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)
Gadopiclenol (contrast-enhanced magnetic resonance imaging, ≥ 2 years)

of 19 September 2024

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 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 gadopiclenol on 1 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 28 March 2024.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 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 gadopiclenol 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 gadopiclenol.

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 Gadopiclenol (Elucirem) in accordance with the product information

This medicinal product is for diagnostic use only.

Elucirem is indicated in adults and children aged 2 years and older for contrast-enhanced magnetic resonance imaging (MRI) to improve detection and visualization of pathologies with disruption of the blood-brain-barrier (BBB) and/or abnormal vascularity of:

- the brain, spine, and associated tissues of the central nervous system (CNS);
- the liver, kidney, pancreas, breast, lung, prostate, and musculoskeletal system.

It should be used only when diagnostic information is essential and not available with unenhanced MRI.

Therapeutic indication of the resolution (resolution of 19 September 2024):

"see approved therapeutic indication"

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults, adolescents and children aged 2 years and older for whom contrast-enhanced magnetic resonance imaging is indicated to improve detection and visualization of pathologies with disruption of the blood-brain-barrier and/or abnormal vascularity in body areas

Appropriate comparator therapy for gadopiclenol:

- Gadobutrol or gadoteridol or gadoteric acid

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.

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

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.

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

on 1. In addition to gadopiclenol, the approved active ingredients gadobenic acid, gadobutrol, gadoteridol, gadoteric acid and gadoxetic acid from the group of paramagnetic MRI contrast agents are available for contrast enhancement in magnetic resonance imaging (MRI).

on 2. Non-medicinal treatments are not considered in the present therapeutic indication.

on 3. There are no resolutions of the G-BA on an amendment to the Pharmaceuticals Directive: Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the present therapeutic indication.

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

When determining the appropriate comparator therapy for gadopiclenol for adults, adolescents and children aged 2 years and older for whom contrast-enhanced magnetic resonance imaging is indicated to improve detection and visualization of pathologies with disruption of the blood-brain-barrier and/or abnormal vascularity in body areas, the evidence search identified seven systematic reviews and two American guidelines that investigate contrast-enhanced imaging procedures in various clinical pictures such as hepatocellular carcinoma, liver fibrosis, glioblastoma or malignant ovarian tumours.

Gadolinium-containing contrast agents are recommended both in the available evidence and in the recommendations of the scientific-medical societies.

The medicinal products listed above are generally approved in the therapeutic indication under assessment. The therapeutic indication includes contrast enhancement in MRI of the areas of brain, spine and associated tissues of the central nervous system as well as the areas of liver, kidneys, pancreas, breast, lungs, prostate and musculoskeletal system. The active ingredients gadobutrol, gadoteridol and gadoteric acid are eligible according to the marketing authorisation for the contrast enhancement of cranial or spinal MRI as well as for imaging MR examinations of pathological structures in the entire body.

Due to the limitations - specified in the respective marketing authorisations - to the contrast-enhanced examination of only certain organs and body regions, the active ingredients gadobenic acid and gadoxetic acid, which are only approved for MRI examinations of the liver, are not considered to be equally appropriate compared to the active ingredients gadoteric acid, gadobutrol and gadoteridol.

Based on the available evidence and taking into account the recommendations of the scientific-medical societies, the active ingredients gadoteric acid, gadobutrol and gadoteridol are equally appropriate therapy options in the present therapeutic indication. The marketing authorisation of contrast agents containing gadolinium must be observed.

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 gadopiclenol is assessed as follows:

For adults, adolescents and children aged 2 years and older for whom contrast-enhanced magnetic resonance imaging is indicated to improve detection and visualization of pathologies with disruption of the blood-brain-barrier and/or abnormal vascularity in body areas, an additional benefit is not proven.

Justification:

No studies were presented by the pharmaceutical company for the assessment of the additional benefit of gadopiclenol. The two additionally presented PICTURE and PROMIS studies were not used by the pharmaceutical company to derive an additional benefit due to the lack of patient-relevant endpoints.

The PICTURE and PROMIS studies are blinded, randomised, controlled cross-over studies with a similar study design, comparing gadopiclenol with gadobutrol. 256 and 304 patients were enrolled respectively. They were either first given gadopiclenol as a contrast agent and then gadobutrol for the subsequent MRI, or the treatment sequence was reversed. The second MRI visit took place at an interval of 2 to 14 days. Adults with known or highly suspected lesions in the CNS with a disrupted blood-brain barrier in the focal area were enrolled in the PICTURE study. The PROMISE study enrolled adults who had known abnormalities or lesions or suspected, contrast-enhanced abnormalities or lesions in at least one of the following body areas: head and neck, thorax (including chest), abdomen (including liver, pancreas and kidneys), pelvis (including uterus, ovaries and prostate) and musculoskeletal regions (including extremities). The primary endpoint of each study was the visualization of the lesions with regard to the assessment of the demarcation of the margin, the internal morphology and the degree of contrast enhancement. In addition, a safety follow-up was carried out one day after the MRI to collect short-term adverse events (AEs).

Due to the study design, the PICTURE and PROMISE studies are unsuitable for illustrating the diagnostic-therapeutic chain with gadopiclenol in comparison to the diagnostic-therapeutic chain with gadobutrol. However, an investigation of the entire diagnostic-therapeutic chain would not be necessary if it were shown or it was sufficiently certain that gadopiclenol has direct patient-relevant advantages over the established contrast agent and the therapeutic consequence of the use of gadopiclenol does not differ pertinently from that of the established contrast agent (concordance question). It is assumed that gadopiclenol as a new contrast agent is only intended to replace the contrast agents specified in the appropriate comparator therapy, without gadopiclenol as a new diagnostic agent identifying or excluding additional or other patients. Based on this prerequisite, the two studies could in principle be suitable for a corresponding concordance question.

Due to the study design of the PICTURE and PROMISE studies, only short-term AEs can be collected. Long-term side effects, which may only occur months or years after application or after repeated administration of the contrast agent, are not collected due to the short follow-up period of a maximum of 14 days. Irrespective of this, due to the cross-over design, it is not possible to clearly assign AEs to the intervention or comparator therapy after the second administration of contrast agent. In both studies, there was no advantage of gadopiclenol over gadobutrol for short-term AEs. This also means that the requirement that the available data can be used for a concordance analysis is not met.

The pharmaceutical company did not consider responding to the concordance question. Overall, no data that fulfil the necessary requirements for the assessment of additional benefit were presented. In the overall assessment, an additional benefit of gadopiclenol compared to the appropriate comparator therapy is therefore not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Elucirem with the active ingredient gadopiclenol.

Elucirem is indicated in adults and children aged 2 years and older for contrast-enhanced magnetic resonance imaging to improve detection and visualization of pathologies with disruption of the blood-brain-barrier and/or abnormal vascularity of:

- the brain, spine, and associated tissues of the central nervous system;
- the liver, kidney, pancreas, breast, lung, prostate, and musculoskeletal system.

The G-BA determined therapy with gadobutrol or gadoteridol or gadoteric acid as the appropriate comparator therapy.

The pharmaceutical company presented the two RCTs PICTURE and PROMIS to compare gadopiclenol with gadobutrol, but they were not used to derive an additional benefit. The data presented do not allow a comparison of the diagnostic-therapeutic chain. Furthermore, neither direct patient-relevant advantages of gadopiclenol compared to gadobutrol nor a concordance with regard to a treatment decision following the diagnosis could be shown.

Overall, no data that fulfil the necessary requirements for deriving an additional benefit were presented. In the overall assessment, an additional benefit of gadopiclenol compared to the appropriate comparator therapy is therefore 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 G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier. Due to the limited epidemiological data basis on the incidence and prevalence of this therapeutic indication, these patient numbers are determined on the basis of the number of MRI examinations performed on an outpatient and inpatient basis per year. The methodological approach of the pharmaceutical company in the dossier is subject to uncertainties overall due to included services that are not covered by the therapeutic indication of gadopiclenol, missing information on extrapolations to 2024 and unclear age adjustments. As a result, an overestimation of the patient numbers can therefore be assumed.

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 Elucirem (active ingredient: gadopiclenol) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 10 September 2024):

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

Treatment with gadopiclenol should only be initiated and monitored by trained healthcare professionals with technical experience in performing contrast-enhanced MRIs with gadolinium.

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 September 2024).

According to the product information for gadopiclenol, gadobutrol, gadoteridol and gadoteric acid, these active ingredients are diagnostic agents. They should only be used if the diagnostic information is necessary and data cannot be collected without contrast-enhanced MRI. The use of the diagnostic agents was therefore limited to a single dose.

For dosages depending on body weight (BW), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" and "Microcensus 2017 – body measurements of the population" were used as a basis. The average body weight of an adult is 77.7 kg[2] and that of a 2-year-old child 14.1 kg[3].

The costs for the MRI examination are not shown because this is carried out both for the medicinal product under assessment and for the appropriate comparator therapy and are therefore deducted.

