Justification

Gemeinsamer Bundesausschuss

to 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 Ixekizumab (New Therapeutic Indication: Axial Spondyloarthritis)

of 21 January 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:

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient ixekizumab (Taltz) was listed for the first time on 1 March 2017 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 26 November 2019, the pharmaceutical company filed an application to postpone the date for the start of the benefit assessment procedure for ixekizumab in the therapeutic indication axial spondyloarthritis according to Section 35a, paragraph 5b SGB V. At its session on 16 January 2020, the G-BA approved the motion to postpone the relevant date in accordance with Section 35a, paragraph 5b SGB V. The benefit assessment of ixekizumab in the therapeutic indication axial spondyloarthritis begins at the same time as the benefit assessment of ixekizumab in the therapeutic indication plaque psoriasis in children from the age of 6 years, at the latest within four weeks after approval of the therapeutic indication plaque psoriasis in children from the age of 6 years in accordance with Chapter 5, Section 8, number 2 VerfO, at the latest six months after the first relevant time point (4 weeks after marketing authorisation of the therapeutic indication axial spondyloarthritis).

On 2 June 2020, ixekizumab received a marketing authorisation extension for the therapeutic indication axial spondyloarthritis. The marketing authorisation extension for the therapeutic indication plaque psoriasis in children and adolescents aged 6 years and older was granted on 26 June 2020. Both authorisation extensions are classified as a major variation of Type 2

according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 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 23 July 2020, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 3 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 ixekizumab with the new therapeutic indication plaque psoriasis from 6 years/ axial spondyloarthritis.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 2 November 2020, 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 ixekizumab 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, and the written statements presented on this in the written and oral hearing procedure as well as the addendum to the benefit assessment (patient numbers) prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA assessed the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative) according to 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 set aside in the benefit assessment of ixekizumab.

In light of the above and taking into account the written statements received and the oral hearing, the G-BA has arrived at 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 ixekizumab (Taltz) in accordance with the product information

Axial spondyloarthritis

Ankylosing spondylitis (radiographic axial spondyloarthritis)

Taltz is indicated for the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy.

Non-radiographic axial spondyloarthritis

Taltz is indicated for the treatment of adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs).

Therapeutic indication of the resolution (resolution of 21 January 2021):

See new therapeutic indication according to marketing authorisation

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a1) Adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy

Appropriate comparator therapy for ixekizumab:

- A TNF-α inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an IL17 inhibitor (secukinumab)

a2) Adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to therapy with biological antirheumatic drugs (bDMARDs)

Appropriate comparator therapy for ixekizumab:

- Switching to another biological disease-modifying antirheumatic: TNF-α inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or IL17 inhibitor (secukinumab)

b) Adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs)

Appropriate comparator therapy for ixekizumab:

- A TNF-α inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab)

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 according to 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 applications 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 addition to non-steroidal anti-inflammatory drugs (NSAIDs) for the symptomatic therapy of pain and inflammation, glucocorticoids and biologics are also approved for this therapeutic indication. In the therapeutic indication, biologics are covered by the marketing authorisation after a failure to respond to conventional therapies (or if NSAIDs are

contraindicated). In the present indication area, these are the active ingredients adalimumab, golimumab, certolizumab pegol, and etanercept as well as the IL17 inhibitor secukinumab. Infliximab is approved only for part of the intended therapeutic indication (for r-axSpA) but not for nr-axSpA.

On 2. A non-medicinal treatment at the expense of the SHI system cannot be considered as an appropriate comparator therapy in the therapeutic indication.

On 3. For the treatment of non-radiographic axial spondyloarthritis (therapeutic indication b), the G-BA has not passed any resolutions on the benefit assessment of medicinal products with new active ingredients according to 35a SGB V. For the treatment of the radiographic form of axial spondyloarthritis (ankylosing spondylitis; therapeutic indication a), a resolution of the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V of 2 June 2016 is available for the active ingredient secukinumab.

On 4. The generally accepted state of medical knowledge was illustrated by systematic research for guidelines and reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy in accordance with Section 35a SGB V". In addition, the scientific medical societies and the Drug Commission of the German Medical Association (AkdÄ) were involved in writing on questions of comparator therapy in the present indication in accordance with Section 35a, paragraph 7 SGB V.

