Decitabine/cedazuridine (acute myeloid leukaemia)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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No advisor on medical and scientific questions was involved in the present dossier assessment.

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No patients or families were involved in the present dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AML	acute myeloid leukaemia
AUC	area under the curve
CTCAE	Common Terminology Criteria for Adverse Events
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

I 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 decitabine/cedazuridine. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 4 March 2024.

Research question

The aim of the present report is the assessment of the added benefit of fixed combination of decitabine and cedazuridine (hereinafter referred to as decitabine/cedazuridine) in comparison with the appropriate comparator therapy (ACT) in patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of decitabine/cedazuridine

Therapeutic indication	**ACT**[a, b, c]
Treatment of adult patients with newly diagnosed acute myeloid leukaemia[d] who are ineligible for standard induction chemotherapy.	▪ Azacitidine or ▪ **decitabine** or ▪ glasdegib in combination with low-dose cytarabine or ▪ venetoclax in combination with azacitidine or ▪ venetoclax in combination with decitabine
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 A Section 4.2.2 is printed in **bold**. b It is assumed that for all patients in the therapeutic indication at the time of therapy with decitabine/cedazuridine, best supportive care treatment alone is not an option. c. The added benefit can be proven in comparison with one of the cited treatment options; this can typically be achieved in the context of a single-comparator study. d. In accordance with the G-BA, it is assumed that patients with acute promyelocytic leukaemia are not comprised by the therapeutic indication. This patient population differs in terms of aetiology and therapeutic approach. ACT: appropriate comparator therapy; AML: acute myeloid leukaemia; G-BA: Federal Joint Committee	

The company followed the G-BA's specification by identifying decitabine as the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Concurring with the company's assessment, the check of completeness of the study pool did not identify any relevant studies for the comparison of decitabine/cedazuridine versus the ACT specified by the G-BA. The company conducted an information retrieval on further investigations with decitabine/cedazuridine and identified the RCT ASTX727-02, on the basis of which the approval of decitabine/cedazuridine was granted. Whilst describing the ASTX727-02 study in its dossier as not suitable for the assessment of the added benefit in comparison with the ACT, the company presented it as best available evidence for decitabine/cedazuridine for the presentation of the medical benefit in the dossier. From the study, it derived a medical benefit based on the oral administration form of decitabine/cedazuridine, which it considers to pose a lower treatment burden for patients and to therefore justify an additional benefit.

The approach of the company is not appropriate. The ASTX727-02 study is an open-label RCT investigating orally administered decitabine/cedazuridine compared to intravenously administered decitabine. The design of the ASTX727-02 study means that the study is not suitable for the assessment of added benefit of decitabine/cedazuridine in patients with newly diagnosed acute myeloid leukaemia who are ineligible for standard induction chemotherapy. The reason for this is that the treatment duration for both decitabine/cedazuridine and the comparator therapy decitabine in the controlled phase of the ASTX727-02 study, which would allow a comparison of decitabine/cedazuridine with the ACT, is too short at 1 treatment cycle each. This is because both for decitabine/cedazuridine and for the comparator therapy decitabine, the respective Summary of Product Characteristics (SPC) specifies a minimum treatment duration of 4 cycles. The company therefore presented no suitable data for assessing the added benefit of decitabine/cedazuridine in comparison with the ACT.

Results on added benefit

There are no suitable data available for the assessment of decitabine/cedazuridine compared to the ACT in adult patients with newly diagnosed acute myeloid leukaemia who are ineligible for standard induction chemotherapy. There is no hint of an added benefit of decitabine/cedazuridine 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]

Table 3 shows a summary of probability and extent of the added benefit of decitabine/cedazuridine.

Table 3: Decitabine/cedazuridine – probability and extent of added benefit

Therapeutic indication	**ACT[a, b]**	**Probability and extent of added benefit**
Treatment of adult patients with newly diagnosed acute myeloid leukaemia[d] who are ineligible for standard induction chemotherapy.	▪ Azacitidine or ▪ **decitabine** or ▪ glasdegib in combination with low-dose cytarabine or ▪ venetoclax in combination with azacitidine or ▪ venetoclax in combination with decitabine	Added benefit not proven

a. Presented is the ACT specified by the G-BA in cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 A Section 4.2.2 is printed in **bold**.
b It is assumed that for all patients in the therapeutic indication at the time of therapy with decitabine/cedazuridine, best supportive care treatment alone is not an option.
c. The added benefit can be proven in comparison with one of the cited treatment options; this can typically be achieved in the context of a single-comparator study.
d. In accordance with the G-BA, it is assumed that patients with acute promyelocytic leukaemia are not comprised by the therapeutic indication. This patient population differs in terms of aetiology and therapeutic approach.

ACT: appropriate comparator therapy; AML: acute myeloid leukaemia; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

[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].

I 2 Research question

The aim of the present report is the assessment of the added benefit of fixed combination of decitabine and cedazuridine (hereinafter referred to as decitabine/cedazuridine) in comparison with the ACT in patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy.

The research question presented in Table 3 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of decitabine/cedazuridine

Therapeutic indication	**ACT**[a, b]
Treatment of adult patients with newly diagnosed acute myeloid leukaemia[d] who are ineligible for standard induction chemotherapy.	▪ Azacitidine or ▪ **decitabine** or ▪ glasdegib in combination with low-dose cytarabine or ▪ venetoclax in combination with azacitidine or ▪ venetoclax in combination with decitabine
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 A Section 4.2.2 is printed in **bold**. b It is assumed that for all patients in the therapeutic indication at the time of therapy with decitabine/cedazuridine, best supportive care treatment alone is not an option. c. The added benefit can be proven in comparison with one of the cited treatment options; this can typically be achieved in the context of a single-comparator study. d. In accordance with the G-BA, it is assumed that patients with acute promyelocytic leukaemia are not comprised by the therapeutic indication. This patient population differs in terms of aetiology and therapeutic approach. ACT: appropriate comparator therapy; AML: acute myeloid leukaemia; G-BA: Federal Joint Committee	

The company followed the G-BA's specification by identifying decitabine as the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

I 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 lists on decitabine/cedazuridine (status: 15 December 2023)
- bibliographical literature search on decitabine/cedazuridine (last search on 15 December 2023)
- search in trial registries/trial results databases for studies on decitabine/cedazuridine (last search on 15 December 2023)
- search on the G-BA website for decitabine/cedazuridine (last search on 15 December 2023)

To check the completeness of the study pool:

- search in trial registries for studies on decitabine/cedazuridine (last search on 21 March 2024); for search strategies, see I Appendix A of the full dossier assessment

Direct comparison

Concurring with the company's assessment, the check did not identify any relevant randomized controlled trials (RCTs) for the comparison of decitabine/cedazuridine versus the ACT specified by the G-BA.

Further investigations

The company conducted an information retrieval on further investigations with decitabine/cedazuridine and identified the RCT ASTX727-02 [3], on the basis of which the approval of decitabine/cedazuridine was granted. The company conducted no information retrieval on further investigations with the ACT.

A check for completeness of the study pool presented by the company was waived because the data submitted by the company under "Further investigations" are unsuitable for the benefit assessment. The unsuitability is justified below.

Evidence presented by the company

Whilst describing the ASTX727-02 study in its dossier as not suitable for the assessment of the added benefit in comparison with the ACT, the company presented it as best available evidence for decitabine/cedazuridine for the presentation of the medical benefit in the dossier. From the study, it derived a medical benefit based on the oral administration form of decitabine/cedazuridine, which it considers to pose a lower treatment burden for patients and to therefore justify an additional benefit.

The approach of the company is not appropriate. The ASTX727-02 study is an open-label RCT investigating orally administered decitabine/cedazuridine compared to intravenously administered decitabine in patients with myelodysplastic syndrome, chronic myelomonocytic leukaemia or AML. In the dossier, the company presented analyses on the part of the study conducted in Europe and Canada, which includes only patients with AML. Adult patients with newly diagnosed *de novo* or secondary AML who are ineligible for standard induction chemotherapy were included. The study consists of 2 consecutive phases: an actively controlled phase and a single-arm extension phase. At the beginning of the actively controlled phase, a total of 89 patients with AML were randomly assigned to the two treatment arms in a 1:1 ratio. The treatment was carried out with decitabine/cedazuridine or decitabine for the duration of 1 cycle (28 days) followed by treatment switching to the respective other therapy for the duration of 1 further cycle. Following these two treatment cycles, all patients received decitabine/cedazuridine as part of the single-arm phase of the study until disease progression or unacceptable toxicity. The primary outcome of the study was the 5-day total exposure of decitabine after treatment with the fixed combination decitabine/cedazuridine compared to intravenously administered decitabine (measured by area under the curve [AUC]).

The design of the ASTX727-02 study means that the study is not suitable for the assessment of added benefit of decitabine/cedazuridine in patients with newly diagnosed acute myeloid leukaemia who are ineligible for standard induction chemotherapy. According to the SPC, treatment with decitabine/cedazuridine must be carried out for at least 4 treatment cycles of 28 days each [4]. Treatment with intravenously administered decitabine is also recommended for at least 4 treatment cycles of 28 days each according to the SPC [5]. Consequently, the treatment duration for both decitabine/cedazuridine and the comparator therapy decitabine in the controlled phase of the ASTX727-02 study, which would allow a comparison of decitabine/cedazuridine with the ACT, is too short at 1 treatment cycle each. The company therefore presented no suitable data for assessing the added benefit of decitabine/cedazuridine in comparison with the ACT.

I 4 Results on added benefit

There are no suitable data available for the assessment of decitabine/cedazuridine compared to the ACT in adult patients with newly diagnosed acute myeloid leukaemia who are ineligible for standard induction chemotherapy. There is no hint of an added benefit of decitabine/cedazuridine in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of decitabine/cedazuridine in comparison with the ACT is summarized in Table 5.

Table 5: Decitabine/cedazuridine – probability and extent of added benefit

Therapeutic indication	**ACT[a, b, c]**	**Probability and extent of added benefit**
Treatment of adult patients with newly diagnosed acute myeloid leukaemia[d] who are ineligible for standard induction chemotherapy.	▪ Azacitidine or ▪ **decitabine** or ▪ glasdegib in combination with low-dose cytarabine or ▪ venetoclax in combination with azacitidine or ▪ venetoclax in combination with decitabine	Added benefit not proven

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company according to the inclusion criteria in Module 4 A Section 4.2.2 is printed in **bold**.
b It is assumed that for all patients in the therapeutic indication at the time of therapy with decitabine/cedazuridine, best supportive care treatment alone is not an option.
c. The added benefit can be proven in comparison with one of the cited treatment options; this can typically be achieved in the context of a single-comparator study.
d. In accordance with the G-BA, it is assumed that patients with acute promyelocytic leukaemia are not comprised by the therapeutic indication. This patient population differs in terms of aetiology and therapeutic approach.

ACT: appropriate comparator therapy; AML: acute myeloid leukaemia; 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.

The G-BA decides on the added benefit.

I 6 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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