Cabotegravir
(HIV-1 infection in adolescents)

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

EXTRACT

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Cabotegravir, Rilpivirine, HIV Infections, Adolescent, Benefit Assessment

Medical and scientific advice

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

Patient and family involvement

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
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIV-1	human immunodeficiency virus type 1
INI	integrase inhibitor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NNRTI	non-nucleoside reverse transcriptase inhibitor
Q1M	once a month
Q2M	every 2 months
RCT	randomized controlled trial
RNA	ribonucleic acid
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 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 cabotegravir (in combination with rilpivirine). 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 12 February 2025.

Research question

The aim of this report is to assess the added benefit of cabotegravir, in combination with rilpivirine (hereinafter cabotegravir + rilpivirine), in comparison with the appropriate comparator therapy (ACT) in adolescents (at least 12 years of age and weighing at least 35 kg) with human immunodeficiency virus type 1 (HIV-1) infection, who are virologically suppressed (HIV-1 ribonucleic acid [RNA] < 50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the non-nucleoside reverse transcriptase inhibitor (NNRTI) and integrase inhibitor (INI) class.

Treatment concept for the combination therapy cabotegravir + rilpivirine

In this combination therapy treatment concept, the drugs cabotegravir + rilpivirine are initially administered orally for 4 weeks during an optional lead-in phase. The intramuscular route of administration of the 2 drugs is then implemented according to 1 of 2 approved treatment regimens: either every 2 months (Q2M), or once a month (Q1M).

According to the Summary of Product Characteristics (SPC), long-term intramuscular treatment with cabotegravir + rilpivirine consists of 2 phases: an initiation phase (consisting of 2 consecutive intramuscular injections 1 month apart) and a continuation phase (long-term dosing Q2M or Q1M). If necessary, intramuscular treatment can also be bridged with a daily oral intake of both drugs for up to 2 months. The assessment of the added benefit of cabotegravir + rilpivirine refers to the entire treatment concept, consisting of the oral lead-in phase and continuous intramuscular administration.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of cabotegravir + rilpivirine

Therapeutic indication	**ACT**[a]
Adolescents (at least 12 years of age and weighing at least 35 kg) with HIV-1 infection, who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class	Individualized antiretroviral therapy chosen from the approved drugs, taking into account prior treatment(s) and the reason for the treatment switch, particularly treatment failure due to virological failure and possible associated resistance development, or due to side effects[b]
a. Presented is the ACT specified by the G-BA. b. The use of the drugs in compliance with the approval must be observed. Here, in particular, the age-appropriate use of the drugs. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1; INI: integrase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; RNA: ribonucleic acid	

The company followed the G-BA's specification of the ACT.

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 48 weeks were used for the derivation of added benefit.

Results

Consistent with the findings of the company, a review of the completeness of the study pool did not identify any relevant randomized controlled trials (RCTs) for the direct comparison of cabotegravir + rilpivirine with the ACT specified by the G-BA.

Overall, the company did not present any data for the assessment of the added benefit of cabotegravir + rilpivirine in comparison with the ACT in its dossier.

Results on added benefit

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of cabotegravir + rilpivirine 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 cabotegravir + rilpivirine.

Table 3: Cabotegravir + rilpivirine – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adolescents (at least 12 years of age and weighing at least 35 kg) with HIV-1 infection, who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class	Individualized antiretroviral therapy chosen from the approved drugs, taking into account prior treatment(s) and the reason for the treatment switch, particularly treatment failure due to virological failure and possible associated resistance development, or due to side effects[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The use of the drugs in compliance with the approval must be observed. Here, in particular, the age-appropriate use of the drugs.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1; INI: integrase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; RNA: ribonucleic acid

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 this report is to assess the added benefit of cabotegravir, in combination with rilpivirine (hereinafter cabotegravir + rilpivirine), in comparison with the ACT in adolescents (at least 12 years of age and weighing at least 35 kg) with HIV-1 infection, who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class.

Treatment concept for the combination therapy cabotegravir + rilpivirine

In this combination therapy treatment concept, the drugs cabotegravir + rilpivirine are initially administered orally for 4 weeks during an optional lead-in phase. The intramuscular route of administration of the 2 drugs is then implemented according to 1 of 2 approved treatment regimens: either Q2M, or Q1M [3,4].

