Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Lisdexamfetamine dimesylate (new therapeutic indication: ADHD, adult patients)

of 17 October 2019

Contents

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for 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 shall pass a resolution on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

On 18 March 2013, the active ingredient lisdexamfetamine dimesylate received marketing authorisation for the treatment of attention deficit hyperactivity disorder (ADHD) in children aged 6 and over. On 1 June 2013, the medicinal product with the trade name Elvanse was listed for the first time in the LAUER-TAXE®.

On 26 February 2019, this active ingredient was also granted marketing authorisation for the treatment of attention deficit hyperactivity disorder (ADHD) in adults. On 1 May 2019, the new medicinal product with this therapeutic indication (trade name: Elvanse Adult) was placed on the market.

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 30 April 2019.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 August 2019, 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 lisdexamfetamine dimesylate 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 lisdexamfetamine dimesylate.

In the light of the above and taking into account the comments received and the oral hearing, the G-BA has arrived at 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 lisdexamfetamine dimesylate (Elvanse Adult®) in accordance with product information

Elvanse® Adult is indicated as part of an overall therapeutic strategy for the treatment of attention deficit hyperactivity disorder (ADHD) in adults.

Elvanse Adult® is not indicated for all adult patients, and the decision to use this medicinal product must take into account the patient's profile. This entails a comprehensive assessment of the severity and chronicity of the patient's symptoms, the potential for abuse, misuse, or diversion, and clinical response to previous medicinal therapies for the treatment of ADHD.

The treatment must be carried out under the supervision of a specialist for behavioural disorders. The diagnosis should be based on a complete anamnesis and examination of the patient according to current DSM criteria or ICD guidelines. The diagnosis must not be based solely on the presence of one or more symptoms. Adults must have symptoms of ADHD that have existed since childhood. This should be confirmed retrospectively (through patient treatment documentation or, if not available, appropriate structured tools or interviews). According to the clinical assessment, ADHD should be of at least moderate severity, be expressed as at least moderate functional impairment in two or more situations (such as social, academic and/or occupational performance), and affect several aspects of the life of the individual concerned.

The specific aetiology of this syndrome is unknown. A specific diagnostic test is not available. An adequate diagnosis requires the consideration of medical and special psychological, pedagogical sources as well as the social environment.

An overall therapeutic strategy usually includes psychological, pedagogical, behavioural, occupational, social and pharmacotherapeutic measures and aims at stabilising the adult patient with a behavioural syndrome that may be characterised by the following chronic symptoms in the anamnesis: short attention span, distractibility, impulsiveness, and hyperactivity.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with attention deficit hyperactivity disorder (ADHD) since childhood with at least moderate severity (at least moderate functional impairment in two or more situations and affecting several aspects of life) who have already received medicinal therapy:

A patient-individual therapy involving the selection of atomoxetine and methylphenidate in which the possible continuation or resumption with a medicinal product already used must also be examined and described as part of an overall therapeutic strategy.

b) Adults with attention deficit hyperactivity disorder (ADHD) since childhood with at least moderate severity (at least moderate functional impairment in two or more situations and affecting several aspects of life) who have not yet been treated with medication:

Atomoxetine or methylphenidate as part of an overall therapeutic strategy.

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication 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 Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. Methylphenidate and atomoxetine are approved for the treatment of adults with attention deficit hyperactivity disorders as part of an overall therapeutic strategy.

On 2. ADHD treatment is part of an overall therapeutic strategy that includes non-medicinal interventions. Because medicinal products may be prescribed only if other measures have proved inadequate, further non-medicinal measures cannot be considered as appropriate comparator therapy.

On 3. There are no resolutions on the benefit assessment of medicinal products in the therapeutic indication ADHD in adult patients.

For lisdexamfetamine dimesylate in the therapeutic indication children and adolescents with ADHD, there is a resolution on the benefit assessment in accordance with Section 35a SGB V dated 14 November 2013.

According to the resolution of the G-BA last amended on 5 July 2019 on statutory exclusion from prescriptions for the provision of medicinal products and authorised exceptions (Medicines Directive, Annex III to No. 44), stimulants (e.g. psychoanaleptica, psychoenergetics, and caffeine-containing substances) are excluded from provision in accordance with Section 31 SGB V. Excluded is the prescription as part of an overall therapeutic strategy for adults from the age of 18 with hyperkinetic disorder or attention deficit/hyperactivity disorder (ADS/ADHD) if the disease already existed in childhood if other measures alone have proven to be inadequate.

On 4. The generally accepted state of medical knowledge was illustrated by a guideline search and an evidence search. In this respect, it can be stated that the evidence available is limited with regard to the selection of the available medicinal products, atomoxetine and methylphenidate.

For patient population a) which is already receiving or has received medicinal therapy in the past, experience from this previous therapy may lead to a preference for one of the two substances. This situation is taken into account by determining a patient-individual therapy with the selection of atomoxetine and methylphenidate. When considering the previous therapy, the current therapy decision may include a change as well as the continuation or resumption with a medicinal product already used.

For patient population b), which has not yet been treated with medication, no criteria which would prefer one of the substances can be derived. Therefore, both active ingredients are regarded as equally appropriate therapy alternatives for patients.

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

2.1.3 Extent and probability of the additional benefit

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

a) Adults with attention deficit hyperactivity disorder (ADHD) since childhood with at least moderate severity (at least moderate functional impairment in two or more situations and affecting several aspects of life) who have already received medicinal therapy:
An additional benefit is not proven.

b) Adults with attention deficit hyperactivity disorder (ADHD) since childhood with at least moderate severity (at least moderate functional impairment in two or more situations and affecting several aspects of life) who have not yet been treated with medication:
An additional benefit is not proven.

Justification:

To demonstrate an additional benefit of lisdexamfetamine dimesylate compared with the appropriate comparator therapy, 5 RCTs were submitted by the pharmaceutical company. In the absence of direct comparative studies, two adjusted indirect comparisons with 2 RCTs each were performed. Lisdexamfetamine and atomoxetine (SPD489-403 and NCT00510276) and lisdexamfetamine and methylphenidate (NRP104.303 and NCT01259492) were compared using placebo as a bridge comparator. A study with cross-over design (SP489-316) was not used for indirect comparison because no suitable study with the appropriate comparator therapy was identified. The respective duration of application for the 4 studies included, including the initial dose titration, was between 4 and 12 weeks. In the dossier presented, the patient populations were not distributed by a certain appropriate comparator therapy.

The studies submitted are not suitable for establishing an additional benefit of lisdexamfetamine dimesylate compared with the appropriate comparator therapy because for the previous therapy, it was not sufficiently documented that the treatment included an overall therapeutic concept. Nor did the studies guarantee this. It is therefore not to be assumed that the use will be compliant with marketing authorisation. In addition, the duration of the study was too short for a benefit assessment in a chronic disease.

According to the product information, lisdexamfetamine dimesylate, methylphenidate, and atomoxetine are authorised only as part of an overall therapeutic strategy or comprehensive treatment programme. Similarly, Annex III, No. 44 of the Pharmaceuticals Directive provides an exclusion from prescription for stimulants unless ADHD is treated as part of an overall therapeutic strategy and other measures alone have proved insufficient. The corresponding product information states that this overall strategy usually includes psychological, educational, social, and pharmacotherapeutic measures. It must be decided on an patient-individual basis which measures should be considered.

The documents on the lisdexamfetamine studies (NRP104.303, SPD489-316, and SPD489-403) as well as the atomoxetine study (NCT00510276) and the methylphenidate study (NCT01259492) do not show that an overall therapeutic strategy was required or offered as part of the treatment. Earlier or planned measures as part of an overall therapeutic strategy were not documented. There were also some limitations with regard to the therapeutic measures taken in the course of the study.

