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: Plaque Psoriasis in Children and Adolescents)

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 June 2020, ixekizumab received marketing authorisation for a new therapeutic indication 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 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 ixekizumab with the new therapeutic indication (plaque psoriasis in children and adolescents) in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

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

Taltz is indicated for the treatment of moderate to severe plaque psoriasis in children from the age of 6 years and with a body weight of at least 25 kg and adolescents who are candidates for systemic therapy.

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

See new therapeutic indication according to marketing authorisation

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children from the age of 6 years and with a body weight of at least 25 kg and adolescents with moderate to severe plaque psoriasis who are candidates for systemic therapy.

Appropriate comparator therapy:

- Adalimumab or etanercept or ustekinumab

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.

[1] General Methods, Version 6.0 dated 5 November 2020. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

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 the present therapeutic indication, the following active ingredients are generally approved for children and adolescents:

- ciclosporin
- the *TNF-alpha inhibitors* adalimumab and etanercept
- the *interleukin inhibitors* ustekinumab and secukinumab

On 2. Non-medicinal measures are not considered as the sole appropriate comparator therapy in the present therapeutic indication.

On 3. No resolutions of the G-BA have been made in the therapeutic indication (plaque psoriasis in children and adolescents) considered here.

On 4. The general accepted state of medical knowledge on which the decision of the G-BA are based was illustrated by systematic research for guidelines and reviews of clinical studies in this indication.

For the treatment of plaque psoriasis in children and adolescents who are eligible for systemic therapy, the TNF-alpha inhibitors adalimumab and etanercept (severe form of plaque psoriasis) and the interleukin inhibitor ustekinumab (moderate to severe plaque psoriasis) are approved in Germany. The evidence does not support a clinical advantage for any of the three active ingredients that would support a preference in the determination as an appropriate comparator therapy.

The IL-17 inhibitor secukinumab was only recently granted marketing authorisation in plaque psoriasis in children and adolescents. It can therefore not yet be considered established in care in this indication. The early benefit assessment for secukinumab for the treatment of plaque psoriasis in children and adolescents is also still pending.

The use of the active ingredient ciclosporin (severe form of plaque psoriasis) is not recommended for children under 16 years of age in accordance with marketing authorisation. Because ciclosporin is therefore not a treatment option for a predominant proportion of children and adolescents and is also not recommended, ciclosporin is not part of the appropriate comparator therapy.

Accordingly, for children and adolescents aged 6 years and older with plaque psoriasis who are eligible for systemic therapy, the active ingredients adalimumab, etanercept, and ustekinumab are determined to be equally appropriate comparator therapies.

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:

Children from the age of 6 years and with a body weight of at least 25 kg and adolescents with moderate to severe plaque psoriasis who are candidates for systemic therapy.

For children from the age of 6 years and with a body weight of at least 25 kg and adolescents with moderate to severe plaque psoriasis who are candidates for systemic 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 with a sufficiently long study duration compared with the appropriate comparator therapy.

For the derivation of the additional benefit, the pharmaceutical company transfers the results of the IXORA-S study, a multi-centre, actively controlled, two-armed Phase III study comparing ixekizumab with ustekinumab in adult patients with moderate to severe plaque psoriasis to the population of children and adolescents. The IXORA-S study was used for the early benefit assessment of ixekizumab for the treatment of adult patients with moderate to severe plaque psoriasis (resolution of 17 August 2017). The pharmaceutical company compares the data on adults with data on ixekizumab for children and adolescents from the IXORA-PEDS study. The IXORA-PEDS study also provides direct comparative data for comparing ixekizumab with etanercept. However, this study cannot be used for the benefit assessment, in particular because of the study duration of only 12 weeks.

Irrespective of the question of whether a transfer of evidence can be considered in the present therapeutic indication, the evaluations submitted by the pharmaceutical company are unsuitable for the transfer of additional benefit. Although data for the comparison of the IXORA-S and IXORA-PEDS studies are available for evaluation times at week 48 and 52, the pharmaceutical company prepares only 24-week data in the dossier. Furthermore, only results for a part of the patient-relevant endpoints surveyed in the studies are presented.

The procedure for processing the results and transferring the additional benefit is also inconsistent and not appropriate in terms of content. The sub-populations of the IXORA-S and IXORA-PEDS studies formed by the pharmaceutical company for the transfer of evidence are ultimately not referred to in the transfer of the additional benefit; by contrast, the additional benefit of the total population of adults is transferred to all children and adolescents covered by the therapeutic indication. This is not appropriate because the formation of the sub-populations greatly restricted the population of children and adolescents covered by the marketing authorisation.

There is no discussion of the appropriate comparator therapy defined by the G-BA in the therapeutic indication for children and adolescents. The pharmaceutical company does not gather any information on the appropriate comparator therapy in the therapeutic indication of the present research question within the scope of further investigations.

Furthermore, the comparability of the disease courses of adults versus children and adolescents is subject to uncertainties because no evidence suggesting comparability was presented.

The procedure of the pharmaceutical company in obtaining information, processing the results, and transferring the additional benefit of ixekizumab from adults to children and adolescents is thus not appropriate and therefore leads to a data basis that cannot be interpreted, which is why an added benefit cannot be derived.

In the overall view, the G-BA therefore concluded that for children and adolescents with moderate to severe plaque psoriasis, the additional benefit of ixekizumab compared with the appropriate comparator therapy is not proven.

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: “Taltz is indicated for the treatment of moderate to severe plaque psoriasis in children from the age of 6 years and with a body weight of at least 25 kg and adolescents who are candidates for systemic therapy”.

The G-BA determined adalimumab or etanercept or ustekinumab as appropriate comparator therapies.

For the derivation of the additional benefit, the pharmaceutical company transfers the results of the IXORA-S study, a multi-centre, actively controlled, two-armed Phase III study comparing ixekizumab with ustekinumab in adult patients with moderate to severe plaque psoriasis to the population of children and adolescents. Irrespective of the question of whether a transfer of evidence can be considered in the present therapeutic indication, the procedure of the pharmaceutical company in obtaining information, processing the results, and transferring the additional benefit of ixekizumab from adults to children and adolescents is thus not appropriate and therefore leads to a data basis that cannot be interpreted, which is why an added benefit cannot be derived. Furthermore, the comparability of the disease courses of adults versus children and adolescents is subject to uncertainties because no proof suggesting comparability was presented.

In the overall view, the G-BA therefore concluded that for children and adolescents with moderate to severe plaque psoriasis, the additional benefit of 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 the overall view, the calculation of the number is subject to uncertainties; at least for the upper limit, an overestimation of the patient numbers must be assumed.

The subsequent IQWiG investigation on patient numbers also does not contradict the derivation.

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: 8 December 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.

According to the product information, the use of etanercept for the treatment of plaque psoriasis is intended for 24 weeks; however a renewed treatment with etanercept may be indicated.

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				
Adalimumab	1 × every 14 days	26.1	1	26.1
Etanercept	1 × every 7 days	24	1	24
Ustekinumab	1 × every 84 days	4.3	1	4.3

Usage and consumption:

For the calculation of the dosages as a function of body weight, the minimum body weight of 25 kg corresponding to the therapeutic indication to be assessed and the average body measurements from the official representative statistics “Microcensus 2017 – Body measurements of the population” were taken as a basis (average body weight of 17 < 18 year olds: 67.0 kg).[2]

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

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					
Adalimumab	20 mg – 40 mg	20 mg – 40 mg	1 × 20 mg – 1 × 40 mg	26.1 26.1	26.1 × 20 mg – 26.1 × 40 mg
Etanercept	0.8 mg/kg BW from 62.5 kg BW	20 mg – 50 mg	1 × 25 mg – 1 × 50 mg	24 24	24 × 25 mg – 24 × 50 mg
Ustekinumab	18.8 mg– 45 mg	18.8 mg– 45 mg	1 × 45 mg	4.3	4.3 × 45 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 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 IFE	€ 4,175.73	€ 1.77	€ 0.00	€ 4,173.96
Ixekizumab	3 PEN	€ 4,175.73	€ 1.77	€ 0.00	€ 4,173.96
Appropriate comparator therapy					
Adalimumab 20 mg	1 SFI	€ 255.95	€ 1.77	€ 13.56	€ 240.62
Adalimumab 40 mg	6 SFI	€ 2,804.66	€ 1.77	€ 156.90	€ 2,645.99
Etanercept 25 mg[3]	24 DSS	€ 4,290.44	€ 1.77	€ 345.36	€ 3,943.31
Etanercept 50 mg[3]	12 SFI	€ 4,231.41	€ 1.77	€ 340.54	€ 3,889.10
Ustekinumab 45 mg	1 IFE	€ 5,258.42	€ 1.77	€ 297.03	€ 4,959.62
Ustekinumab 45 mg	1 SFI	€ 5,258.42	€ 1.77	€ 297.03	€ 4,959.62
Abbreviations: IFE = injection solution for prefilled syringe; SFI = solution for injection; PEN = injection solution in a prefabricated pen; DSS = dry substance with solvent					

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 (adalimumab, etanercept, and ustekinumab), costs for testing for both active and inactive (latent) tuberculosis infections are regularly incurred. 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 should be tested for the presence of HBV infection before initiating treatment with adalimumab and etanercept. On the other hand, these examinations are not required for the use of ustekinumab and are also not usually required for the use of ixekizumab as a medicinal product to be assessed. For the diagnosis of a suspected chronic hepatitis B, well coordinated steps are necessary[4]. A serological step-by-step diagnostic initially consists

[3] Fixed reimbursement rate
[4] "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

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				
Adalimumab Etanercept 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 for BCG) (GOP 32670)	1	€ 58.00	€ 58.00
Adalimumab Etanercept Ustekinumab	Chest radiograph (GOP 34241)	1	€ 16.24	€ 16.24
Adalimumab Etanercept	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	Anti-HBs antibody (GOP 32617)[5]	1	€ 5.50	€ 5.50
	Anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32823)[6]	1	€ 89.50	€ 89.50

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.

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

4. Process sequence

At its session on 25 June 2019, the Subcommittee on Medicinal Products determined 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.

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	25 June 2019	Determination 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 an assessment of the patient numbers
Working group Section 35a	15 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