IQWiG Reports – Commission No. A18-25

Cariprazine (schizophrenia) –

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

Extract

[1] Translation of the executive summary of the dossier assessment *Cariprazin (Schizophrenie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 July 2018). Please note: This document was translated by an external translator and 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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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) 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 cariprazine. 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 13 April 2018.

Research question

The aim of this report is to assess the added benefit of cariprazine in comparison with the appropriate comparator therapy (ACT) in adult patients with schizophrenia.

For the assessment, 2 research questions were derived from the different therapeutic goals in the treatment of patients with schizophrenia. On the one hand, the treatment of acute symptoms (e.g. after exacerbation or initial diagnosis) and, on the other, long-term treatment and relapse prevention in the stable phase. The research questions and the ACT specified by the G-BA for all therapeutic applications of cariprazine are presented in Table 2.

Table 2[2]: Research questions of the benefit assessment of cariprazine

Research question	Indication	ACT[a, b]
1	Acute treatment of schizophrenia in adults	Amisulpride or aripiprazole[c] or olanzapine[c] or paliperidone[c] or quetiapine or risperidone[c] or ziprasidone
2	Long-term treatment/Relapse prevention of schizophrenia in adults	

a: Presentation of the respective ACT specified by the G-BA for the treatment of schizophrenia in adults.
b: If indicated, adjunctive occupational therapy, psychotherapy and/or sociotherapy in accordance with the respective guidelines should be offered in both treatment arms. Dose optimization in accordance with the respective Summary of Product Characteristics (SPC) is assumed to be an option as well.
c: For maintenance therapy, depot products are available in addition to the oral formulation.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company followed the G-BA's specification by listing all ACT options.

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 were included for deriving an added benefit. The required minimum duration depends on the research question and equals 6 weeks for acute treatment and 12 months for long-term treatment. When considering special patient populations, a shorter study duration of 6 months is also acceptable for long-term treatment. This deviates from the inclusion criteria of the company, which does not limit the study duration for either research question.

[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

Results on research question 1: Acute treatment in adults with schizophrenia

For this research question, the company presented no relevant study for the benefit assessment. In Module 4A, the company presents 2 additional RCTs on acute treatment without using them to derive an added benefit: RGH-MD-04 (hereinafter referred to as MD-04) and RGH-MD-16 (hereinafter referred to as MD-16). The company justifies the two studies' lack of relevance particularly with the absence of a dose modification option. In addition, the company mentions the large percentage of non-Caucasian patients in both studies. From the company's perspective, both factors make it impossible to assume transferability of the study results to the German healthcare situation. The company presents no arguments as to why treatment effects found in non-Caucasians should not be transferable to Caucasians.

The exclusion of the studies MD-04 and MD-06 due to their lack of flexibility in drug dosing is appropriate. The company's rationale for exclusion on the basis of the ethnic background of examined patients, on the other hand, is not followed.

Description of the studies MD-04 and MD-16

The studies MD-04 and MD-16 are randomized, multicentre, double-blind, active and placebo-controlled studies comparing cariprazine with aripiprazole (MD-04) or risperidone (MD-16) in the acute treatment of schizophrenia. The studies included pretreated adults 18 to 60 years of age with a diagnosis which has been established for at least 1 year and a current exacerbation less than 2 weeks in duration at the start of the study. Before study inclusion, the current psychotic episode was assessed as to the manifestation of schizophrenia symptoms by means of PANSS (Positive and Negative Syndrome Scale) and CGI-S (Clinical Global Impression of Severity). The studies each consisted of a 1-week screening phase, in which any drug therapies were washed out, a 6-week treatment phase and a 2-week follow-up observation period for adverse events (AEs). The primary outcome in both studies was the PANSS total score.

Lack of dosing flexibility in studies MD-04 and MD-16

In both studies (MD-04 and MD-16), a fixed treatment regimen was defined a priori for all patients. The studies therefore did not provide for individualized optimization of the investigated therapies (cariprazine, risperidone, aripiprazole). All drugs were either administered in fixed doses, or there were predetermined times at which patient doses had to be modified within the first few study days (in the intervention and comparator arm). The dose modification amount was also defined a priori for all patients in the study. Since the dosing specifications were uniformly defined in advance for all patients, both studies additionally failed to exhaust the approved dosage ranges of the respective drugs. The protocol did not specify subsequent dose modifications based on patient health status within the further course of the studies. Therefore, it is possible that the drugs were overdosed or underdosed in a large percentage of patients in the studies.