Accordingly, the treatment was not performed in accordance with the marketing authorisation as part of an overall therapeutic strategy or comprehensive treatment programme. However, the benefit assessment according to Section 35a SGB V refers to a benefit assessment of medicinal products within the framework of their marketing authorisation. The appropriate comparator therapy also provides for the use of atomoxetine and methylphenidate as part of an overall therapeutic concept. The appropriate comparator therapy was therefore not implemented.

In addition, ADHD is a chronic disease that may require long-term medicinal treatment. The studies on lisdexamfetamine presented in the dossier with a total duration of treatment of four to ten weeks (including the dose titration phases) were too short to cover long-term response and also medium and long-term adverse effects. Thus, the studies are too short to be able to determine an additional benefit.

In summary, the adjusted indirect comparisons presented could not be used to assess the additional benefit compared with the appropriate comparator therapy. Thus, the dossier of the pharmaceutical company did not provide any proof of additional benefit compared with the appropriate comparator therapy.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of a new therapeutic indication for the active ingredient lisdexamfetamine dimesylate. The therapeutic indication assessed here is as follows: Treatment of attention deficit hyperactivity disorders (ADHD) in adults as part of an overall therapeutic strategy.

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

Patient population a) Adults with attention deficit hyperactivity disorder (ADHD) since childhood with at least moderate severity (at least moderate functional impairment in two or more situations and affecting several aspects of life) who have already received medicinal therapy:

The G-BA determined the appropriate comparator therapy to be a patient-individual therapy involving the selection of atomoxetine and methylphenidate in which the possible continuation or resumption with a medicinal product already used must also be examined and described as part of an overall therapeutic strategy.

The pharmaceutical company makes two adjusted indirect comparisons of two studies each on the bridge comparator placebo in order to demonstrate the additional benefit. However, the studies included are not suitable for the benefit assessment because the use of the medicinal products in the studies was not compliant with marketing authorisation, the appropriate comparator therapy was not implemented, and the study duration was too short to assess the additional benefit. Thus, the dossier of the pharmaceutical company did not provide any proof of additional benefit compared with the appropriate comparator therapy.

Therefore, in the overall picture, for patient population a), an additional benefit is not proven.

Patient population b) Adults with attention deficit hyperactivity disorder (ADHD) since childhood with at least moderate severity (at least moderate functional impairment in two or more situations and affecting several aspects of life) who have not yet been treated with medication:

The G-BA determined atomoxetine or methylphenidate to be an appropriate comparator therapy within the framework of an overall therapeutic strategy.

The pharmaceutical company makes two adjusted indirect comparisons of two studies each on the bridge comparator placebo in order to demonstrate the additional benefit. However, the studies included are not suitable for the benefit assessment because the use of the medicinal products in the studies was not compliant with marketing authorisation, the appropriate comparator therapy was not implemented, and the study duration was too short. Thus, the dossier of the pharmaceutical company did not provide any proof of additional benefit compared with the appropriate comparator therapy.

Therefore, in the overall picture, for patient population b), an additional benefit is not proven.

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

The G-BA bases the resolution on the number stated by the pharmaceutical company in the dossier. This results in a number of approx. 73,000 patients for the therapeutic indication of lisdexamfetamine dimesylate in adults. The IQWIG estimates this number to be uncertain.

The pharmaceutical company assumes an ADHD prevalence rate of 0.4% in adults, which results in 243,364 adults with statutory health insurance and ADHD. Based on a current care study, it was assumed that 30% of adult ADHD patients are available for medicinal treatment. However, it is not clear from the publication whether these patients have been pretreated,

which is why no distinction has been made between the sub-populations. This results in a SHI target population (consisting of sub-populations a + b) of 73,009 patients. One uncertainty to be considered is that the proportion of patients treated with medication (30%) only covers the age group between 30 and 50 years. Furthermore, the restriction of the therapeutic indication to at least a moderate severity of the symptomatology was considered only on the basis of the medication quota.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account.