According to the SPC, long-term intramuscular treatment with cabotegravir + rilpivirine consists of 2 phases: an initiation phase (consisting of 2 consecutive intramuscular injections 1 month apart) and a continuation phase (long-term dosing Q2M or Q1M). If necessary, intramuscular treatment can also be bridged with a daily oral intake of both drugs for up to 2 months. The assessment of the added benefit of cabotegravir + rilpivirine refers to the entire treatment concept, consisting of the oral lead-in phase and continuous intramuscular administration.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of cabotegravir + rilpivirine

Therapeutic indication	**ACT[a]**
Adolescents (at least 12 years of age and weighing at least 35 kg) with HIV-1 infection, who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class	Individualized antiretroviral therapy chosen from the approved drugs, taking into account prior treatment(s) and the reason for the treatment switch, particularly treatment failure due to virological failure and possible associated resistance development, or due to side effects[b]
a. Presented is the ACT specified by the G-BA. b. The use of the drugs in compliance with the approval must be observed. Here, in particular, the age-appropriate use of the drugs. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1; INI: integrase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; RNA: ribonucleic acid	

The company followed the G-BA's specification of the ACT.

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 48 weeks were used for the derivation of added benefit. This deviates from the company's inclusion criteria, which did not specify a minimum study duration. The deviation is of no consequence for this assessment, as the company did not present any data on the comparison of cabotegravir + rilpivirine with the ACT.

The company only partially addressed the therapeutic indication of cabotegravir + rilpivirine in its dossier

When stating the research question, the company referred only to the continuation phase of long-term dosing (Q2M, 600 mg cabotegravir + 900 mg rilpivirine). The company did not consider the optional oral lead-in phase, the recommended initiation phase consisting of 2 consecutive intramuscular injections of cabotegravir (600 mg) and rilpivirine (900 mg) 1 month apart, or the approved Q1M treatment regimen.

Regarding the approved treatment regimens, the company stated that only the Q2M dosage is marketed in Germany. It did not provide reasons as to why neither the optional oral lead-in phase nor the recommended initiation phase of long-term dosing was considered. This approach taken by the company is not appropriate. The assessment of the added benefit of cabotegravir + rilpivirine refers to the entire treatment concept, including the oral lead-in phase as well as intramuscular administration consisting of the initiation and continuation phases. The deviation is of no consequence for this assessment, as the company did not present any data on the comparison of cabotegravir + rilpivirine with the ACT.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on cabotegravir (status: 20 December 2024)
- Bibliographical literature search on cabotegravir (last search on 20 December 2024)
- Search of trial registries/trial results databases for studies on cabotegravir (last search on 20 December 2024)
- Search on the G-BA website for cabotegravir (last search on 20 December 2024)

To check the completeness of the study pool:

- Search of trial registries for studies on cabotegravir (last search on 27 February 2025); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company's assessment, the search did not identify any relevant RCTs for the direct comparison of cabotegravir + rilpivirine with the ACT specified by the G-BA.

The company stated that it could not identify any relevant clinical trials that fulfil the criteria for a benefit assessment according to §35a Social Code Book V for cabotegravir + rilpivirine as a long-acting treatment regimen for the given therapeutic indication. It did not present the single-arm study IMPAACT 2017 [5,6], which was submitted to the regulatory authority within the approval procedure, because the study is not comparative and so does not meet the criteria for a benefit assessment according to §35a SGB V for the present therapeutic indication.

Overall, the company thus did not present any data for the assessment of the added benefit of cabotegravir + rilpivirine in comparison with the ACT in its dossier. The company did not claim an added benefit.

I 4 Results on added benefit

No suitable data are available for the assessment of the added benefit of cabotegravir + rilpivirine in comparison with the ACT in adolescents (at least 12 years of age and weighing at least 35 kg) with HIV-1 infection, who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class. There is no hint of an added benefit of cabotegravir + rilpivirine 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 cabotegravir + rilpivirine in comparison with the ACT is summarized in Table 5.

Table 5: Cabotegravir + rilpivirine – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adolescents (at least 12 years of age and weighing at least 35 kg) with HIV-1 infection, who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class	Individualized antiretroviral therapy chosen from the approved drugs, taking into account prior treatment(s) and the reason for the treatment switch, particularly treatment failure due to virological failure and possible associated resistance development, or due to side effects[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The use of the drugs in compliance with the approval must be observed. Here, in particular, the age-appropriate use of the drugs.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HIV-1: human immunodeficiency virus type 1; INI: integrase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; RNA: ribonucleic acid

The assessment described above concurs with that by the company.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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6. ViiV. Clinical Study Report IMPAACT 2017: Phase I/II Study of the Safety, Acceptability, Tolerability, and Pharmacokinetics of Oral and Long-Acting Injectable Cabotegravir and Long-Acting Injectable Rilpivirine in Virologically Suppressed HIV Infected Children and Adolescents - Week 48 Report [unpublished]. 2024.

The full report (German version) is published under https://www.iqwig.de/en/projects/a25-21.html.