Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Ozanimod (new therapeutic indication: ulcerative colitis)

of 16 June 2022

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 the 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient ozanimod (Zeposia) was listed for the first time on 15 July 2020 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 18 November 2021, ozanimod received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 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, 12.12.2008, p. 7).

On 8 December 2021, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, No.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 ozanimod with the new therapeutic

indication (ulcerative colitis, pretreated patients) 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 15 March 2022, 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 ozanimod compared to 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 statements submitted in the written statement and oral hearing procedure. 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 ozanimod.

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 Ozanimod (Zeposia) in accordance with the product information

Zeposia is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

Therapeutic indication of the resolution (resolution of 16.06.2022):

See new therapeutic indication according to marketing authorisation.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, were intolerant to, or were contraindicated for conventional therapy.

Appropriate comparator therapy for ozanimod:

- A TNF-α antagonist (adalimumab or infliximab or golimumab) or vedolizumab or ustekinumab

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

b) Adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor) or a corresponding treatment.

Appropriate comparator therapy for ozanimod:

- A change of therapy to vedolizumab or tofacitinib or ustekinumab or a TNF-α antagonist (adalimumab or infliximab or golimumab), in each case taking into account the marketing authorisation and the previous therapy/ therapies

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 G-BA 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. For the treatment of ulcerative colitis (UC), the medicinal products approved in the therapeutic indication are 5-aminosalicylates (mesalazine, sulfasalazine, olsalazine), glucocorticoids, azathioprine, TNF-α antagonists (infliximab, adalimumab, golimumab), the interleukin inhibitor ustekinumab, the integrin inhibitor vedolizumab and the JAK inhibitors tofacitinib and filgotinib, depending on the severity grade of the disease. 6-mercaptopurine does not have a marketing authorisation in Germany for the treatment of UC.

on 2. A non-medicinal treatment cannot be considered as an appropriate comparator therapy in this therapeutic indication. Surgical resection is a patient-individual decision made on a case-by-case basis, which does not represent the standard case and is not to be taken into account for the determination of the appropriate comparator therapy.

on 3. There is a resolution of the G-BA on the prescribability of Escherichia coli for ulcerative colitis. Escherichia coli was taken off from the exclusion from prescriptions according to AM-RL Annex III No. 22. The prescription of Escherichia coli strain Nissle 1917 is only permitted for the treatment of ulcerative colitis in the remission phase when mesalazine is not tolerated.

Furthermore, in the therapeutic indication, there are resolutions of the G-BA on the benefit assessment of active ingredients according to Section 35a SGB V for the treatment of ulcerative colitis. For the active ingredient vedolizumab, the resolution of 8 January 2015; for the active ingredient tofacitinib, the resolution of 21 February 2019; and for the active ingredient filgotinib, the resolution of 19 May 2022.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as 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 according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V.

On the basis of the established therapy algorithms and approved medicinal products in the present therapeutic indication, the G-BA divided the patient groups as follows:

a) Adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, were intolerant to, or were contraindicated for conventional therapy.

b) Adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor) or a corresponding treatment.

A further differentiation of the patient population, in the sense of patients who have failed any biological therapy, is not undertaken at this time due to a lack of delimiting criteria as well as a lack of uniform therapy recommendations.

The therapeutic indication for ozanimod includes only adult patients with moderately to severe active ulcerative colitis. Based on the systematic literature review, no recommendations can be derived for the use of Escherichia coli in the treatment of moderately to severe active ulcerative colitis after failure of conventional therapy or therapy with biologic agents.

It is assumed that for patients who are still eligible for medicinal therapy, surgical resection represents a patient-individual case-by-case decision when required, which does not represent the standard case and is therefore not to be considered for the determination of the appropriate comparator therapy.

When determining the appropriate comparator therapy for patients, extensive published data and guidelines are available.

a) After failure of conventional therapy, three TNF-α antagonists (adalimumab or infliximab or golimumab) whose efficacy and tolerability are equally supported by the current guidelines are available. A superiority or inferiority of a particular TNF-α antagonist could not be identified. The use of TNF-α antagonists, according to their

marketing authorisation, requires that patients have an inadequate response to, or intolerance or contraindication to, conventional therapy, including corticosteroids and 6-mercaptopurine or azathioprine. The therapeutic indication of the integrin inhibitor vedolizumab and the monoclonal antibody against interleukin 12/13 ustekinumab presupposes that the patients have either responded inadequately to conventional therapy or a biologic agent or no longer respond to it. According to the guideline, these treatment options are equally recommended for patients who respond inadequately to conventional therapy or who cannot tolerate it. A prioritisation of individual biologic agents is currently not given due to the lack of comprehensive head-to-head comparisons, so that current recommendations propose the TNF-alpha inhibitors infliximab, adalimumab, golimumab as well as vedolizumab or ustekinumab as equally appropriate therapy alternatives in the treatment setting after failure of a conventional therapy.

b) With regard to therapeutic efficacy, no evidence-based information was found that any of the active ingredients included in the appropriate comparator therapy is generally preferable in patients with moderately to severe active ulcerative colitis who have already failed to respond to a biologic agent. Thus, the appropriate comparator therapy for these patients includes the TNF-alpha inhibitors infliximab, adalimumab, golimumab, and vedolizumab or ustekinumab or tofacitinb. However, the authorisation status and previous therapy/therapies must be taken into account. A change of the product class or a change within the product class is possible. The active ingredients in question are equally appropriate therapy alternatives in the treatment setting after failure of therapy with a biologic agent.

The JAK inhibitor filgotinib has only recently been approved for the treatment of ulcerative colitis. Due to currently limited experience with this active ingredient in care and the ongoing EMA PRAC procedure on the class effect of JAK inhibitors, filgotinib does not represent a specific appropriate comparator therapy at this time, neither after failure of conventional therapy nor after failure of therapy with a biologic agent.

Change of the appropriate comparator therapy:

In the context of the written statement procedure on the present benefit assessment of ozanimod, the clinical experts stated that the current clinical significance of tofacitinib for the treatment of adults in patient population a) is no longer comparable with the other named treatment options of the appropriate comparator therapy, even taking into account the known side effects. Even taking into account the ongoing EMA PRAC[2]procedure on the class effect of JAK inhibitors, the JAK inhibitor tofacitinib is therefore not an equally appropriate treatment option at this time for a) adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, were intolerant to, or were contraindicated for conventional therapy.

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

[2]Pharmacovigilance Risk Assessment Committee

2.1.3 Extent and probability of the additional benefit

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

a) Adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, were intolerant to, or were contraindicated for conventional therapy.

An additional benefit is not proven.

b) Adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor) or a corresponding treatment.

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit of ozanimod compared with the appropriate comparator therapy in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent, no suitable data are available for the comparison of ozanimod with the appropriate comparator therapy determined by the G-BA.

Instead, the pharmaceutical company presents the results of the TRUE NORTH study, which is a randomised, double-blind, 2-phase (induction and maintenance phases) study comparing ozanimod with placebo. Adult patients (18-75 years) with moderately to severely active ulcerative colitis was enrolled in the study. Patients who had been pretreated with conventional therapies only as well as those who had already received biologic agents for the treatment of ulcerative colitis were enrolled in the study. During the entire study phase, the use of other active ingredients was not planned according to the study protocol.

The TRUE NORTH study is therefore not suitable for assessing the additional benefit of ozanimod in comparison with the G-BA's appropriate comparator therapy, as an active therapy in the sense of the appropriate comparator therapy is not implemented for patients treated with placebo in the study.

In the absence of direct comparator data, the pharmaceutical company examines the possibility of conducting an adjusted indirect comparison via the bridge comparator placebo. To do this, it identifies its RCT TRUE NORTH on the basis of its inclusion criteria on the intervention side.

The pharmaceutical company argues that the TRUE NORTH study, which consists of an induction phase and a maintenance phase, is however not suitable for conducting an adjusted indirect comparison for methodological reasons (including the selection and re-randomisation of ozanimod responders from the induction phase for the maintenance phase). For this reason, the pharmaceutical company refrains from conducting a systematic search for RCTs

with active ingredients of the appropriate comparator therapy and from conducting an adjusted indirect comparison.

In the overall assessment, this means that for a) adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, were intolerant to, or were contraindicated for conventional therapy and for b) adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor) or a corresponding treatment, an additional benefit of ozanimod compared with the appropriate comparator therapy has not been proven in each case.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of ozanimod for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent.

The pharmaceutical company presents the results of the TRUE NORTH study, which is a randomised, double-blind, 2-phase (induction and maintenance phases) study comparing ozanimod with placebo.

For patients treated with placebo in the TRUE NORTH study, active therapy in the sense of the appropriate comparative therapy has not been implemented. The study is therefore not suitable for assessing the additional benefit of ozanimod compared to the G-BA's appropriate comparator therapy.

In the absence of direct comparator data, the pharmaceutical company examines the possibility of conducting an adjusted indirect comparison via the bridge comparator placebo. To do this, it identifies its RCT TRUE NORTH on the basis of its inclusion criteria on the intervention side.

The pharmaceutical company argues that the TRUE NORTH study, which consists of an induction phase and a maintenance phase, is, however, not suitable for conducting an adjusted indirect comparison for methodological reasons. For this reason, the pharmaceutical company refrains from conducting a systematic search for RCTs with active ingredients of the appropriate comparator therapy and from conducting an adjusted indirect comparison.

Therefore, no suitable data are available to assess the additional benefit of ozanimod compared with the appropriate comparator therapy in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic agent.

This does not provide any hint for an additional benefit of ozanimod compared with the appropriate comparator therapy for both patient populations; an additional benefit is therefore not proven in each case.

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).

The information from the benefit assessment procedure for tofacitinib (resolution of 21.02.2019) is used to determine the number of patients in the target population in SHI.

The SHI target population presented at that time in the procedure for tofacitinib was also fraught with uncertainties. Despite the uncertainties, the figures from the tofacitinib study are assessed as less uncertain than those provided by the pharmaceutical company in the present study and the figures of the pharmaceutical company in the benefit assessment procedure on filgotinib (resolution of 19.05.2022).

Based on the documents submitted so far on the SHI target population, taking into account the most current sources, it can be assumed that the number of patients in both patient populations is rather in the upper range.

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 Zeposia (active ingredient: ozanimod) at the following publicly accessible link (last access: 30 May 2022):
https://www.ema.europa.eu/en/documents/product-information/zeposia-epar-product-information_en.pdf

Treatment with ozanimod should only be initiated and monitored by doctors experienced in treating adults with ulcerative colitis.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide a checklist for doctors, a guideline for patients and caregivers as well as a patient reminder card. The training and information material contains, in particular, instructions on how to deal with the side effects potentially occurring with ozanimod and on embryo-foetal toxicity.

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 May 2022).

Treatment period:

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.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Ozanimod	continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Patient population a)				
Adalimumab	continuously, every 14 days	26.1	1	26.1
Golimumab	continuously, every 28 days	13.0	1	13.0
Infliximab	continuously, every 56 days	6.5	1	6.5
Ustekinumab	continuously, every 84 days	4.3	1	4.3
Vedolizumab	continuously, every 14 days	26.1	1	26.1
Patient population b)				
Adalimumab	continuously, every 14 days	26.1	1	26.1
Golimumab	continuously, every 28 days	13.0	1	13.0
Infliximab	continuously, every 56 days	6.5	1	6.5
Tofacitinib	continuously, 2 x daily	365	1	365
Ustekinumab	continuously, every 84 days	4.3	1	4.3
Vedolizumab	continuously, every 14 days	26.1	1	26.1

Consumption:

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.

For the calculation of the consumption of medicinal products to be dosed according to weight, the G-BA generally uses non-indication-specific average weights as a basis. Therefore, an average body weight of 77 kg is assumed for the German population aged 18 years and older, according to the official representative statistics "Microcensus 2017"[3]. Consequently, patient-individual weight differences between women and men, which may be above or below the average value of 77 kg, are not taken into account for the cost calculation.

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					
Ozanimod	0.92 mg	0.92 mg	1 x 0.92 mg	365	365 x 0.92 mg
Appropriate comparator therapy					
Patient population a)					
Adalimumab	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Golimumab	50 mg	50 mg	1 x 50 mg	13	13.0 x 50 mg
Infliximab	5 mg / kg BW	385 mg	4 x 100 mg	6.5	26 x 100 mg
Ustekinumab	90 mg	90 mg	1 x 90 mg	4.3	4.3 x 90 mg
Vedolizumab	108 mg	108 mg	1 x 108 mg	26.1	26.1 x 108 mg
Patient population b)					
Adalimumab	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Golimumab	50 mg	50 mg	1 x 50 mg	13	13.0 x 50 mg
Infliximab	5 mg / kg BW	385 mg	4 x 100 mg	6.5	26 x 100 mg
Tofacitinib	5 mg	10 mg	2 x 5 mg	365	730 x 5 mg
Ustekinumab	90 mg	90 mg	1 x 90 mg	4.3	4.3 x 90 mg
Vedolizumab	108 mg	108 mg	1 x 108 mg	26.1	26.1 x 108 mg

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 Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction

[3] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

of the statutory rebates. If a fixed reimbursement rate is available, this will be used as the basis for calculating the costs.

Costs of the medicinal products:

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					
Ozanimod 0.92 mg	98 HC	€ 6,310.37	€ 1.77	€ 0.00	€ 6,308.60
Appropriate comparator therapy					
Adalimumab 40 mg[4]	6 SFI	€ 2,859.17	€ 1.77	€ 228.57	€ 2,628.83
Golimumab 50 mg	3 IFE	€ 2,605.92	€ 1.77	€ 207.91	€ 2,396.24
Infliximab 100 mg	5 PIC	€ 3,490.53	€ 1.77	€ 280.08	€ 3,208.68
Tofacitinib 5 mg	182 FCT	€ 3,134.85	€ 1.77	€ 0.00	€ 3,133.08
Ustekinumab 90 mg	1 IFE	€ 5,284.67	€ 1.77	€ 298.52	€ 4,984.38
Vedolizumab 108 mg	6 SFI	€ 3,769.65	€ 1.77	€ 212.00	€ 3,555.88
Abbreviations: FCT = film-coated tablets, HC = Hard capsules, IFE = solution for injection in a pre-filled syringe, SFI = solution for injection, PIC = powder for the preparation of an infusion solution concentrate					

LAUER-TAXE® last revised: 15 May 2022

<u>Costs for additionally required SHI services:</u>

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.

Diagnosis of tuberculosis

For active ingredients of the appropriate comparator therapy (adalimumab, golimumab, infliximab, tofacitinib, ustekinumab, vedolizumab), costs are regularly incurred for

[4] Fixed reimbursement rate

examination of 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)). In addition, a chest radiograph is usually required to detect pulmonary tuberculosis. The tuberculin skin test is not presented due to lack of sensitivity and specificity as well as the possibility of "sensitisation". These tests are not required when using ozanimod.

Diagnosis of chronic hepatitis B

Patients must be tested for the presence of HBV infection prior to initiating treatment with adalimumab or golimumab or infliximab or tofacitinib. These studies are not to be carried out regularly when using ozanimmod as the medicinal product to be assessed and when using ustekinumab or vedolizumab as the appropriate comparator therapy. For the diagnosis of suspected chronic hepatitis B, sensibly coordinated steps are required[5]. A step-by-step serological 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.

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
Appropriate comparator therapy for patient populations a and b				
Adalimumab Golimumab Infliximab Tofacitinib Ustekinumab Vedolizumab	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
Adalimumab Golimumab Infliximab Tofacitinib Ustekinumab Vedolizumab	Chest radiograph (GOP 34241)	1	16.45	€ 16.45
Adalimumab Golimumab Infliximab Tofacitinib	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	Anti-HBs antibody (GOP 32617)[6]	1	€ 5.50	€ 5.50

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

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
	Anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32823)[7]	1	€ 89.50	€ 89.50

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount 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 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 containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

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 8 June 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

[7] Invoicing for GOP 32823 possible before or during antiviral therapy with interferon and/or nucleic acid analogues.

On 8 December 2021, the pharmaceutical company submitted a dossier for the benefit assessment of ozanimod to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2, sentence 2 VerfO.

By letter dated 14 December 2021 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 ozanimod.

The dossier assessment by the IQWiG was submitted to the G-BA on 10 March 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 15 March 2022. The deadline for submitting written statements was 5 April 2022.

The oral hearing was held on 25 April 2022.

On 9 May 2022, the IQWiG submitted a new version of IQWiG's dossier assessment to the G-BA. This version 2.0 dated 9 May 2022 replaces version 1.0 of the dossier assessment dated 9 March 2022. The assessment result was not affected by the changes in version 2.0 compared to version 1.0.

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 was discussed at the session of the subcommittee on 8 June 2022, and the draft resolution was approved.

At its session on 16 June 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	8 June 2021	Determination of the appropriate comparator therapy
Working group Section 35a	20 April 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	25 April 2022	Conduct of the oral hearing
Working group Section 35a	03.05.2022; 17.05.2022;	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	24 May 2022	Concluding discussion of the draft resolution

Plenum	16 June 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 June 2022

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken