Gemeinsamer Bundesausschuss

Justification

for 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
Donanemab (Early Alzheimer's disease)

of 16 April 2026

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess 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 studies the pharmaceutical company have 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,
7. number of study participants who participated in the clinical studies at study sites within the scope of SGB V, and total number of study participants.

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 decide 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 donanemab on 1 November 2025 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO). Pursuant to Section 4, paragraph 3, No. 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, No. 1 Rules of Procedure (VerfO), the pharmaceutical company submitted the final dossier to the G-BA on 20 October 2025.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 February 2026 on the website of the G-BA (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 donanemab 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, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA have 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 donanemab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA have made 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 Donanemab (Kisunla) in accordance with the product information

Donanemab is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early symptomatic Alzheimer's disease) who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology.

Therapeutic indication of the resolution (resolution of 16.04.2026):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with a clinical diagnosis of mild cognitive impairment due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology

Appropriate comparator therapy:

Best supportive care

[1] General Methods, version 8.0 from 19.12.2025. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

b) Adults with a clinical diagnosis of mild dementia due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology

Appropriate comparator therapy:

Donepezil *or* galantamine *or* rivastigmine

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 according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
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 they determine 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.

On 1: In the present therapeutic indication, the acetylcholinesterase inhibitors (AChEIs) donepezil, galantamine and rivastigmine are approved for the symptomatic treatment of mild to moderate Alzheimer's dementia.

The active ingredient lecanemab is approved for the treatment of adults with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes with confirmed amyloid pathology.

A dry extract from Ginkgo biloba leaves is approved for improving age-related cognitive impairment and quality of life in cases of mild dementia.

On 2. Occupational therapy, e.g. brain power training, is considered a measure in accordance with the Remedies Directive and the catalogue of remedies.

On 3. There is a resolution of 19 February 2026 on the benefit assessment of the active ingredient lecanemab according to Section 35a SGB V for the treatment of adults with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) non-carriers or heterozygotes with confirmed amyloid pathology.

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present therapeutic indication.
The S3 Guideline on Dementias[2] is particularly relevant for the German healthcare context.

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.

Based on the evidence, there are different therapy recommendations depending on the stage of Alzheimer's disease. In accordance with the marketing authorisation, different therapy options are available for different stages of the disease: Symptomatic antidementia drugs are not approved for the treatment of mild cognitive impairment, whereas AChEIs have been granted marketing authorisation for the treatment of mild to moderate Alzheimer's dementia.

During the present written statement procedure as well as the benefit assessment procedure for lecanemab according to Section 35a SGB V, it was pointed out that Alzheimer's disease is a progressive condition and that transitions from the stage of mild cognitive impairment to dementia are common.

According to the S3 guideline, the clinical differentiation between these stages is based on an assessment of the ability to cope with daily life. In accordance with the authorisation status, the S3 guideline also states that there are different therapy recommendations for the stage of mild cognitive impairment and mild dementia.

[2] DGN e. V. & DGPPN e. V. (ed.) S3 Guideline on Dementias, version 6.0, 24.02.2026, available at: https://register.awmf.org/de/leitlinien/detail/038-013

Against this background, patient group differentiation by mild cognitive impairment or mild dementia due to Alzheimer's disease is made.

Patient population a: Adults with a clinical diagnosis of mild cognitive impairment due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology

No symptomatic pharmacotherapy is approved for the treatment of mild cognitive impairment. Based on the S3 Guideline on Dementias and other evidence, no recommendations on symptomatic pharmacotherapy of mild cognitive impairment can be made. Based on the evidence, no superiority of AChEIs over placebo can be inferred in patients with mild cognitive impairment. Against this background, the S3 Guideline on Dementias does not recommend treatment with AChEIs for patients with mild cognitive impairment.

Ginkgo biloba leaf extract is approved for improving age-related cognitive impairment and quality of life in mild dementia and, based on the evidence, has a minor therapeutic significance.
The active ingredient memantine is only approved for the treatment of patients with moderate to severe Alzheimer's dementia and is only recommended for these patients based on the available evidence.
Similar to donanemab, the active ingredient lecanemab is a new treatment option in the present therapeutic indication. Lecanemab has only recently been approved and is now available in Germany.
Based on the available evidence, it cannot be concluded that lecanemab can be considered the therapy standard for patients with early Alzheimer's disease. Furthermore, no additional benefit of lecanemab for the treatment of adults with early Alzheimer's disease and confirmed amyloid pathology could be identified in the benefit assessment according to Section 35a SGB V.
In summary, Ginkgo biloba leaf extract, memantine and lecanemab are not considered an appropriate comparator therapy for patient group a, taking into account their respective marketing authorisation and the generally recognised state of medical knowledge. The explanations also apply to the appropriate comparator therapy for patient group b (see below).

According to the S3 guideline, cognitive training or cognitive stimulation is recommended for improvement of cognition in patients with mild cognitive impairment. These therapies can be provided as non-medicinal measures within the meaning of the Remedies Directive or the catalogue of remedies (occupational therapy, e.g. brain power training).

In the overall assessment, it cannot be currently concluded on the basis of the generally recognised state of medical knowledge that pharmacological treatment constitutes the therapy standard for mild cognitive impairment caused by Alzheimer's disease. Against this background and taking into account the recommendations for non-medicinal measures, best supportive care is determined to be the appropriate comparator therapy for patient population a.

Best supportive care is defined as the therapy that provides the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve quality of life.

Patient population b: Adults with a clinical diagnosis of mild dementia due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology

AChEIs (donepezil, galantamine and rivastigmine) are approved for the symptomatic treatment of mild to moderate Alzheimer's dementia. Based on the available evidence, the use of AChEIs is recommended for the treatment of patients in the mild to moderate stage of Alzheimer's dementia. This recommendation has the highest level of recommendation in the S3 Guideline on Dementias.

During the present written statement procedure as well as the benefit assessment procedure for lecanemab according to Section 35a SGB V, it was pointed out that not all patients with mild Alzheimer's dementia receive treatment with AChEIs in healthcare. Contraindications and side effects were cited as reasons for this. However, this contrasts with the strong recommendation in the S3 guideline for the use of AChEIs, which is based on high-quality evidence in the form of systematic reviews and meta-analyses and also takes the German healthcare context into account. Against this background, it can be assumed that, according to the generally recognised state of medical knowledge, AChEIs are considered the recommended therapy standard and therefore represent the appropriate therapy for patients with mild Alzheimer's dementia.

With regard to the active ingredients Ginkgo biloba, memantine and lecanemab, please refer to the above explanations. These active ingredients are not considered to be the appropriate comparator therapy for patient group b.

In the overall assessment of the body of evidence, the AChEIs donepezil, galantamine or rivastigmine are determined as the appropriate comparator therapy for adults with a clinical diagnosis of mild dementia due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology. The highest tolerable dose should be aimed for.

The appropriate comparator therapy determined for patient group b comprises several therapeutic alternatives. These therapeutic alternatives are equally appropriate for the comparator therapy. The additional benefit can be demonstrated compared to one of the treatment options mentioned.

Taking into account the S3 guideline recommendation for the use of cognitive procedures in mild dementia, it is also pointed out for patient population b that non-medicinal measures within the meaning of the Remedies Directive or the catalogue of remedies (occupational therapy, e.g. brain power training) can contribute to alleviation of symptoms.

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

Any change to the appropriate comparator therapy requires a decision by the G-BA based on a prior review of the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO.

Change in the appropriate comparator therapy for patient group a

To date, the monitoring wait-and-see approach has been regarded as the appropriate comparator therapy for adults with a clinical diagnosis of mild cognitive impairment due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology.

As explained above, non-medicinal measures within the meaning of the Remedies Directive or the catalogue of remedies (occupational therapy, e.g. brain power training) assume relevant significance in this context, which is reflected in the guideline recommendation of cognitive training or cognitive stimulation for patients with mild cognitive impairment.

Since the application of non-medicinal measures goes beyond the monitoring wait-and-see approach, the G-BA consider it appropriate to determine best supportive care as the appropriate comparator therapy for patient group a in the present case.

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

2.1.3 Extent and probability of the additional benefit

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

a) Adults with a clinical diagnosis of mild cognitive impairment due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology

   The additional benefit is not proven for adults with a clinical diagnosis of mild cognitive impairment due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology.

b) Adults with a clinical diagnosis of mild dementia due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology

   The additional benefit is not proven for adults with a clinical diagnosis of mild dementia due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology.

Justification:

For the benefit assessment, the pharmaceutical company submitted evaluations of the double-blind, randomised controlled trial AACI.

Patients 60 to 85 years of age, who had experienced a gradual and progressive change in memory function for at least 6 months and had a Mini-Mental State Examination (MMSE) score between 20 and 28 points, were enrolled in the study. Patients also had to meet the positron emission tomography (PET) scan criteria regarding the presence of amyloid pathology and tau pathology. At the time of enrolment in the study, it had to be indicated in the case report form that the patient had Alzheimer's disease.
No further criteria regarding the diagnosis of mild cognitive impairment or mild dementia due to Alzheimer's disease were required.

If patients were already receiving symptomatic medication for the treatment of Alzheimer's disease (e.g. AChEI or memantine), the dose had to have been stable for at least 30 days prior to baseline. Patients who had not previously received symptomatic medication for the treatment of Alzheimer's disease were also eligible to participate in the study.

A total of 1,736 patients were randomised to receive treatment with donanemab in the intervention arm or with placebo in the comparator arm. In addition to donanemab or placebo, patients who had been pretreated with symptomatic antidementia drugs in both study arms should continue their respective medication as unchanged as possible. Where medically indicated, adjustment or discontinuation of existing antidementia medication and the initiation of symptomatic antidementia pharmacotherapy in previously untreated patients were permitted. Non-medicinal treatments for Alzheimer's disease were permitted, subject to the same restrictions as medicinal therapies.

The maximum duration of the double-blind treatment phase was 18 months. In the intervention arm, a blinded switch from donanemab to placebo should be made if removal of the amyloid plaques was observed on the PET scan at week 24 or 52.

On the study sub-populations submitted by the pharmaceutical company

As explained above, patient groups are differentiated in this therapeutic indication according to mild cognitive impairment or mild dementia due to Alzheimer's disease. However, no inclusion criteria were defined in the AACI study for the diagnostic differentiation between mild cognitive impairment and mild dementia due to Alzheimer's disease.

Analyses of two sub-populations of the AACI study were presented in the dossier. These were formed by excluding ApoE ε4 homozygotes and those treated with memantine from the total population of the AACI study. In a further step, this population was divided into a sub-population not receiving AChEI therapy at the time of screening and a sub-population receiving AChEI therapy at the time of screening. According to the pharmaceutical company's reasoning, this is intended to represent populations with mild cognitive impairment or mild dementia due to Alzheimer's disease. However, the AChEI treatment setting is unsuitable as an indicator for clinical diagnosis. The approach of differentiating patient groups by stage of the disease based on the AChEI treatment setting (untreated or receiving AChEI therapy) is therefore inappropriate. Consequently, the analyses presented in the dossier are not taken into account.

In their statement, the pharmaceutical company presented analyses of 6 newly formed sub-populations. These were formed by applying additional criteria based on the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating - Global Score (CDR-GS) and - Sum of Boxes (CDR-SB), using the sub-populations - receiving and not receiving AChEI therapy at the time of screening - presented in the dossier.

This results in the following study sub-populations:

ApoE ε4 heterozygotes and non-carriers not receiving memantine treatment and not receiving AChEI therapy at the time of screening (N = 554)			ApoE ε4 heterozygotes and non-carriers not receiving memantine treatment and receiving AChEI therapy at the time of screening (N = 568)		
MMSE 27 - 30 (N = 130)	**CDR-GS 0.5** (N = 392)	**CDR-SB 0.5 - 4** (N = 388)	**MMSE 20 - 26** (N = 495)	**CDR-GS 1 or 2** (N = 232)	**CDR-SB 4.5 - 9** (N = 226)

According to the pharmaceutical company's reasoning, this approach is intended to provide a suitable definition of the two patient groups to be differentiated: The three sub-populations, which do not receive AChEI therapy and are newly formed on the basis of the additional criteria, should include patients with a diagnosis of mild cognitive impairment, whilst the three newly formed sub-populations receiving AChEI therapy should include patients with a diagnosis of mild dementia.

However, defining the sub-populations using a single scale in combination with the criterion regarding prior AChEI therapy (yes vs no) does not necessarily provide a sufficient approximation of the patient groups a (adults with mild cognitive impairment due to Alzheimer's disease) and b (adults with mild dementia due to Alzheimer's disease) to be considered separately in this context. This is justified subsequently.

