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)
Etrasimod (ulcerative colitis, pretreated, ≥ 16 years)

of 2 October 2024

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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 all 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 relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient etrasimod on 15 April 2024 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 12 April 2024.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 July 2024 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of etrasimod 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 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 etrasimod.

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 Etrasimod (Velsipity) in accordance with the product information

Velsipity is indicated for the treatment of patients 16 years of age and older 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 biological agent.

Therapeutic indication of the resolution (resolution of 02.10.2024):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to conventional therapy

Appropriate comparator therapy for etrasimod:

- Adalimumab or golimumab or infliximab or ozanimod or ustekinumab or vedolizumab

b) Adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)

Appropriate comparator therapy for etrasimod:

- Adalimumab or filgotinib or golimumab or infliximab or ozanimod or tofacitinib or ustekinumab or vedolizumab

1 General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. In addition to the medicinal product to be assessed here, the following medicinal products are approved for the treatment of ulcerative colitis in adults: 5-aminosalicylates (mesalazine, olsalazine, sulfasalazine), azathioprine, glucocorticoids, TNF-α antagonists (adalimumab, golimumab, infliximab), interleukin inhibitors (mirikizumab, ustekinumab), the integrin inhibitor vedolizumab, JAK inhibitors (filgotinib, tofacitinib, upadacitinib) and the sphingosine-1-phosphate receptor modulator ozanimod.

In contrast, for 16 and 17-year-olds, only the following active ingredients in addition to the medicinal product to be assessed here are approved for the treatment of ulcerative colitis: 5-aminosalicylates (mesalazine, sulfasalazine), azathioprine, glucocorticoids and the TNF-α antagonists infliximab (only for severe ulcerative colitis) and adalimumab.

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 in the indication of ulcerative colitis. Escherichia coli was exempt from the exclusion from prescription according to Annex III No. 22 of the Pharmaceuticals Directive. 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, for the active ingredient filgotinib, the resolution of 19 May 2022, for the active ingredient ozanimod, the resolution of 16 June 2022, for the active ingredient upadacitinib, the resolution of 16 February 2023 and for the active ingredient mirikizumab, the resolution of 18 January 2024.

There is also a resolution on the off-label use (Annex VI to Section K of the Pharmaceuticals Directive, Part A) of 6-mercaptopurine for immunosuppression in the therapy of chronic inflammatory bowel disease (resolution of 21 October 2021).

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 and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to conventional therapy

b) Adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)

A further differentiation of the patient population, in the sense of subjects 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.

Extensive published data and guidelines are available for the indication of moderately to severely active ulcerative colitis to be assessed.

Conventional treatment for ulcerative colitis includes 5-aminosalicylates, azathioprine, glucocorticoids and 6-mercaptopurine. These active ingredients or product classes are therefore no longer considered as appropriate comparator therapy for the present treatment setting.

Accordingly, TNF-α antagonists (adalimumab, golimumab, infliximab), interleukin inhibitors (mirikizumab, ustekinumab), JAK inhibitors (filgotinib, tofacitinib, upadacitinib), the integrin inhibitor vedolizumab, and the sphingosine-1-phosphate receptor modulator ozanimod as appropriate comparator therapy can still be considered as approved medicinal treatment options.

The current German S3 guideline[2] Ulcerative Colitis equally recommends these active ingredients for patients with moderately to severely active ulcerative colitis who have had an inadequate response or lost response to conventional therapy or therapy with TNF-α antagonists. Individual active ingredients or product classes are not prioritised due to missing or inadequate comparator data.

However, in view of the fact that the use of JAK inhibitors is associated with an increased risk of serious side effects[3], the G-BA believes that filgotinib, tofacitinib and upadacitinib do not have the same significance in clinical care as the other active ingredients recommended in the guidelines in the earlier treatment setting, i.e. after failure of or intolerance to conventional therapy. The JAK inhibitors filgotinib, tofacitinib and upadacitinib are therefore not determined as appropriate comparator therapy for patient group a).

