Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Cobicistat (New Therapeutic Indication: HIV Infection, Combination with Atazanavir or Darunavir, 12 to < 18 years)

of 1 October 2020

Contents

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of proof provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the proof and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient cobicistat (Tybost®) was listed for the first time on 1 April 2014 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 9 March 2020, cobicistat received the marketing authorisation for a new therapeutic indication classified as a major variation of Type 2 according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 1 April 2020, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient cobicistat with the new therapeutic indication in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 July 2020 on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of cobicistat compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has assessed the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria

laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of cobicistat.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of cobicistat (Tybost®) in accordance with the product information

Tybost is indicated as a pharmacokinetic enhancer of atazanavir 300 mg once daily or darunavir 800 mg once daily as part of antiretroviral combination therapy in human immunodeficiency virus-1 (HIV-1) infected adults and adolescents aged 12 years and older weighing at least 35 kg co-administered with atazanavir or weighing at least 40 kg co-administered with darunavir. (See sections 4.2, 4.4, 5.1, and 5.2.)

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adolescent patients aged 12 to < 18 years with HIV-1 infection

Ritonavir in combination with atazanavir or darunavir

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. For the treatment of HIV-1 infection in adolescent patients from the age of 12 years, the approved active ingredients are:

Protease inhibitors (PI):
Atazanavir, darunavir, fosamprenavir, ritonavir, tipranavir, lopinavir/ritonavir

Nucleosidal and nucleotidal reverse transcriptase inhibitors (NRTI):
Abacavir, eidanosine, emtricitabine, lamivudine, stavudine, tenofovir alafenamide, tenofovir disoproxil, zidovudine

Non-nucleosidal reverse transcriptase inhibitors (NNRTI):
Efavirenz, etravirine, nevirapine, rilpivirine

Integrase inhibitors (INI):
Dolutegravir, elvitegravir, raltegravir

Other antiviral agents:
Enfuvirtide (entry inhibitor), maraviroc (entry inhibitor)

To improve pharmacokinetics, especially in combination with the active ingredients atazanavir and darunavir used in the therapy of HIV-1 infection, only the active ingredient ritonavir is approved in Germany.

On 2. Non-medicinal treatment is not considered.

On 3. Resolutions on procedures according to Section 35a SGB V:

Dolutegravir/lamivudin of 6 February 2020
Doravirine/lamivudine/tenofovir disoproxil of 4 July 2019
Doravirine of 4 July 2019
Bictegravir/emtricitabine/tenofovir alafenamide of 20 December 2018
Dolutegravir/rilpivirine of 6 December 2018
Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (new therapeutic indication) of 5 July 2018
Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil (new therapeutic indication) of 3 May 2018
Darunavir/cobicistat/emtricitabine/tenofovir alafenamide of 16 March 2018
Dolutegravir (new therapeutic indication) of 21 September 2017
Emtricitabine/rilpivirine/tenofovir alafenamide of 5 January 2017
Emtricitabine/tenofovir alafenamide of 3 November 2016
Rilpivirine (new therapeutic indication) of 16 June 2016
Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide of 16 June 2016
Dolutegravir/abacavir/lamivudine of 19 March 2015
Cobicistat of 18 September 2014
Dolutegravir of 7 August 2014
Emtricitabine/rilpivirine/tenofovir disoproxil (new therapeutic indication) of 19 June 2014
Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil of 5 December 2013
Emtricitabine/rilpivirine/tenofovir disoproxil of 5 July 2012
Rilpivirine of 5 July 2012

In the therapeutic indication pharmacokinetic enhancement of active ingredients in an antiretroviral combination therapy for the treatment of HIV-1 infection, there is no proof of an additional benefit for the treatment of adult patients in the resolution of the Federal Joint Committee for cobicistat dated 18 September 2014.

On 4. The generally accepted state of medical knowledge was determined by an evidence search. For the treatment of adolescents above 12 years of age infected with human immunodeficiency virus type 1 (HIV-1), the active ingredients listed under 1 are available according to the respective approved therapeutic indication. Ritonavir is approved as a pharmacokinetic enhancer and also in combination with atazanavir or darunavir for

patients from the age of 2 years with HIV infection. Ritonavir thus represents the only appropriate comparator therapy for pharmacokinetic enhancement in the present therapeutic indication.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment contract.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of cobicistat in combination with atazanavir or darunavir is assessed as follows:

For adolescent patients aged 12 to < 18 years with HIV-1 infection, an additional benefit is not proven.

Justification:

For this patient population, the pharmaceutical company did not present any study that would have been suitable for the assessment of the additional benefit of cobicistat in the present therapeutic indication compared with the appropriate comparator therapy.