The S3 Guideline of the German Association for Psychiatry, Psychotherapy and Psychosomatics states that the adverse effects of and response patterns to antipsychotics vary from

person to person, which requires a differentiated approach, e.g. to dosing. In addition, it explicitly states that the appropriate dose cannot be reliably predicted for individual cases, and further dose modification is therefore often necessary after titration. Generally, the antipsychotic dose should be as low as possible.

It is well known that the treatment effect and side effect profile can be overestimated or underestimated depending on the chosen dosage, dose escalation or lack of titration option of the employed antipsychotics. As to the application of fixed-dose antipsychotic drugs, Heres 2006 concludes that it fails to offer the therapeutic flexibility necessary in the treatment of schizophrenia.

In summary, the rigid dosing regimens in studies MD-04 and MD-16 fail to meet the requirements of acute schizophrenia treatment. The studies MD-04 and MD-16 are therefore generally unsuitable for assessing the added benefit of cariprazine versus the ACT. This conclusion is in line with the company's assessment.

Results on research question 2: Long-term treatment/Relapse prevention in adults with schizophrenia

For this research question, the company identifies 1 relevant study, RGH-188-005 (hereinafter referred to as 188-005) for the comparison of cariprazine with risperidone. The check for completeness of the study pool revealed 1 additional study relevant for the benefit assessment, study A002-A7. This is an RCT conducted between 2012 and 2015 in Asia (presumably in Japan only) which compared cariprazine with risperidone in adults with chronic schizophrenia. The company excluded study A002-A7 from its assessment. To justify this decision, the company stated that exclusively non-Caucasian patients were included in the study, and in its opinion, the cariprazine dosage was also outside the marketing authorization.

The company did not supply any further information or arguments on why it considered the results of the non-Caucasian patient population in study A002-A7 non-transferable to the German healthcare situation. As regards the cariprazine dosage regimen in study A002-A7, the company correctly states that doses outside the marketing authorization (9 mg daily) were also permitted to be used in the study. No specific information is available as to how many patients received the off-label dose for how long. The available data do show, however, that this probably affected only a few patients to a relevant extent and therefore had little influence on study results.

The company's rationale is not plausible. The A002-A7 study is considered relevant and has been included in this benefit assessment.

Descriptions of the included studies 188-005 and A002-A7

Design of study 188-005

Study 188-005 is a randomized, double-blind, multicentre, parallel-group study conducted in Europe to compare cariprazine with risperidone. The study included adult patients aged

between 18 and 65 years with chronic schizophrenia. Criteria for study inclusion were stable schizophrenia without acute exacerbation within 6 months prior to screening and the presence of predominant negative symptoms. The latter had to persist for at least 6 months before the start of the study on the basis of medical records and the judgement of the investigator. The extent of negative symptoms was additionally determined by means of the PANSS. Patients had to have a PANSS factor score for negative symptoms (PANSS-FNS) of at least 24 and a score of at least 4 on a minimum of 2 of the PANSS negative symptom items "Flat affect", "Avolition", and "Poverty of speech" (corresponding to PANSS symptoms N1, N4, and N6).

Patients were randomized to 2 study arms, a cariprazine arm with a target dose of 4.5 mg/day and a risperidone arm with a target dose of 4 mg/day. Alongside the study drug, patients were initially allowed to continue their existing antipsychotic treatment as co-medication, which had to be gradually reduced and discontinued no later than 4 weeks after the start of the study.

The study consisted of a 28-day screening phase, a 26-week treatment phase, and a 2-week follow-up. The primary outcome of the study was the mean change in negative symptoms (as measured by PANSS-FNS).

For studies on the long-term treatment of schizophrenia, a study duration of 12 months is recommended to demonstrate stable treatment response. However, deviations may be permissible when considering specific patient groups. Given that the special patient population with negative symptoms was being looked at, in line with EMA recommendations, a study duration of 26 weeks is considered sufficient for assessing the added benefit of cariprazine. In light of the specific population investigated in study 188-005, conclusions based on said study can be drawn exclusively about adult patients with predominant negative symptoms of schizophrenia.

Limited dose optimization options in study 188-005

In the first 3 weeks of study 188-005, all patients had to follow a uniform, rigid dosing regimen.

For a period of 2 weeks, cariprazine and risperidone were initially uptitrated to the uniform target doses specified a priori for all patients: For cariprazine, the initial dose of 1.5 mg/day was increased weekly by 1.5 mg/day in all patients until the target dose of 4.5 mg/day was reached; within the same period, the risperidone dose was gradually increased in 1.0 mg increments from 2.0 mg to the target dose of 4.0 mg. The target doses were continued unchanged for another week.

Starting from the 4th treatment week, both study arms offered the option of dose modifications. However, this option was limited: In case of poor tolerability, 1 dose reduction to 3 mg cariprazine or risperidone was allowed; in case of impending psychotic deterioration, the dose could be increased once to 6 mg cariprazine or risperidone. Only 1 dose reduction or increase based on the target dose were permissible. In addition, the study protocol recommended maintaining the target dose or returning to it, if possible, after any modification.

The uniform specification of dose modification times and the restriction of the number of dosing steps in study 188-005 deviate from the concept of individually adjusted therapy. However, individualized dose optimization is a core aspect of schizophrenia treatment. The S3 Guideline of the German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN; currently being revised) mentions a differentiated approach in schizophrenia treatment. In addition, the Guideline and the Summaries of Product Characteristics for cariprazine and risperidone state that individually optimized treatment should be provided at the lowest effective dose. Given the limited dose modification options of cariprazine and risperidone, the 188-005 study was not designed to determine such an optimal dose for each individual patient. In addition, study 188-005 did not offer the entire range of approved doses of either drug (cariprazine: 1.5 to 6 mg/day; risperidone: 2 to 16 mg/day). The minimum doses approved for cariprazine and risperidone (1.5 mg/day or 2.0 mg/day) were no longer permitted to be used starting from the study's 2nd treatment week.

However, study documents show that dose modifications were made in only a relatively small proportion of the study population and that both study arms were affected to about the same degree (19.1% in the cariprazine arm and 22.2% in the risperidone arm). The percentage of patients who had both a dose increase and a dose reduction was 11.3% in the cariprazine arm and 14.8% in the risperidone arm. It remains unclear to what extent the investigators' recommendation to maintain the target dose affected the rate of dose modifications in the study or to what extent the latter reflects the actual modification needs. Despite the limited optimization options, however, a sufficient comparison between cariprazine and risperidone can be assumed on the basis of the comparable percentages of patients with dose modifications. The described limitation reduces the reliability of the results of study 188-005. This was taken into account in the conclusion regarding the added benefit.

Design of study A002-A7

The study A002-A7 is an open-label, randomized, multicentre parallel-group study performed in Asia (presumably in Japan only) comparing cariprazine with risperidone. The study included pretreated adult patients between 20 and 74 years of age with chronic schizophrenia. Study inclusion required a PANSS total score of no more than 120. The study consisted of an observation phase of no more than 4 weeks, a 48-week treatment phase, and a 12-week follow-up. According to study documents, no primary outcome was defined in the study.

Patients were assigned to study arms stratified by age (< 65, ≥ 65 years) and randomized to 3 study arms: 2 cariprazine arms with a daily target dose of 3 mg and 6 mg, respectively, and 1 risperidone arm with a target dosage of 4 mg/day. At the start of the treatment phase, the dosage was gradually increased in each study arm until the target dosage was reached. The cariprazine dosage was increased by 1.5 mg daily, starting from the initial dosage of 1.5 mg/day. The target dosage of 3 mg was therefore already reached on the 2nd treatment day, and the target dosage of 6 mg on the 4th treatment day. The initial risperidone dosage of 2 mg/day was increased in a single step to 4 mg on the 3rd treatment day.

After the target dosage was reached, it was to be continued unchanged until Day 29 in the cariprazine arms and until Day 15 in the risperidone arm. Afterwards, a flexible dosing regimen was offered, where dose increases were to be initiated if the CGI-I (Clinical Global Impression of Improvement) was unchanged or had deteriorated and if treatment was well tolerated. In case of poor tolerability, it was permitted to reduce the dosage at any time or to discontinue the study medication for a maximum of 3 days. It was permitted to use cariprazine in dosages between 1.5 mg and 9 mg and risperidone between 2 mg and 12 mg.

Limitations of study A002-A7

At the beginning of the treatment phase, a daily dose increase was undertaken in the cariprazine arms. The marketing authorization specifies slower dose increases, however. Since the dose increase took place in the first few days of the treatment phase and a flexible dosing regimen was applied thereafter, the influence on the results of the investigated outcomes can be considered minor.

Furthermore, cariprazine dosages are approved in a range between 1.5 mg/day and 6 mg/day. In study A002-A7, a dosage increase to 9 mg/day was also possible. In some cases, cariprazine was therefore administered outside the approved range. However, the study documents do not show how many patients were treated with dosages outside the marketing authorization and over which time period. The only available information on this topic is that the dose of 9 mg was the most common daily dose used by 7% of the patient population in each of the two cariprazine arms. However, other patients may also have been treated with this dose over a sufficiently long time period to cause a relevant effect on study results.

Results of study A002-A7 not usable

Despite the described limitations, the relevance of study A002-A7 for this benefit assessment is not questioned. However, at an early time in the study, there was a very high percentage of patients with premature treatment discontinuation. By Week 24, a total of about 46% of patients had already discontinued therapy. By the end of the study (Week 48), this percentage rose to 54%. It must be noted that the percentage of treatment discontinuations differed considerably between study arms (73.2% for cariprazine 3 mg, 52.4% for cariprazine 6 mg, and 33% for the risperidone arm). On the other hand, the reasons for treatment discontinuation listed in the study documents fail to plausibly explain the between-group differences in treatment discontinuation rates. Overall, this led to the results of study A002-A7 not being used to derive an added benefit of cariprazine.

Results

Mortality

All-cause mortality

For the outcome all-cause mortality, deaths recorded as part of the recording of AEs were used. By the end of the treatment phase, no deaths arose in the cariprazine study arm. One death was

recorded in the risperidone arm. Taken together, this does not result in a hint of added benefit of cariprazine in comparison with risperidone; an added benefit is therefore not proven.

Morbidity

Schizophrenia symptoms (PANSS)

For the outcome schizophrenia symptoms as measured by the PANSS, analyses on the mean change from the start of the study are considered for the total score and associated subscales.

For the PANSS total score, subscales on positive symptoms (positive scale and factor score for positive symptoms) and the General Psychopathology scale, no statistically significant difference is found between treatment groups. This does not result in a hint of added benefit; an added benefit is therefore not proven.

Each of the considered PANSS subscales on negative symptoms (negative scale and factor score for negative symptoms) show a statistically significant difference in favour of cariprazine. For both subscales, however, the respective 95% confidence interval of the standardized mean difference (Hedges' g) was not fully outside the irrelevance range of −0.2 to 0.2. Hence, the effect cannot be rated as relevant. For the negative symptoms, this means that there is no hint of added benefit of cariprazine in comparison with the ACT; an added benefit is therefore not proven.

Depressive symptoms (CDSS)

The CDSS total score calculated to determine depressive symptoms showed no statistically significant difference between study arms. This does not result in a hint of added benefit of cariprazine in comparison with risperidone; an added benefit is therefore not proven.

Relapse

For the outcome relapse, data are available on a combined outcome which was defined post hoc by the company. It consists of different components which represent various symptom expressions by means of the PANSS and CGI-S as well as events by means of the MedDRA SMQs "Psychosis and psychotic disorders", "Suicide/self-injury" and "Hostility/aggression". This constellation defined post hoc is not justified and has not been included in this benefit assessment. Consequently, there is no hint of added benefit of cariprazine for the outcome of relapse; an added benefit is therefore not proven.

Personal and Social Performance (PSP)

For the outcome Personal and Social Performance (PSP), a statistically significant difference in favour of cariprazine was found, relative to the total score, for the mean change from study start. The 95% confidence interval of the standardized mean difference (Hedges' g) is fully outside of the irrelevance range of −0.2 to 0.2. This is interpreted as a relevant effect. For PSP, this results in a hint of added benefit of cariprazine in comparison with risperidone.

Health-related quality of life

For the assessment of the added benefit of cariprazine, no data are available in the outcome category health-related quality of life. This does not result in a hint of added benefit of cariprazine in comparison with risperidone; an added benefit is therefore not proven.

Adverse events

SAEs

For the outcome SAEs, no statistically significant difference between treatment groups was found. This does not result in a hint of greater or lesser harm of cariprazine in comparison with risperidone; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

For the outcome discontinuation due to AEs, no statistically significant difference between treatment groups was found. This does not result in a hint of greater or lesser harm of cariprazine in comparison with risperidone; greater or lesser harm is therefore not proven.

Suicidality (C-SSRS)

For the outcome suicidal ideation and behaviour, as measured by means of the C-SSRS, no statistically significant difference between treatment groups was found. This does not result in a hint of greater or lesser harm of cariprazine in comparison with risperidone; greater or lesser harm is therefore not proven.

Extrapyramidal syndromes (EPS)

Dyskinesia (AIMS)

For the outcome dyskinesia, no statistically significant difference between treatment groups was found. This does not result in a hint of greater or lesser harm of cariprazine in comparison with risperidone; greater or lesser harm is therefore not proven.

Akathisia (BARS)

For the outcome akathisia, no relevant data were available. Due to the inadequate calculation of the total score, the analysis presented by the company is unsuitable for deriving an added benefit. Consequently, there is no hint of greater or lesser harm of cariprazine in comparison with risperidone; greater or lesser harm is therefore not proven.

Parkinsonism (SAS)

For the outcome Parkinsonism, no statistically significant difference between treatment groups was found. Consequently, there is no hint of greater or lesser harm of cariprazine in comparison with risperidone; greater or lesser harm is therefore not proven.

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

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

Usable data for the assessment of the added benefit of cariprazine were available exclusively for the population of patients with schizophrenia and predominant negative symptoms. For this patient population, a positive effect resulted in the category non-serious/non-severe symptoms/ late complications for the outcome Personal and Social Performance.

For this patient population, there is therefore a hint of non-quantifiable added benefit of cariprazine in comparison with the ACT.

For the other patients of the target population (patients without predominant negative symptoms), the company did not present any usable data. For this patient population, an added benefit is not proven.

Table 3 presents a summary of the probability and extent of the added benefit of cariprazine.

Table 3: Cariprazine – probability and extent of added benefit

Research question	Indication	ACT[a]	Probability and extent of added benefit
1	Acute treatment of schizophrenia in adults	Amisulpride or aripiprazole[b] or olanzapine[b] or paliperidone[b] or quetiapine or risperidone[b] or ziprasidone	Added benefit not proven
2	Long-term treatment/Relapse prevention of schizophrenia in adults		*Patients with predominant negative symptoms:* ▪ Hint of non-quantifiable added benefit *Other patients of the target population[c]* ▪ Added benefit not proven
a: Presentation of the ACT specified by the G-BA. If indicated, adjunctive occupational therapy, psychotherapy and/or sociotherapy in accordance with the respective guidelines should be offered in both treatment arms. Dose optimization in accordance with the respective Summary of Product Characteristics (SPC) is assumed to be an option as well. b: For maintenance therapy, depot products are available in addition to the oral formulation. c: Patients without predominant negative symptoms ACT: appropriate comparator therapy; G-BA: Federal Joint Committee			

[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].

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. The G-BA decides on the added benefit.

Note:

An addendum (A18-50) to dossier assessment A18-25 has been published.

References for English extract

Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-25-cariprazine-schizophrenia-benefit-assessment-according-to-35a-social-code-book-v.9568.html.