According to the S3 Guideline on Dementias, diagnosis of mild cognitive impairment is made on the basis of clinical findings and neuropsychological evidence of cognitive impairment, with the patient's ability to cope with daily life and their unrestricted independence in the activities of daily living being retained either fully or to a large extent.

On the formation of sub-populations using the MMSE

The MMSE has a scale range of 0 to 30 points. To represent the sub-populations with mild cognitive impairment and mild dementia, the pharmaceutical company used a score range of 27 to 30 and 20 to 26, respectively.

Although the S3 Guideline on Dementias describes the MMSE as a brief test suitable for objective assessment of cognitive impairment in the general practice setting, it is only an indicative screening procedure. Furthermore, the MMSE only represents cognition and is therefore unsuitable for making a differentiation, taking into account the retained ability to cope with daily life. The MMSE is therefore unsuitable for distinguishing between mild cognitive impairment and mild dementia. The sub-populations formed on the basis of the MMSE are therefore not used here.

On the formation of sub-populations based on CDR summary scores

The CDR is evaluated as a summary score (CDR-GS or CDR-SB) and comprises the categories of cognition and activities of daily living, each with 3 domains.

In the written statement procedure, the CDR-GS, in particular, was described as a scale that is well established in healthcare for diagnostic purposes. However, the memory domain is given greater weighting in the algorithm used to calculate the CDR-GS. In the calculation of the CDR-SB, by contrast, all domains are given equal weighting, which means that the domain relating to activities of daily living is potentially given greater consideration. In the written statement procedure, it was also pointed out that a summary score does not allow for reliable conclusions to be drawn about the values in the individual domains.

When the study population is divided according to CDR summary scores, it cannot be concluded with certainty that subjects with largely retained ability to cope with daily life were

assigned to the sub-population with mild cognitive impairment, and that subjects with more severe limitations in the ability to cope with daily life were assigned to the sub-population with mild dementia.

Corresponding uncertainty arises in relation to the cut-off values used by the pharmaceutical company based on the CDR-GS (0.5 points: mild cognitive impairment; 1 or 2 points: mild dementia) and the CDR-SB (0.5 to 4 points: mild cognitive impairment; 4.5 to 9 points: mild dementia).
According to the CDR-GS, even a score of 0.5 points may indicate significant limitations in activities of daily living, thus the presence of mild (early-stage) dementia. Similarly, with regard to the CDR-SB, it is possible to achieve a score of 4.5 points in cases of questionable impairment to daily life. On the contrary, a score of 4 may be recorded even with only a moderate impairment to daily life.

Furthermore, the S3 Guideline on Dementias does not contain any recommendations on criteria based on CDR summary scores for the diagnosis and demarcation of the stages of mild cognitive impairment and mild dementia.

Conclusion on the suitability of the MMSE and CDR tools for the formation of sub-populations

In summary, the MMSE is unsuitable for distinguishing between mild cognitive impairment and mild dementia. The limitations described above apply to the CDR-GS and CDR-SB. Overall, the definition based on the individual scales, in combination with the criterion of prior AChEI therapy, does not necessarily provide a sufficient approximation of the patient groups a (adults with mild cognitive impairment due to Alzheimer's disease) and b (adults with mild dementia due to Alzheimer's disease) to be considered separately in this context. The extent to which the sub-populations formed may still be suitable for representing the relevant patient groups a and b for the benefit assessment is assessed separately for each patient group.

On the data basis for patient group a

The patient group a comprises adults with a clinical diagnosis of mild cognitive impairment due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology.

The pharmaceutical company presented analyses for this patient group based on three study sub-populations, which do not receive AChEI therapy at the time of screening and each of which meets an above-described additional criterion, based on the MMSE, CDR-GS or CDR-SB.

For the reasons outlined, operationalisation using the MMSE is unsuitable for representing a population that adequately corresponds to patient group a.

Since the populations with a CDR-GS of 0.5 and a CDR-SB of 0.5 to 4.0 overlap by 98% (based on CDR-SB) and 97% (based on CDR-GS), respectively, they are considered together.

The extent to which these populations include patients who meet the diagnostic criteria for mild cognitive impairment is assessed below.

Given the requirement for a CDR-GS score of 0.5, it cannot be assumed that patients with mild Alzheimer's dementia (not receiving AChEI therapy) have been sufficiently excluded from the sub-populations presented for patient group a.
In this context, comparisons were made with the MCI population from the CLARITY AD study, which investigated the safety and efficacy of lecanemab in early Alzheimer's disease. In the CLARITY AD study, the criteria according to the National Institute on Ageing and Alzheimer's Association (NIA-AA) were used for diagnosis and staging. The requirements laid down by the

NIA-AA, which focus on impairment in activities of daily living to distinguish between mild cognitive impairment and mild dementia due to Alzheimer's disease, are comparable to the approach outlined in the S3 Guideline on Dementias.
The patient characteristics from the CLARITY AD study show that half of the patients with mild Alzheimer's dementia had a CDR-GS score of 0.5. Overall, it can be assumed that each of the study sub-populations - according to the CDR - presented for patient group a contains a high percentage of patients with mild Alzheimer's dementia.
Against this background, it cannot be ruled out that the formation of sub-populations subject to the absence of AChEI therapy, which is however recommended in the S3 guideline for the treatment of mild Alzheimer's dementia, may lead to a potentially significant risk of bias in the effects in favour of the intervention.

In the overall assessment, the data based on the study sub-populations formed by the pharmaceutical company for patient group a are currently not used for the benefit assessment. Thus, no suitable data are available for patient group a.

On the data basis for patient group b

The patient group b comprises adults with a clinical diagnosis of mild dementia due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology.

The pharmaceutical company presented analyses for this patient group based on three study sub-populations, which receive AChEI therapy at the time of screening and each of which meets an above-described additional criterion, based on the MMSE, CDR-GS or CDR-SB.

For the above reasons, operationalisation using the MMSE is unsuitable for representing a population that adequately corresponds to patient group b.

Since the populations with a CDR-GS of 1 or 2 and a CDR-SB of 4.5 to 9.0 overlap by 95% (based on CDR-SB) and 92% (based on CDR-GS), respectively, they are considered together.