2.1.4 Summary of the assessment

For the patient population of adolescents aged 12 to < 18 years with HIV-1 infection, the pharmaceutical company did not present a study that would have been suitable for assessing the additional benefit of cobicistat in combination with atazanavir or darunavir compared with ritonavir in combination with atazanavir or darunavir.

Overall, an additional benefit of cobicistat in combination with atazanavir or darunavir for adolescent patients with HIV-1 infection is not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA takes into account the patient numbers given in the dossier of the pharmaceutical company. However, these are subject to uncertainties because of the limited epidemiological data basis on incidence and prevalence in the present indication as well as the lack of information on projections and adjustments in the dossier. Overall, the patient numbers can be assumed to be underestimated.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Tybost® (active ingredient: cobicistat) at the following publicly accessible link (last access: 1 July 2020):

https://www.ema.europa.eu/documents/product-information/tybost-epar-product-information_de.pdf

Treatment with cobicistat should only be initiated and monitored by specialists who are experienced in the treatment of patients with HIV infection.

2.4 Treatment costs

To calculate the costs of the medicinal products, the required number of packs of a particular potency was first determined on the basis of consumption. Based on the determined number of packages required, the medicinal product costs were then calculated based on the costs per package after deduction of the statutory rebates. In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130a SGB V (paragraph 1, 1a, 3a) and Section 130, paragraph 1 SGB V.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is different for each individual patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

Tybost® must always be taken together with the antiretroviral medicinal products atazanavir or darunavir. Ritonavir also needs to be taken as a pharmacological enhancer together with other antiretroviral medicinal products; however, it can be taken in other combinations besides atazanavir and darunavir.

Because the base therapy with which the protease inhibitors atazanavir and darunavir combined with cobicistat are to be applied in each case does not regularly differ from the base therapy to be applied within the framework of the appropriate comparator therapy, the presentation of the treatment costs for the base therapy is omitted.

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 September 2020).

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Cobicistat	continuously, 1 × daily	365	1	365
+ atazanavir	continuously, 1 × daily	365	1	365
+ darunavir	continuously, 1 × daily	365	1	365
Appropriate comparator therapy				
Ritonavir	continuously,	365	1	365

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
	1 × daily			
+ atazanavir	continuously, 1 × daily	365	1	365
+ darunavir	continuously, 1 × daily	365	1	365

Usage and consumption:

The average body measurements from the official representative statistics “Microcensus 2017 - body measurements of the population” were used to calculate the dosages as a function of the body weight (average body weight of 47.1 kg for adolescents ≥ 12 years and 77.0 kg for adults ≥ 18 years).[2]

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Cobicistat	150 mg	150 mg	1 × 150 mg	365	365 × 150 mg
+ atazanavir	300 mg	300 mg	1 × 300 mg	365	365 × 300 mg
+ darunavir	800 mg	800 mg	1 × 800 mg	365	365 × 800 mg
Appropriate comparator therapy					
Ritonavir	100 mg	100 mg	1 × 100 mg	365	365 × 100 mg
+ atazanavir	300 mg	300 mg	1 × 300 mg	365	365 × 300 mg
+ darunavir	800 mg	800 mg	1 × 800 mg	365	365 × 800 mg

[2] German Federal Office For Statistics, Wiesbaden 2018: http://www.gbe-bund.de/

Costs:

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Cobicistat	90 FCT	€ 131.03	€ 1.77	€ 6.83	€ 122.43
Atazanavir	60 HC	€ 779.81	€ 1.77	€ 37.44	€ 740.60
Darunavir	60 FCT	€ 745.29	€ 1.77	€ 35.76	€ 707.76
Appropriate comparator therapy					
Ritonavir	180 FCT	€ 249.20	€ 1.77	€ 11.61	€ 235.82
Atazanavir	60 HC	€ 779.81	€ 1.77	€ 37.44	€ 740.60
Darunavir	60 FCT	€ 745.29	€ 1.77	€ 35.76	€ 707.76
Abbreviations: FCT = film-coated tablets, HC = hard capsules					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 September 2020

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be assessed and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

After the positive opinion was granted, the Subcommittee on Medicinal Products defined the appropriate comparator therapy at its session on 25 February 2020.

On 1 April 2020, the pharmaceutical company submitted a dossier for the benefit assessment of cobicistat to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 2 April 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient cobicistat.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 June 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 1 July 2020. The deadline for submitting written statements was 22 July 2020.

The oral hearing was held on 11 August 2020.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 22 September 2020, and the proposed resolution was approved.

At its session on 1 October 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	18 February 2020	Determination of the appropriate comparator therapy
Working group Section 35a	5 August 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	11 August 2020	Conduct of the oral hearing
Working group Section 35a	19 August 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	22 September 2020	Concluding discussion of the draft resolution
Plenum	1 October 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 1 October 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken