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)
Upadacitinib (new therapeutic indication: Crohn's disease, pretreated)

of 19 October 2023

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 upadacitinib (Rinvoq) was listed for the first time on 1 February 2020 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 12 April 2023, upadacitinib 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, sentence 7).

On 24 April 2023, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient upadacitinib with the new

therapeutic indication "RINVOQ is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent." 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 dossier assessment. The benefit assessment was published on 1 August 2023 on the G-BA website (www.g-ba.de), therefore 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 upadacitinib 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 was not used in the benefit assessment of upadacitinib.

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 Upadacitinib (Rinvoq) in accordance with the product information

Crohn's disease

RINVOQ is indicated for the treatment of adult patients with moderately to severely active Crohn's disease 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 19.10.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy

Appropriate comparator therapy for upadacitinib:

A TNF-α antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)

b) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)

Appropriate comparator therapy for upadacitinib:

A change of therapy to a TNF-α antagonist (adalimumab or infliximab) or integrin inhibitors (vedolizumab) or interleukin inhibitors (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 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. Taking into account the specifications in the respective product information, medicinal products that are generally approved in the therapeutic indication, in addition to the medicinal product to be assessed here, are corticosteroids (topical, systemic: prednisone, prednisolone, hydrocortisone acetate, methylprednisolone budenoside), Indian psyllium seed and psyllium seed husk, immunosuppressants (azathioprine, methotrexate) as well as 5-aminosalicylates (mesalazine, sulphasalazine), TNF-α antagonists infliximab and adalimumab, the interleukin inhibitors ustekinumab and risankizumab as well as the integrin inhibitor vedolizumab. The therapeutic indications for mesalazine, sulphasalazine, methotrexate and budesonide are only partially consistent with the indication "moderately to severely active Crohn's disease".

on 2. A non-medicinal treatment cannot be considered as an appropriate comparator therapy in this therapeutic indication. Surgical resection is a patient-individual option that requires a case-by-case decision and is not the standard case. Thus, surgical resection is not to be considered for the determination of the appropriate comparator therapy.

on 3. In the therapeutic indication of Crohn's disease, there are resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient vedolizumab dated 8 January 2015 and for the active ingredient risankizumab dated 15 June 2023.

In addition, there is a resolution on the amendment to the Pharmaceuticals Directive (AM-RL): Annex VI (off-label use) - 6-mercaptopurine for immunosuppression in the therapy of chronic inflammatory bowel diseases (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 therapeutic indication.

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 therapeutic indication according to Section 35a, paragraph 7 SGB V.

Extensive published data as well as guidelines are available for determining the appropriate comparator therapy for patients who are eligible for systemic therapy. 5-aminosalicylates, corticosteroids and immunosuppressants were not further considered in the determination of the appropriate comparator therapy, as the therapeutic indication of upadacitinib requires an inadequate response or no longer present response or intolerance to conventional therapy. Indian psyllium and psyllium husks are only used as supportive therapy in Crohn's disease and are therefore not considered as an appropriate comparator therapy.

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 Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy.
b) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor).

a) After failure of conventional therapy, two TNF-α antagonists whose efficacy and tolerability are equally supported by the current guidelines (including the German S3 guideline) are available. The administration of TNF-α antagonists requires patients who have responded inadequately despite complete and adequate therapy with a glucocorticoid and/or an immunosuppressant, or who have been intolerant to such therapy, or in whom such therapy is contraindicated. According to the current German S3 guideline, the integrin inhibitor vedolizumab and the interleukin inhibitor ustekinumab are also considered equivalent to TNF-α antagonists after failure of conventional therapy. Based on the generally recognised state of medical knowledge and taking into account the German standard of care, the interleukin inhibitor risankizumab is not determined as appropriate comparator therapy for patient population as in the present resolution. Thus, the appropriate comparator therapy for

patient population an includes the TNF-alpha inhibitors infliximab and adalimumab, as well as the integrin inhibitor vedolizumab and the interleukin inhibitor ustekinumab.

b) When determining the appropriate comparator therapy for patients who failed a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor), the evidence search showed the availability of four options – infliximab, adalimumab, the integrin inhibitor vedolizumab and the interleukin inhibitor ustekinumab. With regard to therapeutic efficacy as well as to the question of the side-effect profile or the safety risk, no evidence-based information was found that one of the four active ingredients mentioned is generally preferable in patients who have a failed response to a biologic agent. As already described above, no prioritisation can be made within the TNF-α antagonists either. In addition to a change of product class, a change within the product class can also be considered. The addition of "A change of therapy to" merely clarifies linguistically that the unchanged continuation of the previous therapy is not regarded as implementation of the appropriate comparator therapy. Based on the generally recognised state of medical knowledge and taking into account the German standard of care, the interleukin inhibitor risankizumab is not determined as appropriate comparator therapy for patient population b in the present resolution. Thus, the appropriate comparator therapy for patient population b includes the TNF-alpha inhibitors infliximab and adalimumab, as well as the integrin inhibitor vedolizumab and the interleukin inhibitor ustekinumab. These active ingredients are equally suitable therapeutic alternatives in the described treatment setting.

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 upadacitinib is assessed as follows:

a) <u>Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy</u>

An additional benefit is not proven.

b) <u>Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)</u>

An additional benefit is not proven.

Justification:

For adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent, there are no direct comparator studies of upadacitinib versus the appropriate

comparator therapy. Furthermore, no indirect comparison was submitted. Accordingly, there are no relevant data for the benefit assessment of upadacitinib.

Thus, for a) adults with moderately to severely active Crohn's disease who have had an inadequate response, lost response or were intolerant to conventional therapy and for b) adults with moderately to severely active Crohn's disease who have had an inadequate response, lost response or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor), an additional benefit of upadacitinib 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 a new therapeutic indication for the active ingredient upadacitinib.

The therapeutic indication assessed here is as follows: "for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent."

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

a) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy
b) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy (TNF-α antagonist or integrin inhibitor or interleukin inhibitor).

Patient group a)

The G-BA determined a TNF-α antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab) as the appropriate comparator therapy.

Neither direct comparator studies versus the appropriate comparator therapy nor indirect comparisons were presented.

Therefore, no data relevant for the benefit assessment of upadacitinib are available, so an additional benefit for the patient population a is not proven.

Patient group b)

The G-BA determined a change of therapy to a TNF-α antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab) as the appropriate comparator therapy.

Neither direct comparator studies versus the appropriate comparator therapy nor indirect comparisons were presented.

Therefore, no data relevant for the benefit assessment of upadacitinib are available, so an additional benefit for the patient population b 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).

The data is based on the patient numbers from the dossier of the pharmaceutical company.

Overall, the number of patients is subject to uncertainty. Operationalisation of patient population b as such with a change in therapy from one biologic agent to another results in a tendency to underestimate for this patient population. Operationalisation of patient population a as the percentage of patients who did not change a biologic agent results in a tendency to overestimate for this patient population. The quantitative extent of the under or overestimation cannot be conclusively assessed.

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 Rinvoq (active ingredient: upadacitinib) at the following publicly accessible link (last access: 21 June 2023):

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

Treatment with upadacitinib should only be initiated and monitored by doctors experienced in treating Crohn's disease.

The product class of Janus kinase (JAK) inhibitors underwent a risk assessment procedure by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA), which has been concluded on 10 March 2023 by the European Commission's[1] legally binding decision in all EU Member States. The new warnings and precautions for use included in the product information must be followed.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (incl. patient card). In particular, the training and information material contains instructions on how to deal with any side effects caused by upadacitinib, especially in serious and opportunistic infections, including TB and herpes zoster, as well as birth defects (pregnancy risk), MACE, VTE and malignancies.

Prior to initiation of therapy with upadacitinib, it is recommended checking the vaccination status of the patients.

The recommended starting dose of upadacitinib is 45 mg once daily for 12 weeks. Prolonged induction for a further 12 weeks at a dose of 30 mg once daily may be considered for patients who have not achieved sufficient therapeutic benefit after the initial 12-week induction. Upadacitinib should be discontinued for these patients if there is no evidence of therapeutic benefit after 24 weeks of treatment.

1 https://www.ema.europa.eu/en/documents/referral/janus-kinase-inhibitors-jaki-article-20-procedure-ema-confirms-measures-minimise-risk-serious-side_en.pdf

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: 1 October 2023).

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.