Both the German S3 guideline[2] of 2019 and the current European ASAS-EULAR guideline[3] of 2016/2017 provide for the evidence-based use of NSAIDs in conventional (first-line-) therapy of axSpA (symptomatic or continuous use). After failure of therapy with NSAIDs or conventional therapy, the use of biologics (bDMARDs) is recommended based on the evidence available. Conventional, classic DMARDs (e.g. MTX, sulphasalazine, and leflunomide) are neither approved for use in the therapeutic indication axSpA nor is their use supported by the evidence available. The guidelines distinguish between the older TNF-α inhibitors and the newer biologics. However, within the active ingredient class of TNF-α inhibitors, no distinction is made in the therapy recommendation; within the TNF-α inhibitors approved in Germany, there is therefore no prioritisation. Furthermore, there are no head-to-head comparisons of the active ingredients that would allow prioritisation; for the most part, the evidence is based on RCTs with placebo comparisons.

In the overall view, the treatment recommendations for axial spondyloarthritis after failure of conventional therapy focus on the use of biologics. For the therapeutic indication, it is assumed that, after failure of conventional therapy or NSAIDs, it is not (or no longer) indicated for patients to continue conventional therapy with NSAIDs or glucocorticoids alone according to the estimation of the doctor.

Treatment recommendations rarely explicitly distinguish between the radiographic and non-radiographic forms of axSpA. A distinction according to the severity of axSpA is also not clear in the underlying evidence: Neither the German S3 guideline, nor the EULAR-LL[3] nor the EMA guideline[4] differentiate in their recommendations on axSpA according to severity. Rather, in everyday care, a therapy decision is made depending on the manifestation of the disease (e.g. axial, peripheral), the failure of previous therapies, and the activity of the disease. The indication of axSpA is divided into the two disease forms: "radiographic axSpA (r-axSpA/"classic" ankylosing spondylitis (AS)/ ankylosing spondylitis)" and "axial spondyloarthritis without radiographic evidence of AS" (non-radiographic form/nr-axSpA). This

2 German Society for Rheumatology (DGRh; Deutsche Gesellschaft für Rheumatologie). Axial spondyloarthritis, including ankylosing spondylitis and early forms; S3 guideline [online]. AWMF register number 060-003. Version 2019. Berlin (GER): Working Group of the Scientific Medical Societies (AWMF; Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften); 2019. [Access: 7 April 2020].

3 ASAS-EULAR recommendations: Van der Heide D et al., Ann Rheum Dis 2017;0:1–14.

4 EMA Guideline on the clinical investigation of medicinal products for the treatment of Axial Spondyloarthritis – Adopted guideline (CPMP/EWP/4891/03 Rev.1) 12 October 2017; EMA Draft Guideline on the clinical investigation of medicinal products for the treatment of Axial Spondyloarthritis - Draft (CPMP/EWP/4891/03 Rev.1) 2016.

sub-division also corresponds to the sub-division in the therapeutic indication of the previously approved medicinal products and is adopted below for the sub-division into patient groups.

a)

The therapeutic indication “adult patients with active ankylosing spondylitis who have had an inadequate response to conventional therapy” includes both patients who have had an inadequate response to treatment with non-steroidal anti-inflammatory drugs (NSAIDs) (“second-line treatment”) and patients who have had an inadequate response to previous therapy with biological antirheumatic drugs (“third-line treatment”). Because these two patient populations differ in the clinical course to date as well as with regard to the therapy recommendations, a subdivision of patient population a into two sub-populations a1 and a2 is made (as is also done accordingly in the current guidelines).

For the therapy of r-axSpA after failure of NSAIDs, all approved TNF-α inhibitors as well as the interleukin-17 inhibitor secukinumab, which has been approved since 2015, can be considered. Especially for patients with certain comorbidities, the recommendations from the latest guidelines available in the indication unanimously consider the use of the IL17 inhibitor secukinumab as an equal-ranking alternative to the proven TNF-α inhibitors. Thus, according to the current state of medical knowledge, the approved TNF-α inhibitors and secukinumab can be considered as equally appropriate comparator therapies for the “second-line treatment” of r-axSpA.

For “third-line treatment” of r-axSpA after failure of a first TNF-α inhibitor or IL17 inhibitor, the evidence is overall weaker compared with “second-line treatment”. Regardless of this, even after failure of a biologic, the evidence available does not allow prioritisation within the active ingredients TNF-α inhibitors or secukinumab considered for “third-line treatment”. Rather, it depends on comorbidities and patient-individual criteria as well as on the previous therapy to which further bDMARD is switched after failure of an initial therapy with a bDMARD. Against this background, in this line of therapy of active, radiographic axSpA, a switch to another approved bDMARD that is established in use is currently considered appropriate. A further differentiation of the patient populations (e.g. also with regard to a failure on 1 vs >1 bDMARD) is not undertaken at this time because of the lack of uniform therapy recommendations.
Taking into account the respective authorisation status of the medicinal products in conjunction with the clinical course and against the background of the available body of evidence, TNF-α inhibitors (etanercept or adalimumab or infliximab or golimumab or certolizumab pegol) or an IL17 inhibitor (secukinumab) are determined as the appropriate comparator therapy for the treatment of adult patients with active ankylosing spondylitis who have had an inadequate response to conventional therapy (patient group a1). For adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to therapy with biological antirheumatic drugs (bDMARDs) (patient group a2), switching to another biological disease-modifying antirheumatic: TNF-α-Inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or IL17 inhibitor (secukinumab) is considered appropriate.

b)

There is little specific evidence for the non-radiological form (nr-axSpA) as distinct from the radiological form (r-axSpA). Thus, in the guidelines, most of the current therapy recommendations are transferred from r-axSpA to nr-axSpA or summarised under axSpA in order to satisfy the treatment of nr-axSpA in everyday care. After failure of conventional therapy, biologics are also used for the treatment of the non-radiographic sub-type of axSpA. As a result, the appropriate comparator therapy between radiographic and non-radiographic axSpA differs only with regard to biologics not approved for nr-axSpA (currently infliximab). The IL-17 inhibitor secukinumab was only recently granted marketing authorisation in nr-axSpA. It can therefore not yet be considered established in care in this indication. The early benefit assessment for secukinumab in nr-axSpA is also still pending.

Overall, an aggregated body of evidence of lower quality is available for nr-axSpA; a clear subdivision of the nr-axSpA patient population into with/without pre-treatment with biologics can also not yet be derived with sufficient certainty from the available guidelines or from the further evidence. Against this background, a subdivision into different lines after the failure of a conventional therapy is currently dispensed with in this indication.
Taking into account the respective authorisation status of the medicinal products in conjunction with the clinical course and against the background of the available aggregated evidence, TNF-α inhibitors are determined to be the appropriate comparator therapy for the treatment of adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation as evidenced by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have had an inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs). Etanercept or adalimumab or golimumab or certolizumab pegol are considered equally appropriate options. It should be added that also in this population, it is assumed that a change within the active ingredient class is indicated in the case of failure of a TNF-α inhibitor. Continuation of inadequate therapy with a TNF-α inhibitor does not correspond to the appropriate comparator therapy.

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

2.1.3 Extent and probability of the additional benefit

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

a1) Adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy

For adult patients with active ankylosing spondylitis who have had an inadequate response to conventional therapy, the additional benefit for ixekizumab compared with the appropriate comparator therapy is not proven.

Justification:

In the dossier for the assessment of the additional benefit of ixekizumab, the pharmaceutical company does not present any suitable directly comparative studies compared with the appropriate comparator therapy. Furthermore, no indirect comparisons were presented to address the question of the benefit assessment.

The COAST-V study is a double-blind, randomised, controlled, multi-centre study. A total of 341 adult patients with active ankylosing spondylitis were included. They had not previously received treatment with a biological disease-modifying antirheumatic drug (bDMARD) and had had an inadequate response or intolerance to conventional therapy with at least 2 non-steroidal anti-inflammatory drugs (NSAIDs). Patients were randomised to 2 different therapy schemes (2- or 4-weekly [Q2W or Q4W]) with ixekizumab, treatment with adalimumab, or administration of placebo. Only the Q4W treatment with an initial dose of 160 mg ixekizumab corresponds to the dosing guidelines of the product information. After 16 weeks, patients in the adalimumab and placebo arms were switched to treatment with ixekizumab. All patients were continued on ixekizumab until Week 52.

With an active-controlled study duration of 16 weeks, the COAST-V pivotal study (RCT with placebo and adalimumab) is too short to enable appropriate statements on the question of the early benefit assessment.

a2) Adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to therapy with biological antirheumatic drugs (bDMARDs)

For adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to therapy with biological antirheumatic drugs (bDMARDs), the additional benefit of ixekizumab compared with the appropriate comparator therapy is not proven.

