX were seen at week 52 in remission in two of the three available operationalisations, including for the main analysis of operationalisation of remission via the CDAI. Overall, for the endpoint disease remission, an advantage is derived for filgotinib + MTX over adalimumab + MTX. Also, in low disease activity, there is a statistically significant advantage for filgotinib + MTX over adalimumab + MTX in one of the two operationalisations considered.

For the endpoints on joint status, there are effects in favour of filgotinib + MTX over adalimumab + MTX; however, these are not clinically relevant. In the other morbidity endpoints fatigue, physical functional status, pain, health status and for patient-reported disease activity, there were no statistically significant differences between filgotinib + MTX and the appropriate comparator therapy adalimumab + MTX.

In the quality of life category, there was no statistically significant difference between the filgotinib + MTX and adalimumab + MTX treatment groups.

In the category of side effects, no advantages or disadvantages can be derived for filgotinib + MTX versus adalimumab + MTX overall at week 52.

In the overall view, there are exclusively positive effects for filgotinib + MTX compared to adalimumab + MTX at week 52, which are not offset by any disadvantages. The positive effects of filgotinib + MTX compared with the appropriate comparator therapy in remission and low disease activity are confirmed neither in further morbidity endpoints on symptomatology nor in

quality of life, but are assessed overall as a more than slight improvement in the therapy-relevant benefit that has not yet been achieved.

Based on these considerations, the information in the dossier and the results of the benefit assessment, the extent of additional benefit for filgotinib in combination with MTX compared with the appropriate comparator therapy adalimumab + MTX for the treatment of adult patients with moderate to severe rheumatoid arthritis for whom first-time therapy with biotechnologically produced DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated is classified as minor.

Reliability of data (probability of additional benefit)

With the FINCH1 study, a randomised, double-blind Phase III study is available for the evaluation of the additional benefit.
The potential for bias is rated as low for all endpoints on mortality, health-related quality of life and side effects. Within the category of morbidity, there is a high risk of for bias for all other morbidity endpoints except for the two endpoints on joint status. This is due to the high proportion of patients who were classified as non-responders due to missing values or discontinuation of the study medication.

In addition, the study design chosen in the FINCH1 study results in uncertainties for the assessment of the additional benefit. The substitution strategies and sensitivity analyses presented for the benefit assessment cannot eliminate the existing uncertainties on the reliability of the results with sufficient certainty. This is particularly the case for the morbidity endpoint remission, where the sensitivity analyses did not confirm the result of the main analysis.

For the present benefit assessment, the entire population of the FINCH1 study was also used as the basis for the benefit assessment, although only a sub-population of the study was treated in accordance with the requirements in the product information. This aspect further limits the significance of the results.

Overall, the uncertainties described above justify a downgrading of the uncertainty of conclusions, so that a hint of an additional benefit is assumed.

c) Adult patients with moderate to severe active rheumatoid arthritis who have had an inadequate response to, or intolerance of, previous treatment with one or more bDMARDs and/or tsDMARDs

For adult patients with moderate to severe active rheumatoid arthritis who have had an inadequate response or intolerance to previous treatment with one or more bDMARDs and/or tsDMARDs, the additional benefit of filgotinib (as monotherapy or in combination with MTX) compared with the appropriate comparator therapy is not proven.

Justification for patient population c1:

No data were submitted with the dossier for the assessment of the additional benefit of therapy with filgotinib as monotherapy compared with the appropriate comparator therapy.

Justification for patient population c2:

No data were submitted with the dossier for the assessment of the additional benefit of therapy with filgotinib in combination with MTX compared with the appropriate comparator therapy.

2.1.4 Summary of the assessment

The present assessment concerts the benefit assessment of the new medicinal product Jyseleca with the active ingredient filgotinib.
The therapeutic indication assessed here is as follows: "For the treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an inadequate response to or are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Jyseleca can be used as monotherapy or in combination with methotrexate (MTX)."

Six patient groups were distinguished for the benefit assessment:

Patient group a1)
For adult patients with moderate to severe active rheumatoid arthritis who do not have any unfavourable prognostic factors[2] and who have responded inadequately to or have not tolerated previous treatment with a disease-modifying anti-rheumatic drug (classical DMARDs, including methotrexate (MTX)), the G-BA determined alternative classical DMARDs, if suitable (MTX, leflunomide, sulfasalazine) as monotherapy or combination therapy, to be the appropriate comparator therapy. For this patient group, the pharmaceutical company does not submit any data with the dossier for the assessment of the additional benefit. For this patient group, the additional benefit of filgotinib as monotherapy compared to the appropriate comparator therapy is not proven.

Patient group a2)
For adult patients with moderate to severe active rheumatoid arthritis who do not have any unfavourable prognostic factors[2] and who have responded inadequately to or have not tolerated previous treatment with a disease-modifying anti-rheumatic drug (classical DMARDs, including methotrexate (MTX)), the G-BA determined alternative classical DMARDs, if suitable (MTX, leflunomide, sulfasalazine) as monotherapy or combination therapy, to be the appropriate comparator therapy. For this patient group, the pharmaceutical company does not submit any data with the dossier for the assessment of the additional benefit. For this patient group, the additional benefit of filgotinib in combination with MTX compared to the appropriate comparator therapy is not proven.

Patient group b1)
For adult patients with moderate to severe active rheumatoid arthritis for whom initial therapy with biotechnologically produced DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated, the G-BA has defined bDMARDs or tsDMARDs(abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib or upadacitinib, in combination with MTX; if appropriate, as monotherapy, taking into account the respective marketing authorisation). As monotherapy, taking into account the respective approval status in case of MTX intolerance or unsuitability). For this patient group, the pharmaceutical company does not submit any data with the dossier for the assessment of the additional benefit. For this patient group, the additional benefit of filgotinib as monotherapy compared to the appropriate comparator therapy is not proven.

Patient group b2)

For adult patients with moderate to severe active rheumatoid arthritis for whom first-time treatment with biotechnology DMARDs (bDMARDs) or targeted synthetic DMARDs (t sDMARDs) is indicated, the G-BA determined bDMARDs or tsDMARDs (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib or upadacitinib, in combination with MTX) as the appropriate comparator therapy.

For this patient group, the pharmaceutical company presents the results of the direct comparison study FINCH1 for the comparison of filgotinib with adalimumab, both in combination with MTX.

In summary, the data presented show statistically significant advantages for filgotinib + MTX over adalimumab + MTX in the morbidity category for remission and low disease activity at week 52, respectively.

For the morbidity endpoints on joint status, statistically significant effects in favour of filgotinib + MTX are available in each case, but their clinical relevance cannot be assessed with sufficient certainty. For the endpoints health status, physical functional status, pain, patient-reported disease activity and fatigue, there were no statistically significant differences between filgotinib + MTX and the appropriate comparator therapy adalimumab + MTX.

In the categories quality of life and side effects, no advantages or disadvantages can be derived for filgotinib + MTX compared to adalimumab + MTX at week 52.

In the overall view, there are exclusively positive effects for filgotinib + MTX compared to adalimumab + MTX at week 52, which are not offset by any disadvantages. Consequently, for this patient group, an overall hint for a minor additional benefit is derived for filgotinib in combination with MTX compared to the appropriate comparator therapy adalimumab + MTX.

Patient group c1)

For adult patients with moderate to severe active rheumatoid arthritis who have had an inadequate response to, or have not tolerated, previous treatment with one or more bDMARDs and/or tsDMARDs, the G-BA has defined as appropriate comparator therapy the change of bDMARD or tsDMARD therapy (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib or upadacitinib, in combination with MTX; if appropriate as monotherapy, taking into account the respective approval status in the case of MTX intolerance or unsuitability; or in patients with severe rheumatoid arthritis, rituximab, taking into account the marketing authorisation) depending on the previous therapy. For this patient group, the pharmaceutical company does not submit any data with the dossier for the assessment of the additional benefit. For this patient group, the additional benefit of filgotinib as monotherapy compared to the appropriate comparator therapy is not proven.

Patient group c2)

For adult patients with moderate to severe active rheumatoid arthritis who have had an inadequate response to, or have not tolerated, previous treatment with one or more bDMARDs and/or tsDMARDs, the G-BA has defined as appropriate comparator therapy the change of bDMARD or tsDMARD therapy (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib or upadacitinib, in combination with MTX; or, in patients with severe rheumatoid arthritis, rituximab, taking into account the marketing authorisation), depending on the previous therapy. For this patient group, the pharmaceutical company does not submit any data with the dossier for the assessment of the additional benefit. For this patient group, the additional benefit of filgotinib in combination with MTX compared to the appropriate comparator therapy is not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The number of patients is the target population in statutory health insurance (SHI).

The data are based on patient numbers, which for patient population A are based on the information provided by the pharmaceutical company in the dossier, taking into account current sources on prevalence, while for patient populations B and C the patient numbers from the previous resolutions of the G-BA in the indication area of rheumatoid arthritis (last from 2020[5]) are taken into account. The number of patients in the SHI target population is in a plausible order of magnitude, even if these figures are subject to uncertainties for the individual questions.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Jyseleca (active ingredient: filgotinib) at the following publicly accessible link (last access: 06 January 2021):
https://www.ema.europa.eu/documents/product-information/jyseleca-epar-product-information_de.pdf

In accordance with the requirements of the European Medicines Agency (EMA) regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient identification card. The training material for medical professionals includes instructions on how to manage the potential side effects associated with filgotinib, particularly severe and opportunistic infections including TB and herpes zoster and the risk for impaired spermatogenesis. The potential effect of filgotinib on sperm production and male fertility in humans is currently unknown. The reversibility of these potential effects is not known. The potential risk of decreased fertility or infertility should be discussed with male patients prior to initiation of treatment.

Therapy should be started by a doctor experienced in the diagnosis and treatment of rheumatoid arthritis.

The use of the drug must also be carefully weighed against established therapies against the background of a comparatively new mode of action and the associated still existing uncertainties in the risk profile.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 March 2021):

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments / patient / year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

[5] Resolution of 16 July 2020 on upadacitinib.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments per patient per year	Treatment duration per treatment (days)	Days of treatment per patient per year
Medicinal product to be assessed:				
Filgotinib	continuously, 1 x daily	365	1	365
methotrexate, if necessary	Continuously, once every 7 days	52.1	1	52.1
Appropriate comparator therapy for patient population a				
Methotrexate	Continuously, once every 7 days	52.1	1	52.1
Leflunomide	continuously, once a day	365	1	365
Sulfasalazine	Continuously, 2 - 3 times a day	365	1	365
Appropriate comparator therapy for patient population b				
Methotrexate	Continuously, 1 x every 7 days	52.1	1	52.1
Adalimumab	Continuously, every 14 days	26.1	1	26.1
Etanercept	Continuously, 1 x every 7 days	52.1	1	52.1
Certolizumab pegol	Continuously, every 14 days	26.1	1	26.1
Golimumab	Continuously, 1 times a day	12	1	12.0
Abatacept	Continuously, 1 x every 7 days	52.1	1	52.1
Tocilizumab	Continuously, 1 x every 7 days	52.1	1	52.1
Baricitinib	Continuously, 1 times a day	365	1	365
Sarilumab	Continuously, 1 x every 14 days	26.1	1	26.1
Tofacitinib	Continuously, 1-2 times a day	365	1	365

Designation of the therapy	Treatment mode	Number of treatments per patient per year	Treatment duration per treatment (days)	Days of treatment per patient per year
Infliximab[6]	Continuously, every 56 days	6.5	1	6.5
Upadacitinib	Continuously, 1 times a day	365	1	365
Appropriate comparator therapy for patient population C				
Methotrexate	Continuously, once every 7 days	52.1	1	52.1
Adalimumab	Continuously, every 14 days	26.1	1	26.1
Etanercept	Continuously, once every 7 days	52.1	1	52.1
Certolizumab pegol	Continuously, every 14 days	26.1	1	26.1
Golimumab	Continuously, 1 times a day	12	1	12.0
Abatacept	Continuously, once every 7 days	52.1	1	52.1
Tocilizumab	Continuously, once every 7 days	52.1	1	52.1
Rituximab	1 x on day 1 and on day 15 of a minimum 182 day cycle[7]	2	1 - 2	2 - 4
Baricitinib	Continuously, 1 times a day	365	1	365
Sarilumab	Continuously, once every 14 days	26.1	1	26.1

[6] Infliximab can also be used subcutaneously as maintenance treatment. The presentation in the cost calculation is limited to the fixed-amount regulated intravenous infusion therapy.

[7] The need for further treatment cycles should be assessed 24 weeks after the previous cycle. Further treatment at this time should be given if there is residual disease activity. Otherwise, further treatment should be delayed until disease activity increases again. This results in a maximum of 2 cycles within one year.

Designation of the therapy	Treatment mode	Number of treatments per patient per year	Treatment duration per treatment (days)	Days of treatment per patient per year
Tofacitinib	Continuously, 1 - 2 times a day	365	1	365
Infliximab[6]	Continuously, every 56 days	6.5	1	6.5
Upadacitinib	Continuously, 1 times a day	365	1	365

Consumption:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. If a fixed reimbursement rate is available, this will be used as the basis for calculating the costs.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 77.0 kg)[8].

Designation of the therapy	Dosage/Indication	Dose/ patient/ Treatment days	Usage by potency / day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed:					
Filgotinib	200 mg	200 mg	1 x 200 mg	365	365 x 200 mg
methotrexate, if necessary	7.5 mg 20 mg	7.5 mg 20 mg	1 x 7.5 mg - 2 x 10 mg	52.1	52.1 x 7.5 mg - 104.2 x 10 mg
Appropriate comparator therapy for patient population a					
Methotrexate	7.5 mg 20 mg	7.5 mg 20 mg	1 x 7.5 mg - 2 x 10 mg	52.1	52.1 x 7.5 mg - 104.2 x 10 mg

[8] Statistisches Bundesamt (Federal Statistic Office), Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/Indication	Dose/ patient/ Treatment days	Usage by potency / day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
Leflunomide	10 mg 20 mg	10 mg 20 mg	1 x 10 mg - 1 x 20 mg	365	365 x 10 mg - 365 x 20 mg
Sulfasalazine	1,000 mg 1,500 mg	2,000 mg 3,000 mg	4 x 500 mg - 6 x 500 mg	365	1,460 x 500 mg - 2,190 x 500 mg
Appropriate comparator therapy for patient population b					
Monotherapies					
Adalimumab	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Etanercept	50 mg	50 mg	50 mg	52.1	52.1 x 50 mg
Certolizumab pegol	200 mg	200 mg	1 x 200 mg	26.1	26.1 x 200 mg
Tocilizumab	162 mg	162 mg	1 x 162 mg	52.1	52.1 x 162 mg
Baricitinib	4 mg	4 mg	1 x 4 mg	365	365 x 4 mg
Sarilumab	200 mg	200 mg	200 mg	26.1	26.1 x 200 mg
	5 mg	10 mg	2 x 5 mg	365	730 x 5 mg
	or				
Tofacitinib	11 mg	11 mg	1 x 11 mg	365	365 x 11 mg
Upadacitinib	15 mg	15 mg	1 x 15 mg	365	365 x 15 mg
Combination therapies with methotrexate					
Methotrexate	7.5 mg 20 mg	7.5 mg 20 mg	1 x 7.5 mg - 2 x 10 mg	52.1	52.1 x 7.5 mg - 104.2 x 10 mg
Adalimumab	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Etanercept	50 mg	50 mg	50 mg	52.1	52.1 x 50 mg
Certolizumab pegol	200 mg	200 mg	1 x 200 mg	26.1	26.1 x 200 mg
Golimumab	50 mg	50 mg	1 x 50 mg	12	12 x 50 mg
Abatacept	125 mg	125 mg	1 x 125 mg	52.1	52.1 x 125 mg
Tocilizumab	162 mg	162 mg	1 x 162 mg	52.1	52.1 x 162 mg
Baricitinib	4 mg	4 mg	1 x 4 mg	365	365 x 4 mg
Sarilumab	200 mg	200 mg	200 mg	26.1	26.1 x 200 mg
Tofacitinib	5 mg	10 mg	2 x 5 mg	365	730 x 5 mg

Designation of the therapy	Dosage/Indication	Dose/ patient/ Treatment days	Usage by potency / day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
	or				
	11 mg	11 mg	1 x 11 mg	365	365 x 11 mg
Infliximab	3 mg/kg bw (231 mg) - 7.5mg/kg bw (577.5 mg)	231 mg 577.5 mg	3 x 100 mg - 6 x 100 mg	6.5	19.5 x 100 mg - 39 x 100 mg
Upadacitinib	15 mg	15 mg	1 x 15 mg	365	365 x 15 mg
Appropriate comparator therapy for patient population c					
Monotherapies					
Adalimumab	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Etanercept	50 mg	50 mg	50 mg	52.1	52.1 x 50 mg
Certolizumab pegol	200 mg	200 mg	1 x 200 mg	26.1	26.1 x 200 mg
Tocilizumab	162 mg	162 mg	1 x 162 mg	52.1	52.1 x 162 mg
Baricitinib	4 mg	4 mg	1 x 4 mg	365	365 x 4 mg
Sarilumab	200 mg	200 mg	200 mg	26.1	26.1 x 200 mg
	5 mg	10 mg	2 x 5 mg	365	730 x 5 mg
	or				
Tofacitinib	11 mg	11 mg	1 x 11 mg	365	365 x 11 mg
Upadacitinib	15 mg	15 mg	1 x 15 mg	365	365 x 15 mg
Combination therapies with methotrexate					
Methotrexate	7.5 mg 20 mg	7.5 mg 20 mg	1 x 7.5 mg - 2 x 10 mg	52.1	52.1 x 7.5 mg - 104.2 x 10 mg
Adalimumab	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Etanercept	50 mg	50 mg	50 mg	52.1	52.1 x 50 mg
Certolizumab pegol	200 mg	200 mg	1 x 200 mg	26.1	26.1 x 200 mg
Golimumab	50 mg	50 mg	1 x 50 mg	12	12 x 50 mg
Abatacept	125 mg	125 mg	1 x 125 mg	52.1	52.1 x 125 mg

Designation of the therapy	Dosage/Indication	Dose/ patient/ Treatment days	Usage by potency / day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
Tocilizumab	162 mg	162 mg	1 x 162 mg	52.1	52.1 x 162 mg
Baricitinib	4 mg	4 mg	1 x 4 mg	365	365 x 4 mg
Sarilumab	200 mg	200 mg	200 mg	26.1	26.1 x 200 mg
Tofacitinib	5 mg	10 mg	2 x 5 mg	365	730 x 5 mg
	or				
	11 mg	11 mg	1 x 11 mg	365	365 x 11 mg
Rituximab	1,000 mg	1,000 mg	2 x 500 mg	2 - 4	4 - 8 x 500 mg
Infliximab	3 mg/kg bw (231 mg) -	231 mg	3 x 100 mg -	6.5	19.5 x 100 mg -
	7,5mg/kg bw (577,5 mg)	577.5 mg	6 x 100 mg		39 x 100 mg
Upadacitinib	15 mg	15 mg	1 x 15 mg	365	365 x 15 mg

