# 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 Guselkumab (new therapeutic indication: Psoriatic Arthritis)

of 20 May 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 submission 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 active ingredient guselkumab (Tremfya) was listed for the first time on 1 December 2017 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 20 November 2020, guselkumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2a letter a to Regulation (EC) No. 1234/2008 of the commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 30 November 2020, i.e. at the latest within four weeks after the disclosure, the pharmaceutical company on the approval of a new area of application, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient guselkumab with the new therapeutic indication (psoriatic arthritis).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 01 March 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 guselkumab 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 guselkumab.

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 guselkumab (Tremfya) in accordance with the product information

Tremfya, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying anti-rheumatic drug (DMARD) therapy.

**Therapeutic indication of the resolution (resolution from the 20/05/2021):**

see approved [new] therapeutic indication.

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with active psoriatic arthritis who have had an inadequate response or have been intolerant to a prior disease-modifying anti-rheumatic drug (DMARD) therapy.

- a TNF-alpha antagonist (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an interleukin inhibitor (ixekizumab or secukinumab or ustekinumab), if necessary in combination with methotrexate

b) Adult patients with active psoriatic arthritis who have had an inadequate response or have been intolerant to a prior therapy with biologic disease-modifying anti-rheumatic drugs (bDMARDs).

- switching to another biological disease-modifying anti-rheumatic drug (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or secukinumab or ustekinumab), if necessary in combination with methotrexate

[1] General Methods, version 6.0 from 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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. In the indication area psoriatic arthritis, the following active substances of different medicinal product classes are approved:

- steroidal anti-rheumatic drugs: prednisolone, prednisone, triamcinolone
- non-steroidal anti-inflammatory drugs (NSAIDs): e.g. acemetacin
- conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs): methotrexate, leflunomide
- biological disease-modifying anti-rheumatic drugs (bDMARDs):
  - TNF-alpha inhibitors: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab
  - Interleukin inhibitors: guselkumab, ixekizumab, secukinumab, ustekinumab
  - the immunosuppressant abatacept
- targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs):
  - JAK inhibitors: tofacitinib, upadacitinib
  - the phosphodiesterase-4 inhibitor apremilast

on 2. Non-drug measures as sole appropriate comparative therapy are not considered in the present therapeutic indication.

on 3. In the therapeutic indication under consideration here, the following resolutions of the G-BA are available:

- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient apremilast from the 6 August 2015.
- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient ixekizumab from the 16 August 2018.
- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient tofacitinib from the 21 February 2019.
- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient secukinumab from the 18 February 2021.

on 4. The general state of medical knowledge, on which the decision of the G-BA is based, was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication.

Guselkumab is approved for patients who have had an inadequate response or who have been intolerant to a prior disease-modifying anti-rheumatic drug. For these patients, treatment with non-steroidal anti-rheumatic drugs or glucocorticoids alone is no longer an adequate therapeutic option. Even if the local injection of glucocorticoids in particular may be used as an add-on therapy in some patients, non-steroidal anti-inflammatory drugs and glucocorticoids do not represent an appropriate therapeutic option in the present therapeutic indication, which is why both product classes are not considered further in the determination of the appropriate comparative therapy.

On a) Adult patients with active psoriatic arthritis who have had an inadequate response or have been intolerant to a prior disease-modifying anti-rheumatic drug (DMARD) therapy.

For patients who have had an inadequate response or intolerance to previous conventional disease-modifying anti-rheumatic (csDMARD) therapy, initial treatment with a bDMARD is indicated. For these patients, therapy with a TNF-alpha inhibitor (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), an interleukin-17 inhibitor (ixekizumab and secukinumab) or an interleukin-12/23 inhibitor (ustekinumab) is recommended according to the current therapy recommendations of the European League Against Rheumatism (EULAR 2020)[2] .