Justification:

In the dossier for the assessment of the additional benefit of ixekizumab, the pharmaceutical company does not present any directly comparative studies compared with the appropriate comparator therapy. Furthermore, no indirect comparisons were presented to address the question of the benefit assessment.

The COAST-W study is a double-blind, randomised, controlled, multi-centre study. A total of 316 adult patients with active ankylosing spondylitis were included. These had previously responded inadequately to therapy with ≥ 2 NSAIDs as well as to 1 or 2 TNF-α inhibitors or each had intolerance to therapy. Patients were randomised to either ixekizumab (with therapy schemes Q2W or Q4W) or administration of placebo.

In the placebo-controlled pivotal study COAST-W, the appropriate comparator therapy is not implemented. There is thus no suitable data available for the early benefit assessment based on this study.

b) Adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs)

For adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs), the additional benefit of ixekizumab compared with the appropriate comparator therapy is not proven.

Justification:

In the dossier for the assessment of the additional benefit of ixekizumab, the pharmaceutical company does not present any directly comparative studies compared with the appropriate comparator therapy. Furthermore, no indirect comparisons were presented to address the question of the benefit assessment.

The COAST-X study is a double-blind, randomised, controlled, multi-centre study. A total of 303 adult patients with active non-radiographic axial spondyloarthritis who had not received prior treatment with bDMARDs were included. Further inclusion criteria included an inadequate response to or intolerance of therapy with ≥ 2 NSAIDs as well as the presence of objective signs of inflammation by evidence of sacroiliitis in MRI or an elevated CRP. Patients were randomised to either ixekizumab (with therapy schemes Q2W or Q4W) or administration of placebo.

In the placebo-controlled pivotal study COAST-X, the appropriate comparator therapy is not implemented. There is thus no suitable data available for the early benefit assessment based on this study.

2.1.4 Summary of the assessment

The present assessment refers to the benefit assessment of a new therapeutic indication for the active ingredient ixekizumab. The therapeutic indication assessed here is as follows:

“Axial spondyloarthritis (axSpA)

Ankylosing spondylitis (radiographic axial spondyloarthritis) Taltz is indicated for the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy.

Non-radiographic axial spondyloarthritis
Taltz is indicated for the treatment of adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs)”.

For the benefit assessment, the following patient groups were distinguished:

a1) Adult patients with active ankylosing spondylitis who have responded inadequately to conventional therapy;

a2) Adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to therapy with biological antirheumatic drugs (bDMARDs);

b) Adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs).

<u>Patient group a1</u>
The G-BA determined a TNF-α inhibitor (etanercept or adalimumab or infliximab or golimumab or certolizumab pegol) or an IL17 inhibitor (secukinumab) as an appropriate comparator therapy. For this patient group, the pharmaceutical company does not present any suitable direct comparative data compared with the appropriate comparator therapy with the dossier for the assessment of the additional benefit. Furthermore, no indirect comparisons were presented to address the question of the benefit assessment. There are thus no suitable data for assessing the additional benefit of ixekizumab. In the overall view, for adult patients with active radiographic axSpA who have had an inadequate response to conventional therapy, the additional benefit of ixekizumab compared with the appropriate comparator therapy is not proven.

<u>Patient group a2</u>
The G-BA determined that switching to another biological disease-modifying antirheumatic drug – a TNF-α inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an IL17 inhibitor (secukinumab) – was an appropriate comparator therapy. For this patient group, the pharmaceutical company does not present any direct comparative data compared with the appropriate comparator therapy with the dossier for the assessment of the additional benefit. Furthermore, no indirect comparisons were presented to address the question of the benefit assessment. There are thus no suitable data for assessing the additional benefit of ixekizumab. In the overall view, for adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to therapy with

biological antirheumatic drugs (bDMARDs), the additional benefit of ixekizumab compared with the appropriate comparator therapy is not proven.

Patient group b
The G-BA determined a TNF-α inhibitor (etanercept or adalimumab or golimumab or certolizumab pegol) as an appropriate comparator therapy. For this patient group, the pharmaceutical company does not present any direct comparative data compared with the appropriate comparator therapy with the dossier for the assessment of the additional benefit. Furthermore, no indirect comparisons were presented to address the question of the benefit assessment. There are thus no suitable data for assessing the additional benefit of ixekizumab.
In the overall view, for adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs), the additional benefit for ixekizumab compared with the appropriate comparator therapy is not proven.

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

The information on the number of patients is based on the target population in statutory health insurance (SHI).
These are based on the data from the dossier of the pharmaceutical company. The figures are based on prevalence and incidence data from diagnosed patients.
In addition, the IQWiG was commissioned in an addendum to consider and compare the patient numbers for both already completed and currently ongoing benefit assessments in the indication of axial spondyloarthritis.
In the addendum, the number of patients with the lowest uncertainties was determined for the respective patient group. The patient numbers shown in the Addendum and in the present resolution are to be understood in the sense of a minimum number in each case.
Because of the uncertainties, no range of patient numbers can be given in each case. At this point in time, an upper limit cannot be defined on the basis of the data presented for the respective patient groups.
In the overall view, the calculation of the number of patients in all three patient populations tends to be underestimated and subject to uncertainties.

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 Taltz (active ingredient: ixekizumab) at the following publicly accessible link (last access: 29 October 2020):

https://www.ema.europa.eu/en/documents/product-information/taltz-epar-product-information_de.pdf

In patients who have not responded to treatment after 16 to 20 weeks, discontinuation of treatment should be considered. In some patients with an initial partial response, the response may improve if treatment is continued beyond 20 weeks.

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: 1 January 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 different for each individual patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/patient/year", the time between individual treatments, and the maximum treatment duration if specified in the product information.

Infliximab can also be used subcutaneously as maintenance therapy. The presentation in the cost calculation is limited to the fixed-price intravenous infusion therapy.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Ixekizumab	1 × every 28 days	13	1	13
Appropriate comparator therapy				
Patient population a1) + a2)				
Adalimumab	1 × every 14 days	26.1	1	26.1
Certolizumab pegol	1 × every 14 days	26.1	1	26.1
Etanercept	1 × every 7 days	52.1	1	52.1
Golimumab	1 × monthly	12	1	12
Infliximab	1 × every 56– 42 days	6.5 – 8.7	1	6.5 – 8.7
Secukinumab	1 × monthly	12	1	12
Patient population b)				
Adalimumab	1 × every 14 days	26.1	1	26.1
Certolizumab pegol	1 × every 14 days	26.1	1	26.1
Etanercept	1 × every 7 days	52.1	1	52.1
Golimumab	1 × monthly	12	1	12

Usage and consumption:

For the calculation of the dosages as a function of body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis (average body weight): 77.0 kg).[5]

In general, initial induction schemes are not taken into account for the cost representation because this 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	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Ixekizumab	80 mg	80 mg	1 × 80 mg	13	13 × 80 mg
Appropriate comparator therapy					
Patient population a1) + a2)					
Adalimumab	40 mg	40 mg	1 × 40 mg	26.1	26.1 × 40 mg
Certolizumab pegol	200 mg	200 mg	1 × 200 mg	26.1	26.1 × 200 mg
Etanercept	50 mg	50 mg	1 × 50 mg	52.1	52.1 × 50 mg
Golimumab	50 mg	50 mg	50 mg	12	12 × 50 mg
Infliximab	5 mg/kg	385 mg	4 × 100 mg	6.5 – 8.7	26 × 400 mg – 34.8 × 400 mg
Secukinumab	150 mg – 300 mg	150 mg – 300 mg	1 × 150 mg – 2 × 150 mg	12	12 × 150 mg – 24 × 150 mg
Patient population b)					
Adalimumab	40 mg	40 mg	1 × 40 mg	26.1	26.1 × 40 mg
Certolizumab pegol	200 mg	200 mg	1 × 200 mg	26.1	26.1 × 200 mg
Etanercept	50 mg	50 mg	1 × 50 mg	52.1	52.1 × 50 mg
Golimumab	50 mg	50 mg	1 × 50 mg	12	12 × 50 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated based on the pharmacy sales price level as well as less the statutory rebates according to Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number