Although it cannot be ruled out that patients may have a CDR-GS of at least 1 or a CDR-SB of at least 4.5 even without significant limitations in activities of daily living, this seems less plausible when considering the CDR and no significant percentages thereof have not yet been observed. A factual situation that differs from that of the sub-populations presented for patient group a arises in this context: In contrast to the high percentage of patients with mild Alzheimer's dementia and a GDR-GS of 0.5, the percentage of patients with mild cognitive impairment and a CDR-GS of at least 1 or a CDR-SB of at least 4.5 is considered to be low overall. It cannot therefore be assumed in this case that the sub-populations - according to the CDR - presented for patient group b include a significant percentage of patients with mild cognitive impairment.

However, further limitations arise with regard to the sub-populations - according to the CDR - presented for patient group b. As explained above, even patients with a CDR-GS score of 0.5 may, in principle, already meet the criteria for diagnosis of mild dementia. Consequently, these patients are not included in the present population based on a CDR-GS score of 1 or 2, although they are, in principle, included in patient group b.

Furthermore, a CDR-GS score of 2 is associated with moderate dementia. No justification has been provided as to why patients with a CDR-GS score of 2 are included in the population defined by CDR-GS. However, the patient characteristics show that the percentage of patients with a CDR-GS score of 2 is less than 10% in both the population with a CDR-GS score of 1 or 2 and the population with a CDR-SB score of 4.5 to 9.0.

Despite the existing limitations, the sub-populations - based on AChEI therapy as well as the CDR-GS and CDR-SB - presented by the pharmaceutical company are considered to be a sufficient approximation to represent patient group b in the overall assessment of the current data basis.

On the other limitations of the AACI study

Missing information on the use of non-medicinal measures

The use of non-medicinal therapies was generally permitted during the study, but these were not systematically offered as part of the study. Overall, it can be assumed that non-medicinal therapies were used whenever medically indicated and available.
However, no information is available on the percentage and type of non-medicinal therapies used during the study.

Missing information on the use of AChEI treatment

The pharmaceutical company presented data on patients receiving AChEI treatment at the start of the study, as well as on patients who permanently discontinue AChEI therapy, undergo changes to their AChEI treatment or dosage, and commence AChEI therapy, respectively, during the study. In contrast, information on dosages or the timing of adjustments to AChEI therapy is unavailable.

However, these would be necessary in order to verify the marketing authorisation compliance of the application for the active ingredients of the appropriate comparator therapy:
According to the requirements of the relevant product information, AChEIs should be titrated to the highest tolerable dose within a defined time interval, taking into account clinical response and tolerability.

Overall, there is no indication that AChEIs were not used in accordance with the product information in patients of the study sub-population b. However, the relevant information for verification is missing.

Missing requirements on how to deal with lack of efficacy or progression to the next stage

According to the product information, donanemab is approved for the treatment of mild cognitive impairment and mild dementia due to Alzheimer's disease. If the disease progresses to the moderate stage, discontinuing treatment before the end of the maximum treatment duration of 18 months should be considered.

The study did not provide for an overall medical assessment regarding progression to moderate Alzheimer's dementia or discontinuation of treatment with donanemab upon progression to the moderate stage of the disease. The percentage of patients affected by this is unclear.

Furthermore, regular evaluation of cognitive function and clinical symptoms is indicated for both donanemab and AChEIs. An overall medical assessment of efficacy, including considerations regarding the discontinuation of donanemab or AChEIs, was not planned.

Apart from discontinuation in compliance with the marketing authorisation once the amyloid plaques have been removed, discontinuation of donanemab was only provided for in the event of certain side effects. AChEIs should be continued as unchanged as possible; adjustments to the therapy were possible where medically necessary.

There is a lack of information on the reasons for the adjustments made to concomitant medication during the study. Overall, it is unclear whether treatment with AChEIs was

discontinued in the absence of therapeutic efficacy, or whether, if applicable, a therapy trial with a different active ingredient (including memantine in cases of progression to the moderate stage of the disease) was initiated.

Uncertainty therefore remains as to whether the treatments in the study were adjusted according to the product information and whether adequate therapies were used upon progression to the next stage of the disease.

Despite the limitations of the AACI study described above, the treatment in the intervention arm and the appropriate comparator therapy are considered to have been implemented sufficiently adequately.

Consequently, the results from the AACI study for patient group b are used in the present benefit assessment.
Due to the study design, which provides for the administration of AChEIs as possible concomitant therapy in both study arms, only data on donanemab as add-on therapy to AChEIs are available for patient group b, but not on donanemab used as monotherapy.

a) Adults with a clinical diagnosis of mild cognitive impairment due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology

The populations presented by the pharmaceutical company are unsuitable for representing the patient group of adults with a clinical diagnosis of mild cognitive impairment due to Alzheimer's disease, who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology, with adequate certainty.

Thus, there are no suitable data on patient group a for assessment of the additional benefit of donanemab compared with the appropriate comparator therapy. An additional benefit is therefore not proven.

b) Adults with a clinical diagnosis of mild dementia due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology

Extent and probability of the additional benefit

Mortality

The results on overall mortality are based on the data on fatal adverse events (AEs).
For the endpoint of overall mortality, there was no statistically significant difference between the treatment arms.

Morbidity

On the analyses based on time-to-event analyses of the time to permanent deterioration in endpoints of the morbidity and quality of life categories

In the dossier and as part of the written statement procedure, time-to-event analyses of permanent deterioration by 15% of the scale range for each of the endpoints on morbidity and quality of life were presented. Results with continuous evaluation are unavailable. Given the progressive nature of the disease, time-to-event analyses of permanent deterioration must be preferred - in terms of content - to responder analyses at the end of the study when assessing endpoints on morbidity and quality of life.

Permanent deterioration was defined as deterioration by the relevant response criterion without subsequent improvement until the end of the study. A one-off or, if applicable, confirmed deterioration, following which only missing values occurred, was also rated as permanent deterioration. This approach is appropriate as it also takes into account deteriorations at the last study visit.

In the statement, additional data and sensitivity analyses, particularly regarding the observations at the end of the randomised study phase (visit 21 at week 76 with a visit window of ± 7 days) were presented. The pharmaceutical company state that all observations attributable to the randomised phase (up to visit 21) were included in the analysis. As some of the surveys took place outside the planned visit window (week 76 + 7 days), additional sensitivity analyses, which take into account only the surveys conducted within the window at visit 21, were presented. The results of the sensitivity analyses are consistent with the main analyses.
Furthermore, data are available showing that a delayed visit 21, and thus an extended observation period, affected roughly the same number of patients in the intervention arm and the comparator arm.
The subsequently submitted data adequately addresses the uncertainty arising from the time-to-event analyses. Consequently, the analyses based on the time-to-event analyses of permanent deterioration by 15% of the scale range in each case (including surveys conducted outside the planned visit window) are used for the benefit assessment.