For patients who have had an inadequate response or have been intolerant to a prior disease-modifying anti-rheumatic drug (DMARD) therapy, the TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), the interleukin-17 inhibitors ixekizumab and secukinumab and the interleukin-12/23 inhibitor ustekinumab, possibly in combination with methotrexate, are therefore determined to be equally appropriate therapeutic options.

On b) Adult patients with active psoriatic arthritis who have had an inadequate response or have been intolerant to a prior biological disease-modifying anti-rheumatic drug (bDMARDs).

For patients who have had an inadequate response or have been intolerant to a prior biological disease-modifying anti-rheumatic drug (bDMARDs), switching to another bDMARD (TNF-alpha inhibitor, interleukin inhibitor) is recommended.

For patients who have had an inadequate response or have been intolerant to a prior biological disease-modifying anti-rheumatic drug (bDMARDs), TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), the interleukin-17 inhibitors ixekizumab and secukinumab and the interleukin-12/23 inhibitor ustekinumab, possibly in combination with methotrexate, were determined to be equally appropriate therapy options. Continuation of an inadequate therapy does not correspond to the implementation of the appropriate comparative therapy.

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

[2] Gossec L, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis 2020;79:700-712.

### 2.1.3 Extent and probability of the additional benefit

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

a) Adult patients with active psoriatic arthritis who have had an inadequate response or have been intolerant to a prior disease-modifying anti-rheumatic drug (DMARD) therapy.

An additional benefit is not proven.

Justification:

The pharmaceutical company submits the studies VOYAGE 1 and VOYAGE 2 for the benefit assessment. Both studies were already subject of the initial evaluation of the active substance guselkumab in the indication plaque psoriasis.

The VOYAGE 1 and VOYAGE 2 studies are randomised, double-blind studies. In both studies, guselkumab was compared to placebo and adalimumab in adult patients with plaque psoriasis. Patients with moderate to severe plaque psoriasis (affected body surface area [BSA] ≥ 10, psoriasis area and severity index [PASI] ≥ 12, and static physician's global assessment [sPGA] ≥ 3) who were eligible for systemic therapy or phototherapy and who were either system therapy naïve or previously treated with systemic therapy were included. The presence of psoriatic arthritis, however, was not a prerequisite for the inclusion of patients in the study. Nevertheless, patients were included in the studies who also had psoriatic arthritis in addition to plaque psoriasis.

It can also be seen from the endpoints assessed that both studies were set up to investigate the efficacy of guselkumab in the indication plaque psoriasis. The primary endpoints of both studies were a PASI 90 response and an Investigator's Global Assessment(IGA) score of 0 or 1. Patient-relevant secondary endpoints were Overall mortality, Remission (PASI 100), endpoints on symptomatology, health-related quality of life, and side effects. Psoriatic arthritis specific endpoints, however, were not collected.

The design of both studies included a 4-week screening phase followed by a 24-week (VOYAGE 2) or 48-week (VOYAGE 1) treatment phase.

*Relevant patient population*

For the present benefit assessment, only those patients are relevant who, in addition to plaque psoriasis, also had psoriatic arthritis. The pharmaceutical company therefore presents evaluations from both studies on subpopulations with patient-reported symptomatic psoriatic arthritis. However, as no information on the characterisation of psoriatic arthritis disease was recorded at start of the study, there is no information on whether patients had active psoriatic arthritis at start of the study (e.g. using the Classification Criteria for the Diagnosis of Psoriatic Arthritis (CASPAR)). Accordingly, no information is available on psoriatic arthritis, the severity of the disease or the number of and damage to the involved joints.

Due to the lack of information on the characterisation of psoriatic arthritis in the VOYAGE 1 and VOYAGE 2 studies, no conclusions on the additional benefit of guselkumab compared with adalimumab for the indication psoriatic arthritis can therefore be derived on the basis of the data presented. An additional benefit is not proven.

b) Adult patients with active psoriatic arthritis who have had an inadequate response or have been intolerant to a prior biological disease-modifying anti-rheumatic drug (bDMARDs).

An additional benefit is not proven.

Justification:

There are no direct comparative studies available for guselkumab, the active ingredient under evaluation, in patients with active psoriatic arthritis who have had an inadequate response or intolerance to prior therapy with bDMARDs.

For the benefit assessment, the pharmaceutical company therefore submits an adjusted indirect comparison via the bridge comparator placebo with two studies on the side of guselkumab and one study on the side of ustekinumab. These are the studies COSMOS and DISCOVER 1 (both with guselkumab vs placebo) on the one hand and PSUMMIT 2 (ustekinumab vs placebo) on the other hand. Since only RCTs versus placebo are available in the relevant therapeutic indication on both the guselkumab and ustekinumab sides, only placebo can be considered as a bridge comparator for an adjusted indirect comparison.

The three studies were each conducted in patients with active psoriatic arthritis who have responded inadequately to or failed to tolerate pre-treatment with disease-modifying anti-rheumatic drugs (DMARDs). In the COSMOS study these are bDMARDs, in the DISCOVER 1 and PSUMMIT 2 studies they are csDMARDs. However, only those patients who have responded inadequately to bDMARDs or have not tolerated them are relevant for the benefit assessment. The pharmaceutical company identifies a relevant sub-population in each of the studies.

*COSMOS study (guselkumab vs placebo)*

The COSMOS study is a double-blind RCT comparing guselkumab with placebo. Patients with active psoriatic arthritis who had an inadequate response to or were intolerant of pre-treatment with up to two TNF-alpha inhibitors were included. The treatment duration was 48 weeks in total, with all patients in the placebo arm being treated with guselkumab from week 24 onwards. The study collected endpoints on Overall mortality, Arthritis-related morbidity, Plaque psoriasis-related morbidity, Health-related quality of life, and side effects.

*DISCOVER 1 study (guselkumab vs placebo)*

The DISCOVER 1 study is a double-blind RCT comparing guselkumab with placebo. Patients with active psoriatic arthritis who responded inadequately to or failed to tolerate pre-treatment with csDMARDs were included. In addition, therapy with up to two TNF-alpha inhibitors could have been given, but had to be stopped at least 4 weeks before start of study. The total treatment duration was 52 weeks, with all patients in the placebo arm receiving guselkumab after 24 weeks. The study collected endpoints on Overall mortality, Arthritis-related morbidity, Plaque psoriasis-related morbidity, Health-related quality of life, and side effects.

*PSUMMIT 2 study (ustekinumab vs placebo)*

The PSUMMIT 2 study is a double-blind RCT comparing ustekinumab with placebo. Patients with active psoriatic arthritis who had an inadequate response or have been intolerant to pre-treatment with csDMARDs and/or non-steroidal anti-inflammatory drugs (NSAIDs), and possibly also to pre-treatment with TNF-alpha inhibitors, were included. The total treatment duration was 52 weeks, with all patients in the placebo arm receiving ustekinumab after 24 weeks. The study collected endpoints on Overall mortality, Arthritis-related morbidity, Plaque psoriasis-related morbidity, Health-related quality of life, and side effects.

*Therapy adjustment in the studies at week 16 (Early Escape)*

In all three studies, there was the option of receiving an adjustment to the existing therapy (early escape) from week 16. The prerequisite for this early escape was in each case that the

number of swollen and pressure-sensitive joints did not decrease by at least 5% within this period.

In the COSMOS and PSUMMIT 2 studies, a switch to the respective intervention occurred at early escape in the placebo arms. In the DISCOVER 1 study, the study treatments remained unchanged in early escape; only the concomitant therapy was adjusted.

*Adjusted indirect comparison of guselkumab versus ustekinumab*

The proportion of patients with a so-called early escape due to non-response at week 16 was very high in both the COSMOS and PSUMMIT 2 studies, which is why the cross-endpoint risk of bias for the results of both the COSMOS and PSUMMIT 2 studies is assessed as high. For example, at the relevant analysis time point (week 24), 48% of patients in the placebo arm in the COSMOS study had switched to guselkumab, and 25% of patients in the placebo arm in the PSUMMIT 2 study had switched to ustekinumab.

