IQWiG Reports – Commission No. A19-40

# Lisdexamfetamine dimesylate (attention deficit/hyperactivity disorder in adults) –

## Benefit assessment according to §35a Social Code Book V[1]

## Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Lisdexamfetamindimesilat (Aufmerksamkeitsdefizit-Hyperaktivitätsstörung bei Erwachsenen) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 July 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] 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 |
| EMA | European Medicines Agency |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| RCT | randomized controlled trial |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SPC | Summary of Product Characteristics |

# 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 referred to as "the company"). The dossier was sent to IQWiG on 30 April 2019.

### Research question

The aim of the present report is the assessment of the added benefit of lisdexamfetamine as part of a comprehensive treatment programme in comparison with the appropriate comparator therapy (ACT) in adults with attention deficit/hyperactivity disorder (ADHD). ADHD should have at least moderate severity (at least moderate functional impairment in 2 or more settings and affecting several aspects of life) and symptoms must have existed since childhood.

Depending on prior drug therapy, the G-BA distinguished between 2 different treatment situations and specified different ACTs for them. This resulted in 2 research questions for the present benefit assessment, which are presented in Table 2.

Table 2: Research questions of the benefit assessment of lisdexamfetamine

| Research question | Subindication | ACT[a] |
|---|---|---|
| **Adults with ADHD with at least moderate severity since childhood[b]** | | |
| 1 | Adults who have already received prior drug therapy | Individual treatment involving the selection of atomoxetine and methylphenidate, in which the possible continuation or resumption with an already used drug must also be examined and presented, as part of a comprehensive treatment programme |
| 2 | Adults without prior drug treatment | Atomoxetine or methylphenidate, as part of a comprehensive treatment programme |

a: Presentation of the respective ACT specified by the G-BA.
b: At least moderate functional impairment in 2 or more settings and affecting several aspects of life.
ACT: appropriate comparator therapy; ADHD: attention deficit/hyperactivity disorder; G-BA: Federal Joint Committee

The company stated that it was following the ACT specified by the G-BA, but subsequently did not differentiate between adults with prior drug treatment and adults without prior drug treatment. It derived the added benefit irrespective of the patients' prior drug treatment.

The present benefit assessment was conducted separately for 2 research questions (patients with prior drug treatment and patients without prior drug treatment) in comparison with the respective ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 6 months were used for the derivation of the added benefit.

**Study pool of the company**

The company identified a total of 3 RCTs that compared lisdexamfetamine versus placebo (NRP104.303, SPD489-316 and SPD489-403). It additionally identified one RCT comparing atomoxetine versus placebo (NCT00510276) and one RCT comparing methylphenidate versus placebo (NCT01259492). Since there were no studies of direct comparisons for the derivation of the added benefit of lisdexamfetamine versus the ACTs, the company presented 2 indirect comparisons (lisdexamfetamine versus atomoxetine and lisdexamfetamine versus methylphenidate) on the basis of the RCTs mentioned above. It did not consider the SPD489-316 study in these indirect comparisons because, according to the company, it found no suitable study for the indirect comparison on the comparator side.

The RCTs with lisdexamfetamine and with atomoxetine or methylphenidate presented by the company are each unsuitable for the present benefit assessment for several reasons, however. In particular, in all 5 RCTs, the duration of treatment with the respective drug compared with placebo was markedly less than 6 months and therefore too short to derive conclusions on the added benefit of lisdexamfetamine versus the ACT in the present therapeutic indication. In addition, according to their German approvals, lisdexamfetamine, atomoxetine and methylphenidate all must be used as part of a comprehensive treatment programme. This is also an explicit part of the ACTs. None of the 5 RCTs ensured a comprehensive treatment programme. Thus, neither the interventions were applied in compliance with the approval, nor the ACT was implemented for the comparison.

**Results**

In its dossier, the company did not provide any suitable data to assess the added benefit of lisdexamfetamine as part of a comprehensive treatment programme in comparison with the ACT in adults with ADHD with at least moderate severity since childhood. This resulted in no hint of an added benefit of lisdexamfetamine in comparison with the ACT; an added benefit is therefore not proven.

**Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]**

Based on the results presented, probability and extent of the added benefit of the drug lisdexamfetamine in comparison with the ACT are assessed as follows:

Table 3 shows a summary of probability and extent of the added benefit of lisdexamfetamine.

Table 3: Lisdexamfetamine – probability and extent of added benefit

| Research question | Subindication | ACT[a] | Probability and extent of added benefit |
|---|---|---|---|
| **Adults with ADHD with at least moderate severity since childhood[b]** | | | |
| 1 | Adults who have already received prior drug therapy | Individual treatment involving the selection of atomoxetine and methylphenidate, in which the possible continuation or resumption with an already used drug must also be examined and presented, as part of a comprehensive treatment programme | Added benefit not proven |
| 2 | Adults without prior drug treatment | Atomoxetine or methylphenidate, as part of a comprehensive treatment programme | Added benefit not proven |

a: Presentation of the respective ACT specified by the G-BA.
b: At least moderate functional impairment in 2 or more settings and affecting several aspects of life.
ACT: appropriate comparator therapy; ADHD: attention deficit/hyperactivity disorder; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

## 2.2 Research question

The aim of the present report is the assessment of the added benefit of lisdexamfetamine as part of a comprehensive treatment programme in comparison with the ACT in adults with ADHD. ADHD should have at least moderate severity (at least moderate functional impairment in 2 or more settings and affecting several aspects of life) and symptoms must have existed since childhood.

[3] 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 to 3 cannot be drawn from the available data). 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, added benefit not proven, or less benefit). For further details see [1,2].

Depending on prior drug therapy, the G-BA distinguished between 2 different treatment situations and specified different ACTs for them. This resulted in 2 research questions for the present benefit assessment, which are presented in Table 4.

Table 4: Research questions of the benefit assessment of lisdexamfetamine

| Research question | Subindication | ACT[a] |
|---|---|---|
| **Adults with ADHD with at least moderate severity since childhood[b]** | | |
| 1 | Adults who have already received prior drug therapy | Individual treatment involving the selection of atomoxetine and methylphenidate, in which the possible continuation or resumption with an already used drug must also be examined and presented, as part of a comprehensive treatment programme |
| 2 | Adults without prior drug treatment | Atomoxetine or methylphenidate, as part of a comprehensive treatment programme |

a: Presentation of the respective ACT specified by the G-BA.
b: At least moderate functional impairment in 2 or more settings and affecting several aspects of life.
ACT: appropriate comparator therapy; ADHD: attention deficit/hyperactivity disorder; G-BA: Federal Joint Committee

The company stated in Module 3 A that it was following the ACT specified by the G-BA, but subsequently did not differentiate between adults with prior drug treatment and adults without prior drug treatment. The company presented data from one indirect comparison with lisdexamfetamine versus atomoxetine and one indirect comparison with lisdexamfetamine versus methylphenidate for the derivation of the added benefit. It derived the added benefit irrespective of the patients' pretreatment status.

Deviating from the company, the present benefit assessment was conducted separately for 2 research questions (patients with prior drug treatment and patients without prior drug treatment) in comparison with the respective ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 6 months were used for the derivation of the added benefit. The company, on the other hand, did not specify a minimum duration of the studies in its inclusion criteria.

## 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 (status: 6 March 2019)
- bibliographical literature search on lisdexamfetamine (last search on 4 February 2019)
- search in trial registries for studies on lisdexamfetamine (last search on 12 February 2019)

- bibliographical literature search on the ACT (last search on 4 February 2019)
- search in trial registries for studies on the ACT (last search on 12 February 2019)

To check the completeness of the study pool:

- search in trial registries for studies on lisdexamfetamine (last search on 10 May 2019)

No relevant study was identified from the check.

**Study pool of the company**

The company identified the RCTs listed in the following Table 5.

Table 5: RCTs presented by the company

| Study | Study category | | |
|---|---|---|---|
| | Study for approval of the drug to be assessed (yes/no) | Sponsored study[a] (yes/no) | Third-party study (yes/no) |
| **Lisdexamfetamine vs. placebo** | | | |
| NRP104.303 [3-9][b] | Yes | Yes | No |
| SPD489-316 [10-15] | Yes | Yes | No |
| SPD489-403 [16-22][c] | Yes | Yes | No |
| **Atomoxetine vs. placebo** | | | |
| NCT00510276 [23-25][c] | No | No | Yes |
| **Methylphenidate vs. placebo** | | | |
| NCT01259492 [26,27][b] | No | No | Yes |

a: Study for which the company was sponsor.
b: Used by the company for the indirect comparison of lisdexamfetamine vs. methylphenidate.
c: Used by the company for the indirect comparison of lisdexamfetamine vs. atomoxetine.
RCT: randomized controlled trial; vs.: versus

In order to derive a benefit, the company's dossier first presented the results of the 3 RCTs that compared lisdexamfetamine with placebo. The company conducted indirect comparisons for the derivation of an added benefit. For this purpose, the company identified one study comparing atomoxetine versus placebo and one study comparing methylphenidate versus placebo. It conducted one indirect comparison with the studies NRP104.303 and NCT01259492 of lisdexamfetamine versus methylphenidate, and one indirect comparison with the studies SPD489-403 and NCT00510276 of lisdexamfetamine versus atomoxetine. The company justified the composition of the study pools for both indirect comparisons with the similarity of the study designs. It did not consider the SPD489-316 study in the indirect comparisons because, according to the company, it found no suitable study for the indirect comparison on the comparator side.

All 5 RCTs presented by the company were unsuitable for the derivation of an added benefit for the following reasons.

***Study duration too short***

The treatment duration with the respective drug versus placebo was too short in all 5 RCTs presented by the company. It was pointed out already in the benefit assessment on the use of lisdexamfetamine in children with ADHD (Commission A13-24) that a short-term study is not sufficient for the assessment of the added benefit [28,29]. Because of the chronic course of ADHD, the European Medicines Agency (EMA) also recommends at least one controlled long-term study with a minimum duration of 6 months in addition to short-term studies [30]. The General Methods of IQWiG 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 [1]. This especially applies if treatment is required for several years, or even lifelong. According to the Summaries of Product Characteristics (SPCs), drug treatment of ADHD may be required over an extended period (over 12 months) for all 3 drugs [31-33]. Hence, a minimum study duration of 6 months is considered necessary for the present research questions.

As shown in Table 10 in Appendix A of the full dossier assessment, the duration of the use of the respective drug in comparison with placebo was 4 to 12 weeks (including titration phase) in all 5 RCTs and hence far below the minimum duration of 6 months required in the present therapeutic indication for the assessment of an added benefit.

In the NCT01259492 study (methylphenidate), after the first placebo-controlled phase of 9 weeks (dose confirmation phase) and one phase in which all patients received methylphenidate (dose optimization phase), there was another placebo-controlled treatment phase of 6 months (maintenance of effect phase). This treatment phase differed from the other randomized treatment phases as it investigated the withdrawal of methylphenidate (see Table 11 in Appendix A of the full dossier assessment).

Overall, all 5 RCTs presented by the company were too short to be able to assess the added benefit of lisdexamfetamine versus the ACT.

***Use of lisdexamfetamine, atomoxetine and methylphenidate not compliant with the approval / appropriate comparator therapy not implemented***

According to the approvals, the drugs lisdexamfetamine, atomoxetine and methylphenidate must be used as part of an overall therapeutic strategy or a comprehensive treatment programme. These additional measures typically include psychological and educational measures, behavioural and occupational therapy, as well as social and even pharmaco-therapeutic measures [31-33]. The ACT specified by the G-BA also includes the use of the drugs atomoxetine or methylphenidate as part of a comprehensive treatment programme. In addition, stimulants, including lisdexamfetamine, are subject to a limitation of prescription under the Pharmaceutical Directive on limitations and exclusions of prescriptions. This includes

an exception for ADHD in adults, provided the disease has existed since childhood, as part of a comprehensive treatment programme if other measures alone have proven to be inadequate [34].

It cannot be inferred from the documents on the lisdexamfetamine studies NRP104.303, SPD489-316 and SPD489-403 or from the atomoxetine study NCT00510276 and the methylphenidate study NCT01259492 (there is no protocol on NCT01259492) that a comprehensive treatment programme was required or offered in the framework of the treatment. All 5 RCTs had numerous restrictions regarding concomitant drug treatment, however. Psychotherapy and behavioural therapy were completely prohibited in the methylphenidate study NCT01259492 and was not mentioned in the lisdexamfetamine studies NRP104.303 and SPD489-316 (see Table 11 in Appendix A of the full dossier assessment). The studies SPD489-403 with lisdexamfetamine and NCT00510276 with atomoxetine only allowed the continuation of psychotherapy without adjustments. There was no information on the number of patients in these 2 studies who continued psychotherapy during the studies. Hence, the RCTs presented by the company do not guarantee approval-compliant treatment as part of an overall therapeutic strategy or a comprehensive treatment programme. The 5 RCTs therefore did not use the interventions in compliance with the SPCs, and, consequently, did not implement the ACTs with methylphenidate or atomoxetine.