Symptomatology using the Clinical Dementia Rating (CDR)

The CDR is a measurement tool for assessing the severity of symptomatology in patients with Alzheimer's disease, based on a semi-structured interview with both the patient and a caregiver.
It is a complex scale with a total of 6 domains: 3 cognitive domains (memory, orientation, judgement and problem solving) and 3 functional domains (community affairs, home and hobbies, personal care). The patient is only questioned about the 3 cognitive domains, while the caregiver is questioned exclusively about the 3 functional domains.

Based on the 6 domain scores, two different total scores can be calculated:

The CDR Sum of Boxes (CDR-SB) is calculated by adding the 6 domain scores together to produce a summary score, with the CDR-SB showing a scale range of 0 to 18.

The CDR Global Score (CDR-GS) is calculated using an algorithm in which, among other things, the memory domain is weighted more heavily than the other 5 domains, and takes point values on an ordinal scale from 0 to 3 points (0 points: no dementia, 0.5 points: questionable dementia, 1 point: mild dementia, 2 points: moderate dementia, 3 points: severe dementia). This means that changes in the course of the disease may occur in several domains, but these are not reflected in the CDR-GS total score.

Time-to-event analyses of the time to permanent deterioration based on the CDR-SB

Analyses of the time to permanent deterioration on the CDR-SB by at least 2.7 points (corresponding to 15% of the scale range) are available. These are used for the benefit assessment.

Based on these analyses, there was no statistically significant difference between the treatment arms in both study sub-populations relevant to patient group b.

Time-to-event analyses of the time to permanent deterioration based on the CDR-GS

In the written statement procedure, time-to-event analyses of the time to permanent deterioration to a CDR-GS ≥ 2 were presented in order to represent the progression to the stage of moderate dementia.

Overall, the CDR-SB demonstrates greater sensitivity than the CDR-GS, particularly in early Alzheimer's disease. Furthermore, it is unclear whether the CDR-GS is suitable for the assessment of disease progression to the moderate stage, as the diagnosis is more complex and cannot be captured by a single tool. Against this background, evaluations based on the CDR-SB are used for the assessment of symptomatology in the present benefit assessment.

Cognition using the Alzheimer's Disease Assessment Scale – Cognitive Subscale 13 (ADAS-Cog13)

The ADAS-Cog is a function test developed to assess the severity of cognitive impairment in Alzheimer's dementia.

The assessment is conducted in the form of an interview with the patient. The items include tasks to be performed by the patient themselves (e.g. on temporal and spatial orientation) as well as subjective assessments by the interviewer (e.g. on speech comprehension). The scores for all items are added up to a summary score; the ADAS-Cog13 scale ranges from 0 to 85 points.

Analyses of the time to permanent deterioration on the ADAS-Cog13 by at least 12.75 points (corresponding to 15% of the scale range) are available. These are used for the benefit assessment.

For the study sub-population formed on the basis of the CDR-GS, these analyses do not show any statistically significant difference between the treatment arms. In contrast, for the study sub-population defined on the basis of the CDR-SB, there was a statistically significant advantage of donanemab.

Although the sub-populations formed on the basis of the CDR-GS and CDR-SB overlap almost completely, the difference in favour of donanemab does not consistently emerge as statistically significant in both sub-populations, meaning that the effect is considered to be unreliable. Against this background, there was no relevant difference in the cognition endpoint for the benefit assessment.

On the Alzheimer's Disease Cooperative Study Instrumental - Activities of Daily Living Inventory (ADCS-iADL) measurement tool

The ADCS-iADL is a tool for assessing impairment in instrumental activities of daily living in patients with Alzheimer's disease through external assessment by informal caregivers.

It was derived from the original Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL), which was developed to assess impairment in activities of daily living in patients with Alzheimer's dementia. According to information provided by the pharmaceutical company, the ADCS-ADL was surveyed in full as part of the study, but only the items relating to instrumental activities of daily living were analysed.

Activities of daily living are generally considered to be patient-relevant in the therapeutic indication of Alzheimer's disease.

However, the ADCS-iADL can only be fully understood in conjunction with the complete questionnaire (ADCS-ADL) and the items not included in the analysis. Furthermore, the ADCS-iADL is surveyed exclusively by external assessment, although it can be assumed that patients with early Alzheimer's disease are still largely capable of assessing impairments in activities of

daily living themselves. Furthermore, the sources provided do not indicate that the ADCS-iADL is designed for patients with mild dementia due to Alzheimer's disease in addition to patients with mild cognitive impairment.

Against this background, the evaluations based on the ADCS-iADL are not used for the present benefit assessment.

On the Integrated Alzheimer's Disease Rating Scale (iADRS) measurement tool

The iADRS was developed to assess treatment effects and disease progression in early Alzheimer's disease. This is a composite scale comprising the ADAS-Cog13 and ADCS-iADL tools.

As explained above, the ADCS-iADL component is not considered to be understandable with adequate certainty in the current data basis. The analyses based on the CDR-SB provide analyses of an established and validated tool for the assessment of symptomatology. In the overall assessment, the analyses based on the iADRS are not used here for the benefit assessment.

On the Mini-Mental State Examination (MMSE) measurement tool

The MMSE is a well-established tool for the assessment of cognition in Alzheimer's disease. The MMSE was originally developed for patients with various neurological conditions, including different types of dementia. The MMSE is performed by a doctor; the scale range is from 0 to 30 points.

The MMSE should be regarded as a validated tool for the assessment of cognition in Alzheimer's dementia; however, the ADAS-Cog13 is a more comprehensive tool that is better suited for the assessment of cognition. Consequently, for the cognition endpoint, the analyses based on the ADAS-Cog13 are used as part of the benefit assessment.

Quality of life

The Quality of Life in Alzheimer's Disease Scale (QOL-AD) is a tool for assessing the health-related quality of life of patients with Alzheimer's disease. The tool comprising a total of 13 items assesses health-related quality of life separately through self-assessment (using a structured interview) and external assessment (using a questionnaire for informal or formal caregivers). The scores for all 13 items (each on a scale of 1 to 4) are added together to produce a summary score, so that the scale ranges from 13 to 52.