Since in the adjusted indirect comparison on the side of the direct comparison of ustekinumab with the bridge comparator placebo (PSUMMIT 2 study) only one study with a high risk of bias is available, the overall uncertainty of the data presented is too high to derive valid statements on the additional benefit of guselkumab compared to the appropriate comparator therapy.

Irrespective of the methodological limitations described above, IQWiG stated that the indirect comparison did not show a statistically significant difference between guselkumab and ustekinumab for any of the endpoints included by the pharmaceutical company.

The presented adjusted indirect comparison of guselkumab versus ustekinumab via the bridge comparator placebo is therefore inappropriate to derive statements on additional benefit due to methodological limitations. An additional benefit is thus not proven for patients with active psoriatic arthritis who have had an inadequate response or have been intolerant to a prior therapy with disease-modifying biological anti-rheumatic drugs (bDMARDs).

### 2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient guselkumab.

The therapeutic indication assessed here is as follows: Tremfya, as monotherapy or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or have been intolerant to a prior disease-modifying anti-rheumatic therapy.

In the therapeutic indication to be considered, two patient groups were distinguished:

a) Adult patients with active psoriatic arthritis who have had an inadequate response or have been intolerant to a prior disease-modifying anti-rheumatic drug (DMARD) therapy.

b) Adult patients with active psoriatic arthritis who have had an inadequate response or have been intolerant to a prior biological disease-modifying anti-rheumatic drug (bDMARDs).

Patient population a)

The G-BA determined a TNF-alpha antagonist (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an interleukin inhibitor (ixekizumab or secukinumab or ustekinumab), if necessary in combination with methotrexate, as an appropriate comparative therapy.

For this patient group, the pharmaceutical company presents the RCTs VOYAGE 1 and VOYAGE 2. In both studies, guselkumab was compared to adalimumab in adult patients with plaque psoriasis. The presence of psoriatic arthritis was not a prerequisite for the inclusion of patients in the study. Nevertheless, patients were included in the studies who also had psoriatic arthritis in addition to plaque psoriasis. At the beginning of the study, however, no information was collected on the characterisation of the psoriatic arthritis disease, so that information on the severity of the disease as well as on the number of and damage to the involved joints is missing.

On the basis of the data presented, it is therefore not possible to derive any statements on the additional benefit of guselkumab compared to adalimumab for the indication psoriatic arthritis. An additional benefit is not proven.

Patient population b)

The G-BA determined the change to another biological disease-modifying anti-rheumatic drug (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or secukinumab or ustekinumab), possibly in combination with methotrexate, as an appropriate comparator therapy.

The pharmaceutical company submits an adjusted indirect comparison of guselkumab versus ustekinumab via the bridge comparator placebo for the patient group to be evaluated due to a lack of direct comparative data of guselkumab versus an active substance of the appropriate comparator therapy. However, due to methodological limitations, the indirect comparison presented is not suitable for deriving an additional benefit. An additional benefit 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).

Due to the methodological approach, the data determined by the pharmaceutical company are overall subject to uncertainties. Therefore, the data from the 2018 G-BA resolution on ixekizumab[3] and from the 2021 resolution on secukinumab[4] are used as a basis.

## 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 Tremfya (active ingredient: guselkumab) at the following publicly accessible link (last access: 24 February 2021):
https://www.ema.europa.eu/en/documents/product-information/tremfya-epar-product-information_de.pdf

Treatment with guselkumab should only be initiated and monitored by specialists who are experienced in the treatment of patients with psoriatic arthritis.

In patients who have not responded to therapy after 24 weeks of treatment duration, discontinuation of treatment should be considered.