However, for patients who require further therapy escalation and thus a broader spectrum of therapy options in this difficultly adjustable treatment setting, as they have already responded inadequately to a biologic agent or have not tolerated it (patient group b), the JAK inhibitors filgotinib, tofacitinib and upadacitinib are viewed to be another suitable therapy option, taking into account the authorisation status and previous therapy (therapies), and are therefore considered as appropriate comparator therapy for this patient group.

After failure of a previous therapy with a biologic agent, especially for active ingredients that do not belong to the product class of TNF-α antagonists, the body of evidence is small overall. The S3 guideline[2] contains specific therapy recommendations for this treatment setting only in the event of failure on TNF-α antagonists. In the event of primary or secondary failure of therapy with TNF-α antagonists, a switch to interleukin inhibitors (mirikizumab, ustekinumab), JAK inhibitors (filgotinib, tofacitinib,

[2] Kucharzik T et al. Updated S3 guideline ulcerative colitis (version 6.2). Z Gastroenterol 2024; 62: 769–858
[3] see product information for Xeljanz (tofacitinib) last revised October 2023, Jyseleca (filgotinib) last revised July 2024, Rinvoq (upadacitinib) last revised July 2024

upadacitinib), the integrin inhibitor vedolizumab, the sphingosine-1-phosphate receptor modulator ozanimod or calcineurin inhibitors should be made after possible intensification of therapy. Switching to an alternative TNF-α antagonist is only recommended as one of the therapy options in the event of secondary failure. Calcineurin inhibitors are not approved in the present therapeutic indication.

Overall, in this line of therapy, a change of product class or a change within the product class is considered appropriate. However, in the event of primary failure on a TNF-α antagonist, switching within the product class is not recommended due to the low success rate. When selecting the active ingredient for patient group b), the previous therapy and also the authorisation status must be taken into account in general.

The active ingredients upadacitinib and mirikizumab were only recently approved in the ulcerative colitis indication (marketing authorisation on 22 July 2022 and 26 May 2023 respectively). No additional benefit of each one of the two active ingredients compared with the appropriate comparator therapy was shown in the benefit assessment. So far, there is only limited experience with these active ingredients in care, which is why the significance cannot be conclusively assessed. Overall, the G-BA therefore came to the conclusion that these active ingredients should not be determined as appropriate comparator therapy in either patient group a) or patient group b).

Based on the available evidence, no recommendations can be derived for the use of Escherichia coli in the treatment of moderately to severely active ulcerative colitis after failure of conventional therapies or therapy with biologic agents.

It is also assumed that a patient-individual, case-by-case decision may be made on surgical resection for patients who are still eligible for medicinal therapy; however, this does not represent the standard case. Thus, surgical resection is not considered for the determination of the appropriate comparator therapy.

In the overall assessment, the active ingredients adalimumab, golimumab, infliximab, ozanimod, ustekinumab and vedolizumab are determined to be equally appropriate therapy options for patient group a) adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to conventional therapy.

For patient group b) adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor), a change of therapy to adalimumab, filgotinib, golimumab, infliximab, ozanimod, tofacitinib, ustekinumab or vedolizumab is determined as the appropriate comparator therapy. For all options, both the previous therapy given in each case and the marketing authorisation of the respective active ingredients must be taken into account. For example, only the TNF-α antagonists adalimumab and infliximab (only for severe ulcerative colitis) are approved for 16 and 17-year-olds. Consequently, only these active ingredients can be considered as appropriate therapy options for 16 and 17-year-olds in both patient groups.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

a) For adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to conventional therapy, the additional benefit is not proven.
b) For adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor), the additional benefit is not proven.

Justification:

No direct comparator data of etrasimod versus the appropriate comparator therapy is neither available for patient group a) nor patient group b).

In the dossier, the pharmaceutical company presented the data from the randomised ELEVATE UC 52 study for the comparison of etrasimod with placebo. Adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to at least one conventional therapy or at least one therapy with a biologic agent or a JAK inhibitor were enrolled. During the entire 52-week study phase, the use of all active ingredients listed in the G-BA's appropriate comparator therapy was prohibited in accordance with the study protocol. The study is thus unsuitable for deriving an additional benefit of etrasimod compared to the appropriate comparator therapy.

In the overall assessment, this means that an additional benefit of etrasimod compared with the appropriate comparator therapy is not proven for both patient group a) adults and adolescents aged 16 years and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to conventional therapy and for patient group b) adults and adolescents aged 16 years and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to a biologic agent (TNF-α antagonist, integrin inhibitor or interleukin inhibitor).

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Velsipity" with the active ingredient etrasimod. Etrasimod is indicated for the treatment of patients 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or a biological agent.

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

a) Adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to conventional therapy
b) Adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)

For both patient groups, there are no direct comparator studies of etrasimod versus the appropriate comparator therapy.

In the dossier, the pharmaceutical company presented the data from the randomised ELEVATE UC 52 study, comparing etrasimod with placebo. Due to the lack of comparison with an active ingredient of the appropriate comparator therapy, the data presented are therefore unsuitable for deriving an additional benefit.

In the overall assessment, an additional benefit of etrasimod over the appropriate comparator therapy is thus not proven for patient group a) as well as patient group b).

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 resolution is based on the information from the dossier assessment of the IQWiG (mandate A24-42). In addition, another source that was subsequently submitted by the pharmaceutical company in the written statement procedure was taken into account. The source by Dignass et al. provides new data on the prevalence of ulcerative colitis in adults in the SHI in 2022, which is favoured due to its timeliness. Furthermore, it is assumed that the sole consideration of the percentage value of 8.8% – instead of a range from 3.9% to 8.8% – is appropriate for patients who are prescribed biologic agents. Moreover, in the absence of suitable data for the breakdown between patient groups a and b, the previous percentage values of 66% and 34% respectively are estimated.

Overall, the number of patients is nevertheless subject to uncertainty. On the one hand, only adults are considered, whereby the number of patients 16 and 17 years of age is estimated to be relatively small. On the other, the routine data analysis on which the calculation is based does not take into account patients who have had an inadequate response to conventional therapy but have not (yet) been switched to a biologic agent.

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 Velsipity (active ingredient: etrasimod) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 15 April 2024):

https://www.ema.europa.eu/en/documents/product-information/velsipity-epar-product-information_en.pdf

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

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (including pregnancy-specific patient pass). The training material contains, in particular, instructions on how to deal with the side effects potentially occurring with etrasimod and on embryo-foetal toxicity.

Prior to treatment with etrasimod, all patients should take an electrocardiogram (ECG) to detect any pre-existing cardiac abnormalities.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 September 2024).

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) 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.

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 varies from patient to patient 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.

In addition to the assessed medicinal product etrasimod, only the active ingredients adalimumab and infliximab are approved for adolescents 16 years of age and older.

For dosages depending on body weight (BW), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were used as a basis (average body weight of those 16 years of age older 66.5 kg and those 18 years of age older 77.7 kg) [4].

Treatment period:

a) Adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to conventional therapy

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Etrasimod	Continuously, 1 x daily	365.0	1	365.0
Appropriate comparator therapy				

4 Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
A TNF-α antagonist (adalimumab or golimumab or infliximab) or vedolizumab or ustekinumab or ozanimod				
Adalimumab	Continuously, every 14 days	26.1	1	26.1
Golimumab	Continuously, every 28 days	13.0	1	13.0
Infliximab[5]	Continuously, every 56 days	6.5	1	6.5
Infliximab	Continuously, every 14 days	26.1	1	26.1
Vedolizumab	Continuously, every 14 days	26.1	1	26.1
Ustekinumab	Continuously, every 84 days	4.3	1	4.3
Ozanimod	Continuously, 1 x daily	365.0	1	365.0

5 Calculation for adolescents 16 years of age and older

b) Adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Etrasimod	Continuously, 1 x daily	365.0	1	365.0
Appropriate comparator therapy				
Vedolizumab or tofacitinib or ustekinumab or filgotinib or ozanimod or a TNF-α antagonist (adalimumab or golimumab or infliximab)				
Vedolizumab	Continuously, every 14 days	26.1	1	26.1
Tofacitinib	Continuously, 2 x daily	365.0	1	365.0
Ustekinumab	Continuously, every 84 days	4.3	1	4.3
Filgotinib	Continuously, 1 x daily	365.0	1	365.0
Ozanimod	Continuously, 1 x daily	365.0	1	365.0
Adalimumab	Continuously, every 14 days	26.1	1	26.1
Golimumab	Continuously, every 28 days	13.0	1	13.0
Infliximab[5]	Continuously, every 56 days	6.5	1	6.5
Infliximab	Continuously, every 14 days	26.1	1	26.1

Consumption:

a) Adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to conventional therapy

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					
Etrasimod	2 mg	2 mg	1 x 2 mg	365.0	365 x 2 mg
Appropriate comparator therapy					
A TNF-α antagonist (adalimumab or golimumab or infliximab) or vedolizumab or ustekinumab or ozanimod					
Adalimumab[5]	80 mg	80 mg	1 x 80 mg	26.1	26.1 x 80 mg
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	13.0	13.0 x 50 mg
Infliximab[5]	5 mg/kg BW = 332.5 mg	332.5 mg	1 x 330 mg	6.5	6.5 x 330 mg
Infliximab	120 mg	120 mg	1 x 120 mg	26.1	26.1 x 120 mg
Vedolizumab	108 mg	108 mg	1 x 108 mg	26.1	26.1 x 108 mg
Ustekinumab	90 mg	90 mg	1 x 90 mg	4.3	4.3 x 90 mg
Ozanimod	0.92 mg	0.92 mg	1 x 0.92 mg	365.0	365 x 0.92 mg

b) Adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)

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					
Etrasimod	2 mg	2 mg	1 x 2 mg	365.0	365 x 2 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
Vedolizumab or tofacitinib or ustekinumab or filgotinib or ozanimod or a TNF-α antagonist (adalimumab or golimumab or infliximab)					
Vedolizumab	108 mg	108 mg	1 x 108 mg	26.1	26.1 x 108 mg
Tofacitinib	5 mg	10 mg	2 x 5 mg	365.0	730 x 5 mg
Ustekinumab	90 mg	90 mg	1 x 90 mg	4.3	4.3 x 90 mg
Filgotinib	200 mg	200 mg	1 x 200 mg	365.0	365 x 200 mg
Ozanimod	0.92 mg	0.92 mg	1 x 0.92 mg	365.0	365 x 0.92 mg
Adalimumab[5]	80 mg	80 mg	1 x 80 mg	26.1	26.1 x 80 mg
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	13.0	13.0 x 50 mg
Infliximab[5]	5 mg/kg BW = 332.5 mg	332.5 mg	1 x 330 mg	6.5	6.5 x 330 mg
Infliximab	120 mg	120 mg	1 x 120 mg	26.1	26.1 x 120 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 of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

a) Adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to conventional therapy

and

b) Adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)

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					
Etrasimod 2 mg	98 FCT	€ 4,183.54	€ 2.00	€ 235.63	€ 3,945.91
Appropriate comparator therapy					
Adalimumab 80 mg[5,6]	3 SFI	€ 2,804.97	€ 2.00	€ 0.00	€ 2,802.97
Adalimumab 40 mg[6]	6 SFI	€ 2,804.97	€ 2.00	€ 0.00	€ 2,802.97
Filgotinib 200 mg	90 FCT	€ 3,048.17	€ 2.00	€ 170.79	€ 2,875.38
Golimumab 50 mg[6]	3 SPF	€ 2,548.84	€ 2.00	€ 0.00	€ 2,546.84
Infliximab 100 mg[5.6]	3 PIC	€ 2,108.56	€ 2.00	€ 167.33	€ 1,939.23
Infliximab 120 mg	6 SPF	€ 4,118.45	€ 2.00	€ 231.91	€ 3,884.54
Ozanimod 0.92 mg	98 HC	€ 5,469.17	€ 2.00	€ 309.05	€ 5,158.12
Tofacitinib 5 mg	182 FCT	€ 2,924.03	€ 2.00	€ 0.00	€ 2,922.03
Ustekinumab 90 mg	1 SFI	€ 3,490.00	€ 2.00	€ 196.02	€ 3,291.98
Vedolizumab 108 mg	6 SFI	€ 3,632.34	€ 2.00	€ 204.15	€ 3,426.19
Abbreviations: FCT = film-coated tablets, HC = hard capsules, SPF = solution for injection in a pre-filled syringe, SFI = solution for injection, PIC = powder for the preparation of an infusion solution concentrate					

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Costs for additionally required SHI services:

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

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

Prior to administration of the active ingredients adalimumab, golimumab, infliximab, vedolizumab, ustekinumab, tofacitinib and filgotinib, patients must be examined for active

6 Fixed reimbursement rate

and inactive ("latent") tuberculosis infections. In addition, patients must be tested for the presence of an infection with hepatitis B prior to initiation of the respective therapy with the TNF-α inhibitors (adalimumab, golimumab and infliximab) and JAK inhibitors (filgotinib, tofacitinib) of the appropriate comparator therapy. Diagnostics to rule out chronic hepatitis B requires sensibly coordinated steps. 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. In certain case constellations, further steps may be necessary in accordance with current guideline recommendations[7].

a) Adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to conventional therapy

and

b) Adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
Adalimumab Golimumab Infliximab Vedolizumab Ustekinumab Tofacitinib Filgotinib	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
	Chest radiograph (GOP 34241)	1	€ 17.42	€ 17.42
Adalimumab Golimumab Infliximab Vedolizumab Ustekinumab Tofacitinib Filgotinib	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	Anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90

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7 S3 guideline on prevention, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/011; https://register.awmf.org/assets/guidelines/021-011l_S3_Prophylaxe-Diagnostik-Therapie-der-Hepatitis-B-Virusinfektion_2021-07.pdf

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1 October .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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) in its currently valid version, surcharges for the production of parenteral solutions with monoclonal antibodies amount to a maximum of € 100 per ready-to-apply unit. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the

resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit

had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

a) Adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to conventional therapy

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for etrasimod (Velsipity); Velsipity® 2 mg film-coated tablets; last revised: August 2024

b) Adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:

Product information for etrasimod (Velsipity); Velsipity® 2 mg film-coated tablets; last revised: August 2024

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 23 May 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. At its session on 23 January 2024, the Subcommittee on Medicinal Products adjusted the appropriate comparator therapy.

On 12 April 2024, the pharmaceutical company submitted a dossier for the benefit assessment of etrasimod to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 15 April 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 etrasimod.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 July 2024, and the written statement procedure was initiated with publication on the G-BA website on 15 July 2024. The deadline for submitting statements was 5 August 2024.

The oral hearing was held on 26 August 2024.

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 24 September 2024, and the proposed draft resolution was approved.

At its session on 2 October 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 May 2023	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	23 January 2024	Adjustment of the appropriate comparator therapy after positive opinion

Working group Section 35a	14 August 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	26 August 2024	Conduct of the oral hearing
Working group Section 35a	4 September 2024 18 September 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	24 September 2024	Concluding discussion of the draft resolution
Plenum	2 October 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 2 October 2024

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

Prof. Hecken