No analyses of the QOL-AD were presented for the currently relevant sub-populations of the study. Consequently, no suitable data are available for the assessment of health-related quality of life.

Side effects

For the overall rates of serious adverse events (SAEs), there was no statistically significant difference between the treatment arms in both study sub-populations relevant to patient group b.

In the endpoint of therapy discontinuation due to adverse events (AEs), there was a statistically significant disadvantage of donanemab in both study sub-populations relevant to patient group b.

Detailed analysis of the endpoint of infusion-related reactions showed a statistically significant disadvantage of donanemab in each of the two study sub-populations relevant to patient

group b. There is a discrepancy between the 95% confidence interval, which covers the zero effect, and the p value (< 0.05).
For the endpoint of symptomatic amyloid-related imaging abnormalities (ARIA) events, there were no statistically significant differences between the treatment arms in both study sub-populations relevant to patient group b, when taking into account symptomatic ARIA with oedema (ARIA-E), serious ARIA-E and serious ARIA with haemosiderin deposition (ARIA-H), respectively. No data are available for the analysis of symptomatic ARIA-H and for combined analyses.

Overall assessment

Data from the AACI study are available for the benefit assessment of donanemab for the treatment of adults with a clinical diagnosis of mild dementia due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology. This is a double-blind, randomised study comparing donanemab with placebo over a maximum treatment period of 18 months, if applicable in addition to continued treatment with symptomatic antidementia drugs.

For patient group b, analyses are available based on two study sub-populations, which were formed by the requirement of prior AChEI therapy in combination with criteria based on the CDR-GS and CDR-SB, respectively. Despite uncertainty regarding the diagnostic staging of mild Alzheimer's dementia, the sub-populations formed can be regarded as a sufficient approximation to represent patient group b. The analyses based on these sub-populations allow for a comparison of donanemab as an add-on to AChEIs versus AChEIs (donepezil, galantamine or rivastigmine) and are used here for the benefit assessment.

With regard to mortality, there were no statistically significant differences between the treatment arms.

For the endpoint of symptomatology, assessed using CDR-SB, in the endpoint category of morbidity, there were no statistically significant differences between the treatment arms.
For the endpoint of cognition assessed using ADAS-Cog13, there was a statistically significant advantage of donanemab in the sub-population defined on the basis of the CDR-SB. In the sub-population formed on the basis of the CDR-GS, by contrast, there was no statistically significant difference between the treatment arms. Since the difference in favour of donanemab is not consistently statistically significant in both sub-populations, the effect is considered to be unreliable. Overall, no relevant difference for the benefit assessment was found for the endpoint of cognition.

For the endpoint category of health-related quality of life, no suitable data are available for the relevant study sub-populations for the benefit assessment.

In the overall rates of SAEs in the endpoint category of side effects, there were no statistically significant differences between the treatment arms.
For the endpoint of therapy discontinuation due to AEs, there was a statistically significant disadvantage of donanemab in both study sub-populations relevant to patient group b.
Detailed analysis of the endpoint of infusion-related reactions showed a statistically significant disadvantage of donanemab in each of the two study sub-populations relevant to patient group b.

Thus, there are no relevant differences for the benefit assessment in the endpoint categories of mortality and morbidity. No suitable data are available for the endpoint category of health-related quality of life. For therapy discontinuation due to AEs in the endpoint category of side effects, there was a statistically significant disadvantage of donanemab.

In a weighted decision, the G-BA concluded that an additional benefit of donanemab for the treatment of adults with a clinical diagnosis of mild dementia due to Alzheimer's disease, who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology, is not proven.

2.1.4 Summary of the assessment

The present benefit assessment refers to the medicinal product Kisunla with the active ingredient donanemab for use in the following therapeutic indication:

"Donanemab is indicated for the treatment of adult patients with a clinical diagnosis of mild cognitive impairment and mild dementia due to Alzheimer's disease (Early symptomatic Alzheimer's disease) who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology."

The following patient populations were distinguished for the benefit assessment:

a) Adults with a clinical diagnosis of mild cognitive impairment due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology

b) Adults with a clinical diagnosis of mild dementia due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology

Data from the AACI study are available for the assessment of the additional benefit. This is a double-blind, randomised study comparing donanemab with placebo over a maximum treatment period of 18 months, if applicable in addition to continued treatment with symptomatic antidementia drugs.

Patient group a

Best supportive care was determined as the appropriate comparator therapy for donanemab.

No suitable data are available for the assessment of the additional benefit in this patient population, as the study sub-populations presented by the pharmaceutical company do not represent patient group a with adequate certainty. The additional benefit of donanemab for the treatment of adults with a clinical diagnosis of mild cognitive impairment due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology is therefore not proven.

Patient group b

Donepezil, galantamine or rivastigmine were determined to be the appropriate comparator therapy for donanemab.

Data based on two sub-populations of the study are used; despite uncertainty regarding the diagnostic staging of mild dementia, these data are considered to be a sufficient approximation to represent patient group b and allow for a comparison of donanemab as an add-on to AChEIs versus AChEIs (donepezil, galantamine or rivastigmine).

With regard to mortality, there were no statistically significant differences between the treatment arms.

For the endpoint of symptomatology, assessed using CDR-SB, in the endpoint category of morbidity, there were no statistically significant differences between the treatment arms. For the endpoint of cognition assessed using ADAS-Cog13, there was a statistically significant advantage of donanemab in one of the two sub-populations analysed; however, there was no statistically significant difference between the treatment arms in the other sub-population. Consequently, the effect in the endpoint of cognition is considered to be unreliable. Overall, there was no relevant difference for the benefit assessment.

For the endpoint category of health-related quality of life, no suitable data are available for the assessment-relevant sub-populations of the study.

In the overall rates of SAEs in the endpoint category of side effects, there were no statistically significant differences between the treatment arms. For the endpoint of therapy discontinuation due to AEs, there was a statistically significant disadvantage of donanemab in both sub-populations analysed.
Furthermore, detailed analysis of the endpoint of infusion-related reactions showed a statistically significant disadvantage of donanemab.

Thus, there are no relevant differences for the benefit assessment in the endpoint categories of mortality and morbidity. No suitable data are available for the endpoint category of health-related quality of life. For therapy discontinuation due to AEs in the endpoint category of side effects, there was a statistically significant disadvantage of donanemab.

In a weighted decision, the G-BA concluded that an additional benefit of donanemab for patient group b is not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The number of patients is based on the target population in statutory health insurance (SHI).