## 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 April 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.

For the cost representation only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

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

Guselkumab is approved alone or in combination with methotrexate for the treatment of adult patients with active psoriatic arthritis. The active substances of the appropriate comparative therapy for both patient groups can also be used both as part of monotherapy and in combination with methotrexate. Thus, the corresponding costs for methotrexate, if applicable, are incurred both for the medicinal product under assessment and for the appropriate comparator therapy and are therefore not listed separately.

Treatment duration:

[3] Benefit assessment resolution of the G-BA on ixekizumab dated 16 August 2018.
[4] Benefit assessment resolution of the G-BA on secukinumab dated 18 February 2021.

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Days of treatment/ patient/ year |
|---|---|---|---|---|
| Medicinal product to be assessed | | | | |
| Guselkumab | Once every 56 days | 6,5 | 1 | 6,5 |
| Appropriate comparator therapy | | | | |
| Patient population a) and b) | | | | |
| Adalimumab | Once every 14 days | 26,1 | 1 | 26,1 |
| Certolizumab pegol | Once every 14 days | 26,1 | 1 | 26,1 |
| Etanercept | Once every 7 days | 52,1 | 1 | 52,1 |
| Golimumab | Once monthly | 12 | 1 | 12 |
| Infliximab | Once every 56 days | 6,5 | 1 | 6,5 |
| Ixekizumab | Once every 28 days | 13 | 1 | 13 |
| Secukinumab | Once monthly | 12 | 1 | 12 |
| Ustekinumab | Once every 84 days | 4,3 | 1 | 4,3 |

Consumption:

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).[5]

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

| Designation of the therapy | Dosage/ application | 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 | | | | | |
| Guselkumab | 100 mg | 100 mg | 1 x 100 mg | 6,5 | 6.5 x 100 mg |
| Appropriate comparator therapy | | | | | |
| Patient population a) and b) | | | | | |
| Adalimumab | 40 mg | 40 mg | 1 x 40 mg | 26,1 | 26.1 x 40 mg |
| Certolizumab pegol | 200 mg | 200 mg | 1 x 200 mg | 26,1 | 26.1 x 200 mg |
| Etanercept | 50 mg | 50 mg | 1 x 50 mg | 52,1 | 52.1 x 50 mg |
| Golimumab | 50 mg | 50 mg | 1 x 50 mg | 12 | 12 x 50 mg |
| Infliximab | 5mg/kg | 385 mg | 4 x 100 mg | 6,5 | 26 x 100 mg |
| Ixekizumab | 80 mg | 80 mg | 1 x 80 mg | 13 | 13 x 80 mg |
| Secukinumab | 150 mg - 300 mg | 150 mg - 300 mg | 1 x 150 mg - 1 x 300 mg | 12 | 12 x 150 mg - 12 x 300 mg |
| Ustekinumab | 45 mg | 45 mg | 1 x 45 mg | 4,3 | 4.3 x 45 mg |

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

Costs:

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 130 a 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.

**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 | | | | | |
| Guselkumab | 2 ILO | € 6,091.60 | € 1.77 | € 0.00 | € 6,089.83 |
| Appropriate comparator therapy | | | | | |
| Adalimumab[6] | 6 ILO | € 2,858.93 | € 1.77 | € 228.57 | € 2,628.59 |
| Certolizumab Pegol[6] | 6 ILO | € 2,858.93 | € 1.77 | € 228.57 | € 2,628.59 |
| Etanercept[6] | 12 ILO | € 2,858.93 | € 1.77 | € 228.57 | € 2,628.59 |
| Golimumab[6] | 3 IFE | € 2,605.68 | € 1.77 | € 207.91 | € 2,396.00 |
| Infliximab[6] | 5 PIK | € 3,490.29 | € 1.77 | € 280.08 | € 3,208.44 |
| Ixekizumab | 3 IFE | € 4,175.73 | € 1.77 | € 0.00 | € 4,173.96 |
| Secukinumab 150 mg | 6 ILO | € 5,173.49 | € 1.77 | € 0.00 | € 5,171.72 |
| Secukinumab 300 mg | 3 ILO | € 5,173.49 | € 1.77 | € 0.00 | € 5,171.72 |
| Ustekinumab | 1 ILO | € 5,258.42 | € 1.77 | € 297.03 | € 4,959.62 |
| Abbreviations: IFE = solution for injection in a pre-filled syringe; ILO = solution for injection; PIK = powder for the preparation of an infusion solution concentrate | | | | | |

LAUER-TAXE® last revised: 15 April 2021

[6] fixed reimbursement rate

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 some active substances of the appropriate comparative therapy (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and ustekinumab), 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 examinations are not required when using guselkumab.