[5] German Federal Office For Statistics, Wiesbaden 2018: http://www.gbe-bund.de/

of packs of a particular potency was first determined based on consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package 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					
Ixekizumab	3 PEN	€ 4,175.73	€ 1.77	€ 0.00	€ 4,173.96
Appropriate comparator therapy					
Adalimumab	6 SFI	€ 2,804.66	€ 1.77	€ 156.90	€ 2,645.99
Certolizumab pegol	6 SFI	€ 4,827.84	€ 1.77	€ 272.44	€ 4,553.63
Etanercept[6]	12 SFI	€ 4,231.41	€ 1.77	€ 340.54	€ 3,889.10
Golimumab	3 IFE	€ 5,559.73	€ 1.77	€ 314.24	€ 5,243.72
Infliximab[6]	5 PIC	€ 3,490.29	€ 1.77	€ 280.08	€ 3,208.44
Secukinumab	6 PEN	€ 5,173.49	€ 1.77	€ 0.00	€ 5,171.72
Abbreviations: IFE = injection solution for prefilled syringe; SFI = solution for injection; PEN = injection solution in a prefabricated pen, PIC = powder for the preparation of an infusion solution concentrate					

Pharmaceutical selling price (LAUER-TAXE®) as last revised: 1 January 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 assessed 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 standard expenditure in the course of the treatment are not shown.

For some of the active ingredients of the appropriate comparator therapy of patient populations a1, a2, and b (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), costs are regularly incurred for testing for both active and inactive (latent) tuberculosis infections. The costs shown refer to 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)) as well as a thoracic X-ray. The tuberculin skin test is not mapped because of lack of sensitivity and specificity as well as the possibility of “sensitisation”. These investigations are not required for the use of ixekizumab.

In addition, patients must be tested for the presence of HBV infection before initiating treatment with adalimumab or certolizumab pegol or etanercept or golimumab or infliximab. On the other hand, these examinations are not required for the use of secukinumab and are also not usually required for the use of ixekizumab as a medicinal product to be assessed. For the diagnosis

[6] Fixed reimbursement rate

of a suspected chronic hepatitis B, well coordinated steps are necessary[7]. A serological step-by-step diagnostic initially consists of the investigation of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. If the HBs antigen is positive, an active HBV infection has been detected.

Overall, the following additional SHI services are necessary for the diagnosis of suspected chronic hepatitis B and for the examinations for tuberculosis infections. These regularly differ between the medicinal product to be assessed and the appropriate comparator therapy and are therefore considered additionally required SHI services in the resolution.

Designation of the therapy	Description of the service	Number	Costs per unit	Costs per patient per year
Medicinal product to be assessed: Ixekizumab				
not applicable				
Appropriate comparator therapy for patient population a1, a2, and b				
Adalimumab Certolizumab pegol Etanercept Golimumab Infliximab	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 for BCG) (GOP 32670)	1	€ 58.00	€ 58.00
Adalimumab Certolizumab pegol Etanercept Golimumab Infliximab	Chest radiograph (GOP 34241)	1	€ 16.24	€ 16.24
Adalimumab Certolizumab pegol Etanercept Golimumab 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

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

[8] Only if HBs antigen negative and anti-HBc antibody positive

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

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (*Hilfstaxe*; contract on price formation for substances and preparations of substances; Sections 4 and 5 Pharmaceutical Price Ordinance) of 1 October 2009 is not fully used to calculate the 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 the *Hilfstaxe* in its currently valid version, surcharges for the production of parenteral preparations containing cytostatic agents of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit are to be payable. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating the *Hilfstaxe*. The cost representation is based on the pharmacy sales 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 according to the regulations in Annex 3 of the *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

At its session on 6 November 2018, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

The appropriate comparator therapy established by the G-BA was reviewed. At its session on 28 July 2020, the Subcommittee on Medicinal Products redefined the appropriate comparator therapy.

On 23 July 2020, the pharmaceutical company submitted a dossier for the benefit assessment of ixekizumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 24 July 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 ixekizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 24 July 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 2 November 2020. The deadline for submitting written statements was 23 November 2020.

The oral hearing was held on 7 December 2020.

By letter dated 22 December 2020, the IQWiG was commissioned with a supplementary assessment of the patient numbers. The addendum prepared by the IQWiG was submitted to the G-BA on 5 January 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 12 January 2021, and the proposed resolution was approved.

At its session on 21 January 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	6 November 2018	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	28 July 2020	Redefinition of the appropriate comparator therapy
Working group Section 35a	2 December 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	7 December 2020	Conduct of the oral hearing
Subcommittee on Medicinal Products	22 December 2020	Commissioning of the IQWiG with the supplementary assessment of the patient numbers
Working group Section 35a	16 December 2020 6 January 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	12 January 2021	Concluding discussion of the draft resolution
Plenum	21 January 2021	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 21 January 2021

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

Prof. Hecken