Treatment with lisdexamfetamine dimesylate may only be initiated and monitored by a specialist for behavioural disorders in adults (specialist for neurology and/or psychiatry or for psychiatry and psychotherapy, specialist for psychosomatic medicine and psychotherapy, medical psychotherapists according to the demand planning guideline). In therapeutically justified cases, in the case of continued treatment in a transitional phase up to the maximum age of 21, prescriptions can also be made by specialists for behavioural disorders in children and adolescents. In exceptional cases, general practitioners may also make follow-up prescriptions if it is ensured that the supervision is carried out by a specialist for behavioural disorders.

The use of stimulants in the course of the treatment, in particular long-term therapy over 12 months, must be documented as well as the assessment of non-treatment periods, which should take place at least once a year.

The potential for abuse, misuse or misappropriation of lisdexamfetamine dimesylate should be considered prior to the prescription.

Officially approved training materials are available for both pre-treatment investigations and ongoing monitoring.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 October 2019).

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Sections 130 and 130 a 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.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year, even if the actual treatment duration is patient-individual and/or is shorter on average.

For atomoxetine, initial doses of 40 mg daily are recommended. The dose is titrated according to clinical efficacy and tolerability. For the cost calculation, the recommended maintenance dose of 80–100 mg daily was selected and depicted.

The recommended starting dose of methylphenidate is 20 mg once daily. At the doctor's discretion, an initial dose of 10 mg/day can also be started. The recommended dose of 20

mg was set as the lower limit for the cost calculation. The maximum daily dose of 80 mg is the upper limit.

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				
Lisdexamfetamine	continuous, 1 × daily	365	1	365
Appropriate comparator therapy				
Atomoxetine	continuous, 1 × daily	365	1	365
Methylphenidate	continuous, 1 × daily	365	1	365

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual mean consumption according to potency
Medicinal product to be assessed					
Lisdexamfetamine	30 mg – 70 mg	30 mg – 70 mg	1 × 30 mg – 1 × 70 mg	365	365 × 30 mg – 365 × 70 mg
Appropriate comparator therapy					
Atomoxetine	80 mg– 100 mg	80 mg - 100 mg	1 × 80 mg - 1 × 100 mg	365	365 × 80 mg - 365 × 100 mg
Methylphenidate	20 mg - 80 mg	20 mg - 80 mg	1 × 20 mg - 2 × 40 mg	365	365 × 20 mg - 730 × 40 mg

Costs of the medicinal product:

Designation of the therapy	Package 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					
Lisdexamfetamine 30 mg	30 HC	€ 109.73	€ 1.77	€ 0.00	€ 107.96
Lisdexamfetamine 70 mg	30 HC	€ 120.29	€ 1.77	€ 0.00	€ 118.52
Appropriate comparator therapy					
Atomoxetine 80 mg	56 HC	€ 158.34	€ 1.77	€ 6.99	€ 149.58
Atomoxetin 100 mg	56 HC	€ 158.34	€ 1.77	€ 6.99	€ 149.58
Methylphenidate 20 mg[2]	56 HC	€ 48.46	€ 1.77	€ 2.96	€ 43.73
Methylphenidate 40 mg[2]	56 HC	€ 89.87	€ 1.77	€ 6.24	€ 81.86
Abbreviations: HC = hard capsules					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 October 2019

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 standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs

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.

[2] Fixed amount

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 27 November 2018.

On 30 April 2019, the pharmaceutical company submitted a dossier for the benefit assessment of lisdexamfetamine dimesylate to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 30 April 2019 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 lisdexamfetamine dimesylate.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 July 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 1 August 2019. The deadline for submitting written statements was 22 August 2019.

The oral hearing was held on 9 September 2019.

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 session of the subcommittee on 8 October 2019, and the proposed resolution was approved.

At its session on 17 October 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	27 November 2018	Determination of the appropriate comparator therapy
Working group Section 35a	3 September 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	9 September 2019	Conduct of the oral hearing
Working group Section 35a	17 September 2019 1 October 2019	Advice on the dossier evaluation of the Institute for Quality and Efficiency in Health Care (IQWiG), evaluation of the written statement procedure
Subcommittee Medicinal product	8 October 2019	Concluding discussion of the proposed resolution
Plenum	17 October 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 17 October 2019

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

Prof Hecken