In addition, patients receiving therapy with adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab should be tested for the presence of HBV infection before initiating the respective treatment. For the diagnosis of suspected chronic hepatitis B, sensibly coordinated steps are required[7]. 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. These examinations are not required when using guselkumab.

In total, additionally required SHI services are required for the diagnosis of suspected chronic hepatitis B and examinations for tuberculosis infections which usually differ between the medicinal product to be evaluated and the appropriate comparative therapy and are consequently considered as additionally required SHI services in the resolution.

[7] "Update of the S3 guideline on prophylaxis, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/011“ https://www.awmf.org/uploads/tx_szleitlinien/021-011l_S3_Hepatitis_B_Virusinfektionen_Prophylaxe_Diagnostik_Therapie_2011-abgelaufen.pdf

| Designation of the therapy | Name of the service | Number/ | Unit cost | Costs per patient per year |
|---|---|---|---|---|
| Medicinal product to be assessed: Guselkumab | | | | |
| not applicable | | | | |
| Appropriate comparator therapy | | | | |
| Adalimumab<br>Certolizumab pegol<br>Etanercept<br>Golimumab<br>Infliximab<br>Ustekinumab | 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 |
| | X-ray thorax (GOP 34241) | 1 | € 16.24 | € 16.24 |
| Adalimumab<br>Certolizumab pegol<br>Etanercept<br>Golimumab<br>Infliximab | HBs antigen (GOP 32781) | 1 | € 5.50 | € 5.50 |
| | anti-HBs antibody (GOP 32617)[8] | 1 | € 5.50 | € 5.50 |
| | anti-HBc antibody (GOP 32614) | 1 | € 5.90 | € 5.90 |
| | HBV-DNA (GOP 32823)[9] | 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 1.10.2009 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 purchase price of the active ingredient, the invoicing of discards, the calculation of application

[8] Only if HBs antigen negative and anti-HBc antibody positive.
[9] Billing of GOP 32823 possible before or during antiviral therapy with interferon and/or nucleic acid analogues.

containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of 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 11 October 2016.

Reviews of the appropriate comparator therapy defined by the G-BA took place. At its session on 7 July 2020, the Subcommittee on Medicinal Products determined the new appropriate comparator therapy.

On 30 November 2020, the pharmaceutical company submitted a dossier for the benefit assessment of guselkumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2, sentence 2 VerfO.

By letter dated 01 December 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 guselkumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 24 February 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 March 2021. The deadline for submitting written statements was 22 March 2021.

The oral hearing was held on 06 April 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 27 April 2021, and the draft resolution was approved.

At its session on 20 May 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee Medicinal products | 11 October 2016 | Determination of the appropriate comparator therapy |
| Subcommittee Medicinal products | 11 September 2017<br>7 July 2020 | Implementation of the appropriate comparator therapy |
| Working group Section 35a | 31 March 2021 | Information on written statement procedures received; preparation of the oral hearing |
| Subcommittee Medicinal products | 6 April 2021 | Conduct of the oral hearing |
| Working group Section 35a | 14 April 2021<br>21 April 2021 | Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure |
| Subcommittee Medicinal products | 27 April 2021 | Concluding consultation of the draft resolution |
| Plenum | 20 May 2021 | Adoption of the resolution on the amendment of Annex XII AM-RL |

Berlin, 20 May 2021

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

Prof. Hecken