For the present resolution, the figures derived from a calculation by the IQWiG based on the information provided by the pharmaceutical company in the dossier are used.

These are based, among other things, on a prevalence estimate based on a routine SHI data analysis and on a restriction to ApoE ε4 non-carriers and heterozygotes in accordance with the marketing authorisation. In the dossier, further steps were taken to determine the percentage of patients who are eligible for treatment with donanemab using Appropriate Use Criteria (AUC) or Appropriate Use Recommendations (AUR) based on the inclusion and exclusion criteria of approval studies for lecanemab and aducanumab. According to the explanations made by the pharmaceutical company, this takes into account, among other things, comorbidities and monitoring guidelines for adverse events (AEs), e.g. ARIA. Overall, this step leads to a restriction of the target population that does not result from the approved therapeutic indication.

The information used in the resolution is based on the derivation of the figures in the dossier and is obtained without taking the limitation to AUC or AUR into account.
The resulting figures represent the best approximation of the SHI target population to date, particularly due to the more appropriate estimate of the prevalence of dementia compared with the information in the lecanemab dossier. It should be noted that a smaller number of patients can be expected, taking into account contraindications, e.g. treatment with anticoagulants, as well as other requirements (e.g. prior registration in the Controlled Access Programme [CAP]). Limitations in the derivation also arise, among other things, in relation to determining the percentage of patients with dementia due to Alzheimer's disease.

Overall, the information is subject to uncertainty.

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 Kisunla (active ingredient: donanemab) at the following publicly accessible link (last access: 16 March 2026):

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

Treatment with donanemab should only be initiated and monitored by specialists in neurology or specialists in psychiatry and psychotherapy who are experienced in the treatment of Alzheimer's disease and are able to promptly carry out magnetic resonance imaging (MRI) diagnostics.

Before starting treatment with donanemab, patients must be tested for ApoE ε4 status and the presence of amyloid-beta pathology must be confirmed by means of a suitable test.

Treatment with donanemab should be continued until the amyloid plaques have been removed. The maximum treatment duration of 18 months should not be exceeded, even if plaque removal is not confirmed.

The benefit-risk ratio of the treatment should be reassessed at regular intervals on a case-by-case basis, taking into account the extent of disease progression.
Discontinuing treatment before the end of the maximum treatment duration of 18 months must be considered if the patient’s condition progresses to moderate Alzheimer’s dementia.

Donanemab may cause amyloid-related imaging abnormalities (ARIA). In addition to ARIA, intracerebral haemorrhages with a diameter of more than 1 cm occurred in patients treated with donanemab.

Before starting treatment with donanemab, a recent (no more than 6 months old) brain MRI must be available to assess whether ARIA is already present. An MRI scan must be performed before the second infusion (in the 1st month), before the third infusion (in the 2nd month), before the fourth infusion (in the 3rd month) and before the seventh infusion (in the 6th month). Patients with ARIA risk factors should undergo an additional MRI scan after one year of treatment (before the twelfth infusion).
If a patient shows symptoms suggestive of ARIA at any point during treatment, a clinical assessment, including an MRI scan, must be carried out.

Treatment with donanemab must not be initiated in patients who are currently receiving anticoagulant therapy.

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 patient identification card. The training material contains, in particular, information on the above-mentioned requirements for treatment with donanemab and warnings about the risks of ARIA.

Treatment with donanemab must be initiated for all patients via a central registration system that forms part of a controlled access programme.

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 February 2026). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

According to the product information of donanemab, the maximum treatment duration is 18 months.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is different 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.

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.

The treatment costs for best supportive care are different from patient to patient. Because best supportive care has been determined as the appropriate comparator therapy for patient group a, this is also reflected in the medicinal product to be assessed. The type and scope of best supportive care can vary depending on the medicinal product to be assessed and the comparator therapy.

Treatment period:

a) Adults with a clinical diagnosis of mild cognitive impairment due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Donanemab	Continuously, 1 x every 28 days	1st Year: 13.0 Subsequent year: 6.0	1	1st Year: 13.0 Subsequent year: 6.0
Best supportive care	Different from patient to patient			
Appropriate comparator therapy				
Best supportive care	Different from patient to patient			

b) Adults with a clinical diagnosis of mild dementia due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Donanemab	Continuously, 1 x every 28 days	1st Year: 13.0 Subsequent year: 6.0	1	1st Year: 13.0 Subsequent year: 6.0
Appropriate comparator therapy				
Donepezil or galantamine or rivastigmine				
Donepezil	Continuously, 1 x daily	365.0	1	365.0
Galantamine	Continuously, 1 x daily	365.0	1	365.0
Rivastigmine	Continuously, 2 x daily	365.0	1	365.0

Consumption:

a) Adults with a clinical diagnosis of mild cognitive impairment due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology

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					
Donanemab	1st year 1st dose 350 mg, 2nd dose 700 mg, 3rd dose 1,050 mg, 4th – 13th dose 1,400 mg Subsequent year: 1,400 mg	1st year 1st dose 350 mg, 2nd dose 700 mg, 3rd dose 1,050 mg, 4th – 13th dose 1,400 mg Subsequent year: 1,400 mg	1st year 1st dose 1 X 350 mg, 2nd dose 2 X 350 mg, 3rd dose 3 X 350 mg, 4th – 13th dose 4 x 350 mg Subsequent year: 1,400 mg	1st year: 13.0 Subsequent year: 6.0	1st year: 46 x 350 mg Subsequent year: 24 x 350 mg
Best supportive care		Different from patient to patient			
Appropriate comparator 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
Best supportive care		Different from patient to patient			

b) Adults with a clinical diagnosis of mild dementia due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology

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					
Donanemab	1st year 1st dose: 350 mg, 2nd dose: 700 mg, 3rd dose: 1,050 mg, 4th – 13th dose: 1,400 mg Subsequent year: 1,400 mg	1st year 1st dose: 350 mg, 2nd dose: 700 mg, 3rd dose 1,050 mg, 4th – 13th dose 1,400 mg Subsequent year: 1,400 mg	1st year 1st dose: 1 x 350 mg, 2nd dose: 2 x 350 mg, 3rd dose 3 X 350 mg, 4th – 13th dose 4 x 350 mg Subsequent year: 1,400 mg	1st year: 13.0 Subsequent year: 6.0	1st year: 46 x 350 mg Subsequent year: 24 x 350 mg
Appropriate comparator therapy					
Donepezil or galantamine or rivastigmine					
Donepezil	1st and subsequent years 5 mg - 10 mg	1st and subsequent years 5 mg - 10 mg	1st and subsequent years 1 x 5 mg – 1 x 10 mg	365.0	1st and subsequent years 365 x 5 mg – 365 x 10 mg
Galantamine	1st and subsequent years 16 mg – 24 mg	1st and subsequent years 16 mg – 24 mg	1st and subsequent years 1 x 16 mg – 1 x 24 mg	365.0	1st and subsequent years 365 x 16 mg – 365 x 24 mg
Rivastigmine	1st and subsequent years 3 mg – 6 mg	1st and subsequent years 6 mg – 12 mg	1st and subsequent years 2 x 3 mg – 2 x 6 mg	365.0	1st and subsequent years 730 x 3 mg – 730 x 6 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 with a clinical diagnosis of mild cognitive impairment due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology

b) Adults with a clinical diagnosis of mild dementia due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology

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					
Donanemab 350 mg	1 CIS	€ 991.15	€ 1.77	€ 54.25	€ 935.13
Appropriate comparator therapy					
Donepezil 5 mg[3]	98 FCT	€ 63.17	€ 1.77	€ 4.10	€ 57.30
Donepezil 10 mg[3]	98 FCT	€ 66.26	€ 1.77	€ 4.35	€ 60.14
Galantamine 16 mg[3]	84 SRC	€ 57.72	€ 1.77	€ 3.67	€ 52.28
Galantamine 24 mg[3]	84 SRC	€ 59.02	€ 1.77	€ 3.77	€ 53.48
Rivastigmine 3 mg[3]	112 HC	€ 69.90	€ 1.77	€ 4.63	€ 63.50
Rivastigmine 6 mg[3]	112 HC	€ 73.02	€ 1.77	€ 4.88	€ 66.37
Abbreviations: FCT = film-coated tablets; HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; SRC = sustained-release hard capsules					

LAUER-TAXE® last revised: 15 February 2026

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 calculation of the additionally required SHI services is based on the fee structure items (FSI) as of the 3rd quarter of 2025 of the uniform value scale (UVS 2025/Q3).

Prior to treatment and before the 2nd, 3rd, 4th and 7th infusion, magnetic resonance imaging

[3] Fixed reimbursement rate

(MRI) examinations must be performed in accordance with the product information. In addition, patients with risk factors for amyloid-related imaging abnormalities (ARIA) should undergo an additional MRI examination prior to the 12th infusion. In addition, MRI should be carried out if a patient shows symptoms suggestive of ARIA.

Designation of the therapy	Designation of the service	Number	Costs per unit	Costs per patient per year
Donanemab	MRI examination of the neurocranium (FSI 34410)	5	€ 130.50	€ 652.50

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 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 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 agents 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-apply unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

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 designate 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 have 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 have 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 data from the product 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 have 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 statutory 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 a clinical diagnosis of mild cognitive impairment due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology

No medicinal product with new active ingredients for use in combination therapy in compliance with the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information of donanemab (Kisunla); Kisunla® 350 mg; last revised: February 2026

b) Adults with a clinical diagnosis of mild dementia due to Alzheimer's disease who are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers with confirmed amyloid pathology

No medicinal product with new active ingredients for use in combination therapy in compliance with the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information of donanemab (Kisunla); Kisunla® 350 mg; last revised: February 2026

2.6 Percentage of study participants at study sites within the scope of SGB V in accordance with Section 35a, paragraph 3, sentence 5 SGB V

The medicinal product Kisunla is a medicinal product placed on the market from 1 January 2025. In accordance with Section 35a, paragraph 3, sentence 5 SGB V, the G-BA must

determine whether a relevant percentage of the clinical studies on the medicinal product were conducted within the scope of SGB V. This is the case if the percentage of study participants who have participated in the clinical studies on the medicinal product to be assessed in the therapeutic indication to be assessed at study sites within the scope of SGB V is at least five per cent of the total number of study participants.

The calculation is based on all studies that were submitted as part of the benefit assessment dossier in the therapeutic indication to be assessed in accordance with Section 35a, paragraph 1, sentence 3 SGB V in conjunction with Section 4, paragraph 6 AM-NutzenV.

Approval studies include all studies submitted to the regulatory authority in section 2.7.3 (Summary of Clinical Efficacy) and 2.7.4 (Summary of Clinical Safety) of the authorisation dossier in the therapeutic indication for which marketing authorisation has been applied for. In addition, studies, which were conducted in whole or in part within the therapeutic indication described in this document, and in which the company was a sponsor or is otherwise financially involved, must also be indicated.

The percentage of study participants in the clinical studies of the medicinal product conducted or commissioned by the pharmaceutical company in the therapeutic indication to be assessed who participated at study sites within the scope of SGB V (German Social Security Code) is < 5% (0%) of the total number of study participants according to the information provided by the pharmaceutical company.

In the dossier, the pharmaceutical company provides details of a total of 7 studies. Uncertainty arises from the absence of SAS extracts and discrepancies between the information in the registry entries and the information provided by the pharmaceutical company in the dossier regarding two of the 7 studies. Furthermore, another study has been identified, in which it is unclear whether this should also be taken into account.

Despite the discrepancies and missing information described above, it can be assumed that the percentage of study participants at study sites within the scope of SGB V remains at 0%.

The clinical studies of the medicinal product in the therapeutic indication to be assessed were therefore not conducted to a relevant percentage within the scope of 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 their session on 9 April 2024, 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. The Subcommittee on Medicinal Products newly determined the appropriate comparator therapy at their session on 9 September 2025.

On 20 October 2025, the pharmaceutical company submitted a dossier for the benefit assessment of donanemab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 23 October 2025 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 donanemab.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 January 2026, and the written statement procedure was initiated with publication on the G-BA website on 2 February 2026. The deadline for submitting written statements was 23 February 2026.

The oral hearing took place on 9 March 2026.

By letter dated 10 March 2026, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 27 March 2026.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the Subcommittee's session on 8 April 2026, and the draft resolution was approved.

At its session on 16 April 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	9 April 2024	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	9 September 2025	New determination of the appropriate comparator therapy
Working group Section 35a	3 March 2026	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	9 March 2026	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	17 March 2026 31 March 2026	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	8 April 2026	Concluding discussion of the draft resolution
Plenum	16 April 2026	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 16 April 2026

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken