

IQWiG Reports – Commission No. A13-24

Lisdexamfetamine dimesylate – Benefit assessment according to § 35a Social Code Book V¹

Extract

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³ Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ADHD	attention deficit/hyperactivity disorder
ADHD-RS	Attention Deficit/Hyperactivity Disorder Rating Scale
CGI-S	Clinical Global Impression Scale of Severity
DSM	Diagnostic and Statistical Manual of Mental Disorders
EMA	European Medicines Agency
G-BA	<i>Gemeinsamer Bundesausschuss</i> (Federal Joint Committee)
IQWiG	<i>Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen</i> (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	<i>Sozialgesetzbuch</i> (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug lisdexamfetamine dimesylate (hereinafter referred to as "lisdexamfetamine"). The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to "the company"). The dossier was sent to IQWiG on 3 June 2013.

Research question

The aim of this report was to assess the added benefit of lisdexamfetamine as part of a comprehensive treatment programme for attention deficit/hyperactivity disorder (ADHD) in children aged 6 years of age and over when response to previous methylphenidate treatment is considered clinically inadequate, in comparison with the appropriate comparator therapy (ACT) atomoxetine.

In accordance with the G-BA, the company cited atomoxetine as ACT for lisdexamfetamine, which is indicated as part of a comprehensive treatment programme for ADHD in children aged 6 years of age and over when response to previous methylphenidate treatment is considered clinically inadequate. The benefit assessment of lisdexamfetamine was conducted in comparison with atomoxetine.

The assessment was conducted based on patient-relevant outcomes and on direct comparative randomized controlled trials (RCTs).

Results

The company presented no relevant study for the assessment of the added benefit of lisdexamfetamine versus the ACT.

The company included the study SPD489-317 in its study pool. This study was unsuitable for the assessment of the added benefit of lisdexamfetamine, however, because, in the study, neither lisdexamfetamine nor atomoxetine were administered according to the German approval status. Hence the ACT specified by the G-BA was also not implemented. Moreover, the study duration was too short for the assessment of the added benefit of lisdexamfetamine.

Lisdexamfetamine and atomoxetine not administered according to their approval / no implementation of ACT

The requirements for the implementation of the intervention and the ACT derive from the German approval status of lisdexamfetamine and atomoxetine. According to the approval for the therapeutic indication of lisdexamfetamine, this is indicated as part of a comprehensive treatment programme.

The Summary of Product Characteristics (SPC) of the ACT atomoxetine also states that the drug is only approved as part of a comprehensive treatment programme.

Hence both treatment with lisdexamfetamine and treatment with atomoxetine are only approved as part of a multimodal treatment for ADHD (comprehensive treatment programme). The SPCs both of lisdexamfetamine and of atomoxetine describe that a comprehensive treatment programme typically includes psychological, educational and social measures. The SPC of lisdexamfetamine additionally regards appropriate educational placement as essential and psychosocial intervention as generally necessary.

The company itself mentioned the necessity of a comprehensive treatment programme in several places in the dossier. For the assessment of the added benefit, it used the study SPD489-317 nevertheless, in which lisdexamfetamine and atomoxetine were considered exclusively as drug treatment, but which did not address a comprehensive treatment programme.

The study did not include offers of psychological, educational or social measures, which could have been used, for example. The patients (and parents) did also not have to undergo consultation to adapt possibly existing measures or take on others (e.g. measures that would have been more suitable for the patients and their families than previous ones).

In addition, it was only possible to a limited extent to continue any non-drug interventions that were started before the start of the study. Only 21.8% of the patients had previously received any non-drug ADHD treatment at all, and only 8% of the patients continued their non-drug treatment in the study.

Hence neither lisdexamfetamine nor atomoxetine were used according to their German approval status in the study SPD489-317. This means at the same time that the ACT specified by the G-BA was not implemented because no comprehensive treatment programme was used for the treatment of children and young people.

Apart from the aspects of the German approval status and the ACT described above, stimulants such as lisdexamfetamine are excluded from prescription according to the Directive for prescribing pharmaceuticals in contracted doctor care, with the exception of prescription for ADHD as part of a comprehensive treatment programme. Hence stimulants can only be prescribed as part of a comprehensive treatment programme for ADHD.

Study duration too short

Apart from the flaws regarding both the use of lisdexamfetamine and atomoxetine in their respective approval status and the ACT, the study duration of the study SPD489-317 included by the company with a treatment duration of 9 weeks in total was too short to assess the added benefit of lisdexamfetamine.

Since ADHD is a chronic disease and, according to the SPC of lisdexamfetamine, a drug treatment of ADHD may be necessary over a longer period of time, the study SPD489-317 was too short to guarantee a treatment and observation duration of sufficient length.

Summary

Overall, the company presented no study suitable for the benefit assessment. Therefore no proof of an added benefit of lisdexamfetamine in comparison with the ACT specified by the G-BA can be inferred from the assessment presented in the company's dossier.

Extent and probability of added benefit, patient groups with therapeutically important added benefit⁴

On the basis of the results presented, the extent and probability of the added benefit of the drug lisdexamfetamine compared with the ACT is assessed as follows:

Table 2: Extent and probability of the added benefit of lisdexamfetamine

Therapeutic indication	ACT	Extent and probability of added benefit
Treatment of ADHD in children aged 6 years of age and over as part of a comprehensive treatment programme when response to previous methylphenidate treatment is considered clinically inadequate	Atomoxetine	Added benefit not proven
ACT: appropriate comparator therapy; ADHD: attention deficit/hyperactivity disorder		

The G-BA decides on added benefit.

⁴ On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1-3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

2.2 Research question

The aim of this report was to assess the added benefit of lisdexamfetamine as part of a comprehensive treatment programme for ADHD in children aged 6 years of age and over when response to previous methylphenidate treatment is considered clinically inadequate, in comparison with the ACT.

In accordance with the G-BA, the company cited atomoxetine as ACT for lisdexamfetamine, which is indicated as part of a comprehensive treatment programme for ADHD in children aged 6 years of age and over when response to previous methylphenidate treatment is considered clinically inadequate. The benefit assessment of lisdexamfetamine was conducted in comparison with atomoxetine.

The assessment was conducted based on patient-relevant outcomes and on direct comparative RCTs.

Further information about the research question can be found in Module 3, Section 3.1, and Module 4, Section 4.2.1 of the dossier, and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on lisdexamfetamine (studies completed up to 10 April 2013)
- bibliographical literature search on lisdexamfetamine (last search on 9 April 2013)
- search in trial registries for studies on lisdexamfetamine (last search on 11 April 2013)

The Institute's own search to check the search results of the company:

- bibliographical literature search on lisdexamfetamine (last search on 18 June 2013)
- search in trial registries for studies on lisdexamfetamine (last search on 11 June 2013)

The study SPD489-317 [3], which directly compared lisdexamfetamine with atomoxetine in the relevant therapeutic indication, was identified from the steps of information retrieval mentioned. This study concurred with the study pool of the company.

The study SPD489-317 was unsuitable for the assessment of the added benefit of lisdexamfetamine in comparison with the ACT specified by the G-BA, however.

[Table 3](#) and [Table 4](#) show the characteristics of the study and of the interventions of study SPD489-317.

Table 3: Characteristics of the study SPD489-317

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
SDP489-317	RCT, double-blind, active-controlled, parallel, multicentre	Children and young people (6-17 years) diagnosed with ADHD according to DSM-IV criteria (and an ADHD-RS-IV Total Score of ≥ 28 at baseline) and clinically inadequate response to MPH	Lisdexamfetamine (N = 132) Atomoxetine (N = 135)	<ul style="list-style-type: none"> ▪ Prerandomization phase^b: 2 weeks ▪ Double-blind phase: <ul style="list-style-type: none"> ▫ titration phase: 4 weeks ▫ maintenance phase: 5 weeks ▪ Follow-up phase: 1 week 	51 centres in Europe (Belgium, Germany, Italy, Poland, Sweden, Spain, Hungary) and North America (Canada, USA) Jun 2010-Jul 2012	Primary: time to first response to treatment (defined as CGI-I value of 1 or 2) Secondary: <ul style="list-style-type: none"> ▪ symptoms ▪ health-related quality of life ▪ AEs
a: Primary outcomes contain information without consideration of the relevance for the present benefit assessment. Secondary outcomes only contain information on relevant available outcomes for this benefit assessment. b: Including discontinuation of ongoing ADHD medication 7 days before the start of the double-blind phase. ADHD: attention deficit/hyperactivity disorder; ADHD-RS: Attention Deficit/Hyperactivity Disorder Rating Scale; AE: adverse event; CGI-I: Clinical Global Impression Scale of Improvement; DSM: Diagnostic and Statistical Manual of Mental Disorders; MPH: methylphenidate; N: number of randomized patients; RCT: randomized controlled trial						

Table 4: Characteristics of the interventions in the study SPD489-317

Study	Intervention	Comparison
SPD489-317	<p>Lisdexamfetamine:</p> <ul style="list-style-type: none">▪ individual dose:▪ 30–70 mg/day▪ titration: starting dose: 30 mg/day dose increase as needed in 20 mg steps to 50 mg/day at the start of the second week, and to 70 mg/day at the start of the third week	<p>Atomoxetine:</p> <ul style="list-style-type: none">▪ individual dose:<ul style="list-style-type: none">▫ patients < 70 kg: ~ 1.2 mg/kg/day (not > 1.4 mg/kg/day)▫ patients ≥ 70 kg: 80–100 mg/day▪ titration:<ul style="list-style-type: none">▫ patients < 70 kg: starting dose: 0.5 mg/kg/day dose increase to approx. 1.2 mg/kg/day at the start of the second week▫ patients ≥ 70 kg: starting dose: 40 mg/day dose increase to 80 mg/day at the start of the second week and, as needed, to 100 mg/day at the start of the third week
<p>Implementation of a comprehensive treatment programme: no information</p> <p>Possibility to continue behavioural therapy if this therapy had been ongoing for at least 1 month at the time of randomization^a. All planned changes of the behavioural therapy had to be discussed with the "Medical Monitor" of the CRO.</p>		
<p>a: 21.8% of the patients received prior non-drug treatment for their ADHD, 8% continued this treatment in the study.</p> <p>ADHD: attention deficit/hyperactivity disorder; CRO: Contract Research Organization; RCT: randomized controlled trial</p>		

The study SPD489-317 was a completed, randomized, double-blind study with a direct comparison of lisdexamfetamine with atomoxetine.

Children and young people aged 6 to 17 years diagnosed with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria and clinically inadequate response to methylphenidate were included in the study. The patients had to present with an ADHD Rating Scale IV (ADHD-RS-IV) Total Score of ≥ 28 at the start of the study after discontinuation of prior ADHD medication. The company described ADHD patients with an ADHD-RS-IV Total Score of ≥ 28 as at least moderately affected. Allocating the Total Score of ≥ 28 to a severity grade is not obvious because the company did not cite any literature for its justification. However, it can be derived from the patient characteristics that the clinical assessment of the ADHD severity by the investigator using an additional scale (Clinical Global Improvement – Severity [CGI-S]) described the patients on average as markedly ill (CGI-S of 5; median/mean [standard deviation]: 5.0/5.0 [0.8]). This assessment exceeded an assessment of moderate illness (CGI-S 4). These data therefore supported the company's claim that the study comprised at least mostly patients with ADHD of at least moderate severity.

Overall, the study SPD489-317 was unsuitable for the benefit assessment of lisdexamfetamine, however, because, in the study, neither lisdexamfetamine nor atomoxetine were administered according to the German approval status. Hence the ACT specified by the G-BA was also not implemented. Moreover, the study duration was too short for the benefit assessment of a drug for the treatment of a chronic disease.

Detailed reasons for exclusion are given below.

Lisdexamfetamine and atomoxetine not administered according to their approval / no implementation of ACT

The requirements for the implementation of the intervention and the ACT derive from the German approval status of lisdexamfetamine and atomoxetine. According to the approval for the therapeutic indication of lisdexamfetamine [4], this is indicated as part of a comprehensive treatment programme. According to the SPC, this programme includes both psychological, educational and social measures as well as pharmacotherapy. The SPC also regards appropriate educational placement as essential and psychosocial intervention as generally necessary.

The SPC of atomoxetine [5] also states that the drug is only approved as part of a comprehensive treatment programme. According to the SPC, a comprehensive treatment programme typically includes psychological, educational and social measures.

Hence both treatment with lisdexamfetamine and treatment with atomoxetine are only approved as part of a multimodal treatment for ADHD. Both SPCs describe the same content of the comprehensive treatment programme.

The company itself mentioned the necessity of a comprehensive treatment programme in several places in the dossier, for example, when it described its ACT in accordance with the G-BA, the treatment options for ADHD and the approval status of lisdexamfetamine (Sections 3.1 and 3.2 in Module 3, and Section 4.2.1 in Module 4). However, it did not define any corresponding criteria for the study inclusion for its dossier (see Section 2.7.2.1 of the full dossier assessment) and used the study SPD489-317 for the assessment of the added benefit, in which lisdexamfetamine and atomoxetine were considered exclusively as drug treatment, but which did not address a comprehensive treatment programme.

The study did not include offers of psychological, educational or social measures, which could have been used, for example. The patients (and parents) did also not have to undergo consultation to adapt possibly existing measures or take on others (e.g. measures that would have been more suitable for the patients and their families than previous ones).

In addition, it was only possible to a limited extent to continue any non-drug interventions that were started before the start of the study. Hence it was clear from the study documents that only a very small proportion of the patients received a comprehensive treatment

programme. The concomitant treatment permitted in the study allowed to continue an ongoing behavioural treatment within the framework of the study only if it had been conducted for at least 1 month at the time of randomization. Only 21.8% of the patients had previously received any non-drug ADHD treatment at all, of which 17.2% had received behavioural treatment and consultations (double counting of patients was not excluded). Other non-drug treatments included measures like family therapy or parents' training. Only 8% of the patients continued their non-drug ADHD treatment in the study.

Hence neither lisdexamfetamine nor atomoxetine were used according to their German approval status in the study SPD489-317. This means at the same time that the ACT specified by the G-BA was not implemented because no comprehensive treatment programme was used for the treatment of children and young people.

Apart from the aspects of the German approval status and the ACT described above, stimulants such as lisdexamfetamine are excluded from prescription according to the Directive for prescribing pharmaceuticals in contracted doctor care, with the exception of prescription for ADHD as part of a comprehensive treatment programme [6]. Hence stimulants can only be prescribed as part of a comprehensive treatment programme for ADHD.

Nowhere in the dossier did the company establish a relation between the requirements and its study included in the benefit assessment and to the use of lisdexamfetamine in the study.

Study duration too short

The company did not define a minimum study duration for the assessment of the added benefit of lisdexamfetamine. The patients in the study SPD489-317 included by the company were treated with the respective study medication for 9 weeks in total during the double-blind phase.

In Section 4.2.5.2 of Module 4, the company described an observation period of 7 to 9 weeks as patient-relevant. It argued that Banaschewski 2010 [7] cited a period of approximately 6 weeks, after which the treatment options would have to be re-assessed if the response was inadequate. According to the company, Mattingly 2013 [8] described that about 75% of the patients who showed a response to treatment after 4 to 6 weeks, also showed a stable treatment response after a period of 5 to 12 months. According to the company, it was shown in Vitiello 2012 [9] that more than half of the patients with clinically inadequate or no response to methylphenidate after 5 weeks also showed no change in treatment response after 6 months. The company finally referred to Atzori 2009 [10], whose result showed that 70% of the patients aged 4 to 16 years who had taken methylphenidate for a month, still had treatment after 36 months or were able to discontinue the medication because they had achieved symptom remission.

The company's arguments did not result in an acceptance of a short-term study as sufficient for assessing the added benefit of a drug for the treatment of a chronic disease. The European

Medicines Agency (EMA [11]) distinguishes between short- and long-term trials in the treatment of ADHD. A treatment duration of at least 6 weeks on stable dose is recommended for short-term trials. The study SPD489-317 fulfilled this criterion because it was clear from the Figure on study design in Module 4 that the dose could be last adapted in week 3 of the titration phase. The time during which the patients were treated with a stable dose of the study medication therefore added up to 6 weeks in total. Because of the chronic course of ADHD, EMA requires demonstration of efficacy to be established in at least one long-term trial in addition to a short-term trial. This study is recommended to have a treatment duration of 6 months.

The General Methods of the Institute [1] also describe that short-term studies for the evaluation of interventions for the treatment of chronic diseases are not usually suitable to achieve a complete benefit assessment. This especially applies if treatment is required for several years, or even lifelong.

ADHD is a chronic disease. According to the SPC of lisdexamfetamine [4], drug treatment of ADHD may be required for a longer period of time. Hence the study SPD489-317 was too short to be able to assess the added benefit of lisdexamfetamine versus the ACT.

Additional comments on dosage and titration of lisdexamfetamine and atomoxetine

The dosage and titration of lisdexamfetamine in the study SPD489-317 was conducted according to the specifications of the SPC [4].

The comparison of the implementation of the dosage and titration of atomoxetine in the study SPD489-317 with the specifications of the SPC [5] showed that the dosage and titration of atomoxetine was generally conducted within the framework of the approval. However, 2 aspects stood out which might influence the interpretation of the study results:

1. According to the SPC of atomoxetine "Patients who do not achieve a satisfactory clinical response (tolerability [e.g. nausea or somnolence] or efficacy) when taking [...] a single daily dose might benefit from taking it as twice daily evenly divided doses in the morning and late afternoon or early evening". In the study, the daily dose of atomoxetine was taken as a single dose in the morning. Because of this, reduced efficacy over the day or more adverse events than after divided doses might have been observed in some patients under the conditions of the study.
2. Dose titration of atomoxetine based on body weight in patients < 70 kg was not performed individually, but based on weight classes. These were tailored to the strengths of atomoxetine capsules available in the study. [Table 5](#) contains the weight classes formed for the study, the corresponding starting doses and target doses envisaged as well as the maintenance doses from the start of the second week.

Table 5: Dosage and titration guidelines for atomoxetine in patients < 70 kg

Body weight at the start of the study [kg] ^a	Target starting dose (0.5 mg/kg) [mg]	Target maintenance dose (~ 1.2 mg/kg; no exceedance of 1.4 mg/kg) [mg]	Dose range of the maintenance dose within the weight class ^b [mg/kg]
22.7–29.9	10	25	1.1–0.8
30.0–44.5	18	40	1.3–0.9
44.6–64.5	25	60	1.3–0.9
64.6–69.9	40	80	1.2–1.1

a: Allowed daily doses of atomoxetine for patients < 70 kg body weight: 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg; dependent on the weight at the start of the study.
b: Institute's calculation

This type of dose titration led to a treatment of the patients in an overall dose range of 0.8 to 1.3 mg/kg. Hence the dosage of some patients was up to a third lower than the target maintenance dose of ~ 1.2 mg/kg recommended in the SPC so that these patients were rather underdosed. This could have led to an underestimation of the efficacy of atomoxetine in some patients in the study. On the other hand, fewer adverse events might have occurred than under the recommended daily dose of approximately 1.2 mg/kg because of the underdosage. The dose range of up to 1.4 mg/kg specified for the study was not exhausted.

Summary

The study SPD489-317 included by the company was unsuitable for answering the present research question. The German approval stipulates a comprehensive treatment programme both for lisdexamfetamine and for atomoxetine, and hence this also forms part of the ACT.

The company adopted the ACT specified by the G-BA. For the assessment of the added benefit of lisdexamfetamine, it used a study nevertheless, in which lisdexamfetamine and atomoxetine were considered exclusively as drug treatment, but which did not address a comprehensive treatment programme. Hence neither lisdexamfetamine nor atomoxetine were used in compliance with their approval. So the ACT specified by the G-BA was also not implemented. Moreover, stimulants for the treatment of ADHD, such as lisdexamfetamine, can only be prescribed as part of a comprehensive treatment programme.

In addition, the treatment duration of the study SPD489-317 was too short.

Hence no study was available that would have been suitable for investigating the added benefit of lisdexamfetamine versus the ACT specified by the G-BA.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment. Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Section 4.3.1.1 of the dossier and in Sections 2.7.2.3.1 and

2.7.2.3.2 of the full dossier assessment. Further information about the study design and the study populations can be found in Module 4, Section 4.3.1.2.1 of the dossier, and in Section 2.7.2.3.2 of the full dossier assessment.

2.4 Results on added benefit

In its dossier, the company presented no assessment of lisdexamfetamine versus the ACT specified by the G-BA. Since no relevant data for the benefit assessment were presented, no proof of added benefit of lisdexamfetamine in comparison with the ACT specified by the G-BA could be derived.

This result deviates from that of the company, which derived an added benefit from the study it included.

Further information about the results on added benefit can be found in Module 4, Section 4.3.1.3 of the dossier, and in Section 2.7.2.4 of the full dossier assessment.

2.5 Extent and probability of added benefit

The result of the assessment of the added benefit of lisdexamfetamine in comparison with the ACT is shown in [Table 6](#)~~Table 6~~.

Table 6: Lisdexamfetamine: extent and probability of added benefit

Therapeutic indication	ACT	Extent and probability of added benefit
Treatment of ADHD in children aged 6 years of age and over as part of a comprehensive treatment programme when response to previous methylphenidate treatment is considered clinically inadequate	Atomoxetine	Added benefit not proven
ACT: appropriate comparator therapy; ADHD: attention deficit/hyperactivity disorder		

This assessment deviates from that of the company, which derived proof of a considerable added benefit of lisdexamfetamine.

The G-BA decides on added benefit.

2.6 List of included studies

Not applicable as the company did not include any relevant study for the assessment of the added benefit of lisdexamfetamine versus the ACT specified by the G-BA in its assessment.

References for English extract

Please see full dossier assessment for full reference list.

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