***Note on the dose titration of lisdexamfetamine, atomoxetine and methylphenidate***

According to the SPC, daily dosing of lisdexamfetamine, atomoxetine and methylphenidate should be individualized to the patients within a recommended dose range [31-33]. Not all studies provided for individual dose titration, however.

Titration in the studies NRP104.303 (lisdexamfetamine) and NCT01259492 (methylphenidate, dose confirmation phase) was up to a dose specified according to randomization. In the NCT01259492 study, there was individual titration in the subsequent dose optimization phase, but without control arm (see Table 11, Appendix A of the full dossier assessment). This study phase was unsuitable for the derivation of an added benefit and was also not considered by the company.

In the lisdexamfetamine study SPD489-316, the dose was initially titrated individually, but without control arm (see Table 11 in Appendix A of the full dossier assessment). Dose adjustment was not allowed in the following placebo-controlled treatment phase (crossover phase). This phase was only 1 week, however.

In the studies SPD489-403 (lisdexamfetamine) and NCT00510276 (atomoxetine), the dose was initially titrated individually. However, the SPD489-403 study (lisdexamfetamine) did not allow subsequent dose adjustments for 6 weeks. In the NCT00510276 study, only limited adjustments were possible during the 12-week treatment phase (see Table 11 in Appendix A of the full dossier assessment). Based on the available data, it cannot be assessed whether the individual adjustments provided for in the study protocols were sufficient.

**Summary**

Overall, there were no data suitable for answering the research questions of the present benefit assessment. On the one hand, this is due to the treatment durations that were too short in all 5 RCTs. On the other, according to their German approvals, lisdexamfetamine, atomoxetine and methylphenidate all must be used as part of a comprehensive treatment programme. This is also an explicit part of the ACTs. None of the 5 RCTs guaranteed the use of the study medication as part of a comprehensive treatment programme, however. Thus, neither the interventions were applied in compliance with the approval, nor the ACT was implemented for the comparison.

## 2.4 Results on added benefit

In its dossier, the company did not provide any suitable data to assess the added benefit of lisdexamfetamine as part of a comprehensive treatment programme in comparison with the ACT in adults with ADHD since childhood with at least moderate severity. This resulted in no hint of an added benefit of lisdexamfetamine in comparison with the ACT; an added benefit is therefore not proven.

## 2.5 Probability and extent of added benefit

Since the company presented no suitable data for the assessment of the added benefit of lisdexamfetamine in comparison with the ACT in adults with ADHD with at least moderate severity since childhood, an added benefit of lisdexamfetamine is not proven for the present therapeutic indication.

The result of the assessment of the added benefit of lisdexamfetamine in comparison with the ACT is summarized in Table 6.

Table 6: Lisdexamfetamine – probability and extent of added benefit

| Research question | Subindication | ACT[a] | Probability and extent of added benefit |
|---|---|---|---|
| **Adults with ADHD with at least moderate severity since childhood[b]** | | | |
| 1 | Adults who have already received prior drug therapy | Individual treatment involving the selection of atomoxetine and methylphenidate, in which the possible continuation or resumption with an already used drug must also be examined and presented, as part of a comprehensive treatment programme | Added benefit not proven |
| 2 | Adults without prior drug treatment | Atomoxetine or methylphenidate, as part of a comprehensive treatment programme | Added benefit not proven |

a: Presentation of the respective ACT specified by the G-BA.
b: At least moderate functional impairment in 2 or more settings and affecting several aspects of life.
ACT: appropriate comparator therapy; ADHD: attention deficit/hyperactivity disorder; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit of lisdexamfetamine versus atomoxetine or methylphenidate and also did not differentiate between patients with prior drug treatment and those without prior drug treatment.

The G-BA decides on the added benefit.

## 2.6 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

**References for English extract**

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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