Costs of the medicinal product:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed:					
Filgotinib	90 FCT	€ 3,933.30	€ 1.77	€ 221.35	€ 3,710.18
Methotrexate 7.5 mg[9]	30 TAB	€ 33.47	€ 1.77	€ 1.77	€ 29.93
Methotrexate 10 mg[9]	30 TAB	€ 41.35	€ 1.77	€ 2.40	€ 37.18
Appropriate comparator therapy					
Abatacept 125 mg	12 ILO	€ 4,622.58	€ 1.77	€ 260.72	€ 4,360.09
Adalimumab 40 mg	6 ILO	€ 2,804.66	€ 1.77	€ 156.90	€ 2,645.99
Baricitinib 4 mg	98 FCT	€ 4,078.46	€ 1.77	€ 229.65	€ 3,847.04
Certolizumab pegol 200 mg	6 ILO	€ 4,827.84	€ 1.77	€ 272.44	€ 4,553.63
Etanercept 50 mg[9]	12 ILO	€ 4,231.41	€ 1.77	€ 340.54	€ 3,889.10
Golimumab 50 mg	3 ILO	€ 5,559.73	€ 1.77	€ 314.24	€ 5,243.72
Infliximab 100 mg[9]	5 PIK	€ 3,490.29	€ 1.77	€ 280.08	€ 3,208.44

[9] fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Leflunomide 10 mg[9]	100 FCT	€ 179.90	€ 1.77	€ 13.36	€ 164.77
Leflunomide 20 mg[9]	100 FCT	€ 280.35	€ 1.77	€ 21.30	€ 257.28
Methotrexate 7.5 mg[9]	30 TAB	€ 33.47	€ 1.77	€ 1.77	€ 29.93
Methotrexate 10 mg[9]	30 TAB	€ 41.35	€ 1.77	€ 2.40	€ 37.18
Rituximab 500 mg	1 IFC	€ 1,777.06	€ 1.77	€ 98.21	€ 1,677.08
Sarilumab 200 mg	6 ILO	€ 4,216.13	€ 1.77	€ 237.51	€ 3,976.85
Sulfasalazine 500 mg[9]	300 FMR	€ 77.96	€ 1.77	€ 5.29	€ 70.90
Tocilizumab 162 mg	12 ILO	€ 5,478.40	€ 1.77	€ 309.60	€ 5,167.03
Tofacitinib 11 mg	91 RET	€ 3,134.61	€ 1.77	€ 0.00	€ 3,132.84
Tofacitinib 5mg	182 FCT	€ 3,134.61	€ 1.77	€ 0.00	€ 3,132.84
Upadacitinib 15 mg	90 RET	€ 3,714.25	€ 1.77	€ 0.00	€ 3,712.48
Abbreviations: FCT = film-coated tablets; IFK = infusion solution concentrate; ILO = solution for injection; PIK = powder for the preparation of an infusion solution concentrate; RET = Retard tablets; TAB = tablets; FMR = film-coated tablets enteric-coated.					

LAUER-TAXE® last revised: 15 March 2021

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

For active substances of the appropriate comparative therapy of patient populations B and C (abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, sarilumab, tocilizumab, tofacitinib, upadacitinib), costs are regularly incurred for testing for both active and inactive ("latent") tuberculosis infections. The costs presented are a blood test (quantitative determination of an in vitro interferon-gamma release after ex vivo stimulation with antigens specific for Mycobacterium tuberculosis-complex (except BCG)) and a chest radiograph. The tuberculin skin test is not mapped due to lack of sensitivity and specificity as well as the possibility of "sensitisation". These studies are also required when using filgotinib.

In addition, patients must be tested for the presence of HBV infection before initiating treatment with abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or rituximab or tofacitinib or upadacitinib. These studies are not required for the use of sarilumab and tocilizumab as appropriate comparator therapy, but are regularly required for the use of filgotinib as the drug to be evaluated. For the diagnosis of suspected chronic

hepatitis B, sensibly coordinated steps are required[10]. A serological step-by-step diagnosis initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. If HBs antigen is positive, an active HBV infection is detected.

Overall, for patient populations B and C, there is no regular difference between the drug to be evaluated and the appropriate comparative therapy with regard to examinations for tuberculosis infections, so that the costs for additionally required SHI services are not presented in the decision for examinations for tuberculosis infections. In deviation from this, additional necessary SHI services are required for the diagnosis of suspected chronic hepatitis B, which usually differ between the drug to be evaluated and the appropriate comparative therapy and are consequently considered as additional necessary SHI services in the decision.

Designation of the therapy	Name of the service	Number/	Unit cost	Costs per patient per year
Medicinal product to be assessed: Filgotinib Appropriate comparator therapy for patient population B and C				
Filgotinib Abatacept Adalimumab Baricitinib Certolizumab pegol Etanercept Golimumab Infliximab Rituximab Sarilumab Tocilizumab Tofacitinib Upadacitinib	Quantitative determination of an in vitro interferon-gamma release after ex vivo stimulation with antigens (at least ESAT-6 and CFP-10) specific for Mycobacterium tuberculosis-complex (except BCG) (GOP 32670)	1	€ 58.00	€ 58.00
Filgotinib Abatacept Adalimumab Baricitinib Certolizumab pegol Etanercept Golimumab Infliximab Rituximab Sarilumab Tocilizumab Tofacitinib Upadacitinib	X-ray thorax (GOP 34241)	1	€ 16.24	€ 16.24
Filgotinib Abatacept Adalimumab Baricitinib Certolizumab pegol	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	anti-HBs antibody (GOP 32617)[11]	1	€ 5.50	€ 5.50

[10] "Update of the S3 guideline on prophylaxis, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/011“ http://www.dgvs.de/fileadmin/user_upload/Leitlinien/Hepatitis_B/Leitlinie_Hepatitis_B.pdf
[11] Only if HBs antigen negative and anti-HBc antibody positive

Designation of the therapy	Name of the service	Number/	Unit cost	Costs per patient per year
Etanercept Golimumab Infliximab Rituximab Tofacitinib Upadacitinib				
	anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32823)[12]	1	€ 89.50	€ 89.50

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe)(Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.
According to special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) all surcharges for the production of parenteral preparations containing cytostatic drugs a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy sales price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs retail pharmacist services (Hilfstaxe).

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 25 June 2019.

A review of the appropriate comparator therapy defined by the G-BA took place. The plenary session last redefined the appropriate comparator therapy in rheumatoid arthritis with the resolution on upadacitinib at its meeting on 16 July 2020.

On 15 October 2020, the pharmaceutical company submitted a dossier for the benefit assessment of filgotinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

[12] Billing of GOP 32823 possible before or during antiviral therapy with interferon and/or nucleic acid analogues.

By letter dated 15 October 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient filgotinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 January 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 15 January 2021. The deadline for submitting written statements was 5 February 2021.

The oral hearing was held on 22 February 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 7 April 2021, and the draft resolution was approved.

At its session on 15 April 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Plenum	16 July 2020	Last re-determination of the appropriate comparator therapy
Working group Section 35a	17 February 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal products	22 February 2021	Conduct of the oral hearing
Working group Section 35a	03 March 2021 31 March 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	07 April 2021	Concluding consultation of the draft resolution
Plenum	15 April 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 April 2021

Federal Joint Committee in accordance with Section 91 SGB V The chairman

Prof. Hecken