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 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.

a) Adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a conventional therapy or corresponding treatment

b) Adults with moderately to severely active Crohn's disease 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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Upadacitinib	Continuously, 1 x daily	365	1	365.0
Appropriate comparator therapy				
A TNF-α antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)				
Adalimumab	Continuously, 1 x every 14 days	26.1	1	26.1
Infliximab	Continuously, 1 x every 56 days	6.5	1	6.5
Ustekinumab	Continuously, 1 x every 84 days	4.3	1	4.3

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Vedolizumab	Continuously, 1 x every 14 days	26.1	1	26.1

Consumption:

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 77.0 kg).[2]

As it is not always possible to achieve the exact calculated dose per day with the commercially available dose potencies, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form.

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					
Upadacitinib	15 mg - 30 mg	15 mg – 30 mg	1 x 15 mg – 1 x 30 mg	365	365 x 15 mg – 365 x 30 mg
Appropriate comparator therapy					
A TNF-α antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)					
Adalimumab	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Infliximab	5 mg/kg BW = 385 mg	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

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

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					
Upadacitinib 15 mg	90 SRT	€ 3,568.25	€ 2.00	€ 143.21	€ 3,423.04
Upadacitinib 30 mg	90 SRT	€ 4,553.82	€ 2.00	€ 183.41	€ 4,368.41
Appropriate comparator therapy					
Adalimumab 40 mg[3]	6 SFI	€ 2,859.20	€ 2.00	€ 228.57	€ 2,628.63
Infliximab 100 mg[3]	5 PIC	€ 3,490.57	€ 2.00	€ 280.08	€ 3,208.49
Ustekinumab 90 mg	1 PEN	€ 5,818.60	€ 2.00	€ 564.02	€ 5,252.58
Vedolizumab 108 mg	6 ILO	€ 3,656.49	€ 2.00	€ 352.34	€ 3,302.15
Abbreviations: SFI = solution for injection; PEN = solution for injection in a pre-filled pen; PIC = powder for the preparation of an infusion solution concentrate, SRT = sustained release tablets					

LAUER-TAXE® last revised: 1 October 2023

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.

The additionally required SHI services for screening for tuberculosis infection are incurred equally for the medicinal product to be assessed and the appropriate comparator therapy, so that they are not presented.

Test for the presence of hepatitis B viral infection prior to the administration of active ingredients of the appropriate comparator therapy (adalimumab and infliximab).

[3] Fixed reimbursement rate

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
Adalimumab Infliximab	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	Anti-HBs antibody (GOP 32617)[4]	1	€ 5.50	€ 5.50
	Anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV DNA (GOP 32817)[5]	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 € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. 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 special agreement on contractual unit costs of retail pharmacist services (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

4 Only if HBs antigen negative and anti-HBc antibody positive

5 Settlement of GOP 32817 for diagnosis of HBV reactivation or before, during, at the end of or after discontinuation of specific antiviral therapy.

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 authorised 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.

In the case of information on "determined" or "undetermined" combinations, the assessed medicinal product can be used in a combination therapy according to this information on the basis of the marketing authorisation under Medicinal Products Act. For the designation, the G-BA, within the scope of its legislative discretion, uses the constellation of a "determined" or an "undetermined" combination as a justifiable interpretation variant.

If a designation as a so-called determined or as a so-called undetermined combination is omitted due to the lack of information on a combination therapy in the product information of the assessed medicinal product, the non-designation in the resolution according to Section 35a, paragraph 3, sentence 1 SGB V does not affect the possibility that the assessed medicinal product can be used in an open-label combination under marketing authorisation regulations.

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 information 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 with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a conventional therapy or corresponding treatment

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.

b) Adults with moderately to severely active Crohn's disease 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

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.

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 28 March 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 24 April 2023, the pharmaceutical company submitted a dossier for the benefit assessment of upadacitinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2, sentence 1 VerfO.

By letter dated 28 April 2023 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 upadacitinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 July 2023, and the written statement procedure was initiated with publication on the G-BA website on 1 August 2023. The deadline for submitting statements was 22 August 2023.

The oral hearing was held on 11 September 2023.

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 10 October 2023, and the proposed resolution was approved.

At its session on 19 October 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	28 March 2023	Determination of the appropriate comparator therapy
Working group Section 35a	5 September 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	11 September 2023	Conduct of the oral hearing,
Working group Section 35a	19 September 2023 4 October 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	10 October 2023	Concluding discussion of the draft resolution
Plenum	19 October 2023	Adoption of the resolution on the amendment of the AM-RL

Berlin, 19 October 2023

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

Prof. Hecken