Gadoteridol is only listed in the LAUER-TAXE® at the manufacturer sales price and can be sold directly to hospitals and doctors in accordance with Section 47 Medicinal Products Act. The calculation is based on the manufacturer sales price of gadoteridol plus 19% value added tax, in deviation from the LAUER-TAXE® data usually taken into account.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Gadopiclenol	Single dose	1	1	1
Appropriate comparator therapy				
Gadobutrol	Single dose	1	1	1
Gadoteridol	Single dose	1	1	1
Gadoteric acid	Single dose	1	1	1

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

[2] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de
[3] Federal Health Reporting. Average body measurements of the population (2017, both sexes, 1 year and older), www.gbe-bund.de

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					
Gadopiclenol	0.1 ml/kg BW = 1.41 ml[4] – 7.77 ml	= 1.41 ml – 7.77 ml	1 x 1.41 ml – 1 x 7.77 ml	1	1 x 1.41 ml – 1 x 7.77 ml
Appropriate comparator therapy					
Gadobutrol	0.1 ml/kg BW = 1.41 ml[5] – 0.3 ml/kg BW = 23.31 ml	1.41 ml – 23.31 ml	1 x 1.41 ml – 1 x 23.31 ml	1	1 x 1.41 ml – 1 x 23.31 ml
Gadoteridol	0.2 ml/kg BW = 2.82 ml[6] – 0.6 ml/kg BW = 46.62 ml	= 2.82 ml – 46.62 ml	1 x 2.82 ml – 1 x 46.62 ml	1	1 x 2.82 ml – 1 x 46.62 ml
Gadoteric acid	0.2 ml/kg BW = 2.82 ml[7] – 0.6 ml/kg BW = 46.62 ml	2.82 ml – 46.62 ml	1 x 2.82 ml – 1 x 46.62 ml	1	1 x 2.82 ml – 1 x 46.62 ml

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 fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Cost (pharmacy sales price or manufacturer sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Gadopiclenol 3.64 g (0.5 mmol/ml)	1 SFI	€ 144.64	€ 2.00	€ 7.67	€ 134.97
Gadopiclenol 4.85 g (0.5 mmol/ml)	1 SFI	€ 189.38	€ 2.00	€ 10.22	€ 177.16

[4] 1 ml = 485.1 mg gadoteridol
[5] 1 ml = 604.72 mg gadobutrol
[6] 1 ml = 279.3 mg gadoteridol
[7] 1 ml = 279.32 mg gadoteric acid

Designation of the therapy	Packaging size	Cost (pharmacy sales price or manufacturer sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Gadobutrol 4.535 g (1.0 mmol/ml)	5 PS	€ 650.41	€ 2.00	€ 83.54	€ 564.87
Gadobutrol 6.047 g (1 mmol/ml)	5 PS	€ 2,141.31	€ 2.00	€ 278.16	€ 1,861.15
Gadoteridol 2.79 g (0.5 mg/ml)	1 SFI	€ 88.00	€ 0.00	€ 0.00	€ 104.72[8]
Gadoteridol 13.97 g (0.5 mg/ml)	1 SFI	320.00	€ 0.00	€ 0.00	€ 380.80[7]
Gadoteric acid 3.77 g (0.5 mmol/ml)	1 SFI	€ 87.61	€ 2.00	€ 10.08	€ 75.53
Gadoteric acid 22.62 g (0.5 mmol/ml)	1 SFI	€ 390.02	€ 2.00	€ 49.55	€ 338.47
Abbreviations: PS = prefilled syringe; SFI = solution for injection					

LAUER-TAXE® last revised: 1 September 2024

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.

Because there are no 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, no costs for additionally required SHI services need to be taken into account.

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.

[8] plus 19% VAT

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:

Adults, adolescents and children aged 2 years and older for whom contrast-enhanced magnetic resonance imaging is indicated to improve detection and visualization of pathologies with disruption of the blood-brain-barrier and/or abnormal vascularity in body areas

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: Elucirem product information)

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 25 October 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 28 March 2024, the pharmaceutical company submitted a dossier for the benefit assessment of gadopiclenol to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 2 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 gadopiclenol.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 June 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 July 2024. The deadline for submitting statements was 22 July 2024.

The oral hearing was held on 5 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 10 September 2024, and the proposed draft resolution was approved.

At its session on 19 September 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	25 October 2022	Determination of the appropriate comparator therapy
Working group Section 35a	31 July 2024	Information on written statements received; preparation of the oral hearing

Subcommittee Medicinal products	5 August 2024	Conduct of the oral hearing,
Working group Section 35a	14 August 2024 4 September 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	10 September 2024	Concluding discussion of the draft resolution
Plenum	19 September 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 19 September 2024

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

Prof. Hecken