Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V)
Autologous anti-CD19-transduced CD3+ cells (relapsed or refractory mantle cell lymphoma); requirement of routine practice data collection and evaluations – change

of 16 November 2023

Contents

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1. Legal basis

According to Section 35a, paragraph 3b, sentence 1 SGB V, the Federal Joint Committee (G-BA) can demand the pharmaceutical company to submit routine practice data collections and evaluations for the purpose of the benefit assessment within a reasonable period of time for the following medicinal products:

1. in the case of medicinal products authorised to be placed on the market in accordance with the procedure laid down in Article 14, paragraph 8 of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1), as last amended by Regulation 162 Rules of Procedure last revised: 16 December 2020 (EU) 2019/5 (OJ L 4, 7.1.2019, p. 24), or for which a marketing authorisation has been granted in accordance with Article 14-a of Regulation (EC) No 726/2004; and
2. for medicinal products approved for the treatment of rare diseases under Regulation No. 141/2000.

2. Key points of the resolution

At its session on 21 July 2022, the G-BA decided on the requirement of routine practice data collection and evaluations for the active ingredient autologous anti-CD19-transduced CD3+ cells (hereinafter referred to as brexucabtagene autoleucel) in accordance with Section 35a SGB V.

The generally recognised state of medical knowledge has further developed following the publication of the resolution on the G-BA website, which is why the comparators need to be adjusted.

This results in changes regarding the requirement of routine practice data collection and evaluations for brexucabtagene autoleucel (relapsed or refractory mantle cell lymphoma) by the G-BA.

On the changes in detail

The present resolution amends the therapy options considered suitable as a comparator of the routine practice data collection in the context of a patient-individual therapy. The therapy option of alternating chemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prendiso(lo)ne) and R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin), R-CHOP/R-DHAP, is deleted. The active ingredient venetoclax is added as another suitable therapy option. This change is justified as follows:

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The comparators for the routine practice data collection and evaluations are determined taking into account the essential criteria for the subsequent determination of the appropriate comparator therapy:

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 products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA 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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

The active ingredients brexucabtagene autoleucel, ibrutinib, lenalidomide and temsirolimus are explicitly approved for the treatment of mantle cell lymphoma. In addition, the following active ingredients are generally approved for the treatment of non-Hodgkin lymphoma: Bendamustine, carmustine, chlorambucil, cyclophosphamide, cytarabine, doxorubicin,

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trofosfamide, pixantrone, dexamethasone, prednisone, prednisolone, vinblastine, vincristine, bleomycin, etoposide, ifosfamide, mitoxantrone, methotrexate.

Non-medicinal treatments include allogeneic and autologous stem cell transplantation as well as radiotherapy.

In the therapeutic indication of relapsed or refractory mantle cell lymphoma, resolutions on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V for the active ingredients pixantrone (resolution of 16 May 2013), ibrutinib (resolution of 21 July 2016) and brexucabtagene autoleucel (resolution of 5 August 2021) are available.

The evidence on the therapy standard for the treatment of relapsed or refractory mantle cell lymphoma after at least two prior therapies including a BTK inhibitor is extremely limited. Various therapy options are mentioned in the present guidelines, whereby reference is made to an individualised treatment decision depending, among others, on the response and duration of remission of the previous treatments as well as the general condition. It is not possible to derive a treatment option that can be considered as the therapy standard for all patients in the present therapeutic indication.[1,2]

In this therapeutic indication, the active ingredients ibrutinib, temsirolimus, lenalidomide as monotherapy and brexucabtagene autoleucel are approved as well as rituximab in combination with fludarabine, cyclophosphamide and mitoxantrone (R-FCM), rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) and rituximab in combination with bendamustine (R-bendamustine) can be prescribed in off-label use in accordance with Annex VI of the Pharmaceuticals Directive.

Brexucabtagene autoleucel represents the intervention of the routine practice data collection and can therefore be ruled out as a comparator.

Since the patient population in this therapeutic indication has already received a BTK inhibitor, ibrutinib can only be considered as a therapy option for those patients who have not received prior ibrutinib therapy or in whom a relapse occurs after a longer treatment-free interval following prior ibrutinib therapy.

According to the available evidence, repeat immunochemotherapy in the form of R-FCM, R-CHOP or R-bendamustine is only indicated for adults with a late relapse after prior therapy. R-FCM is also an intensive therapy which, among others, due to myelotoxicity, can only be considered as a therapy option for patients with a sufficiently good general condition. R-bendamustine is a treatment option for adults with a reduced general condition.

For lenalidomide as monotherapy and temsirolimus, no clear therapy recommendation can be derived from the available guidelines, the written statements of the DCGMA (Drugs

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1 Alberta Health Services (AHS). Lymphoma [online]. Edmonton (CAN): AHS; 2019. (Clinical practice guideline; volume LYHE-002 V16).

2 National Comprehensive Cancer Network (NCCN). B-cell lymphoma. NCCN evidence blocks; version 3.2022 [online]. Plymouth Meeting (USA): NCCN; 2022.

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Commission of the German Medical Association) and the German Society for Haematology and Medical Oncology and further literature on the specific treatment setting after BTK inhibitor prior therapy[3]. By G-BA's resolution of 21 July 2016, an indication of a considerable additional benefit of ibrutinib compared to temsirolimus in adults with relapsed or refractory mantle cell lymphoma was found. The available evidence shows that lenalidomide is also a relevant treatment option in combination with rituximab on a patient-individual basis due to higher response rates.

In addition, the above-mentioned treatment options are no longer considered for adults with at least two previous therapies if they have already been used in an earlier line of therapy.

Overall, it can be concluded that it is not possible to determine an appropriate comparator therapy for all patients with at least two previous therapies covered by this therapeutic indication on the basis of the approved active ingredients. In the present guidelines, the written statements of the AkdÄ and the DGHO and the further literature on the specific treatment setting after BTK inhibitor prior therapy, the following further patient-individual treatment options are recommended, which are put to off-label use and for which there is significant evidence from single-arm studies:

- Bortezomib ± rituximab[4,5]
- Lenalidomide + rituximab[6]
- VRCAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone)[7,8]
- R-BAC (rituximab + bendamustine + cytarabine)[9]
- Rituximab + chlorambucil[10]

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[3] Burkart M, Karmali R. Relapsed/Refractory Mantle Cell Lymphoma: Beyond BTK Inhibitors. J Pers Med. 2022 Mar 1;12(3):376. doi: 10.3390/jpm12030376. PMID: 35330376; PMCID: PMC8954159.

[4] Goy A, Bernstein SH, Kahl BS, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicentre phase 2 PINNACLE study. Ann Oncol 2009;20:520-525.

[5] Baiocchi RA, Alinari L, Lustberg ME, et al. Phase 2 trial of rituximab and bortezomib in patients with relapsed or refractory mantle cell and follicular lymphoma. Cancer 2011;117:2442-2451.

[6] Wang M et al. Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: a phase 1/2 clinical trial. Lancet Oncol. 2012 Jul;13(7):716-23. doi: 10.1016/S1470-2045(12)70200-0. Epub 2012 Jun 6. PMID: 22677155.

[7] Robak T et al; LYM-3002 investigators. Frontline bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) versus rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in transplantation-ineligible patients with newly diagnosed mantle cell lymphoma: final overall survival results of a randomised, open-label, phase 3 study. Lancet Oncol. 2018 Nov;19(11):1449-1458.

[8] Fisher RI et al. Multicentre phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. J Clin Oncol. 2006 Oct 20;24(30):4867-74. doi: 10.1200/JCO.2006.07.9665. Epub 2006 Sep 25. PMID: 17001068.

[9] McCulloch R et al. Efficacy of R-BAC in relapsed, refractory mantle cell lymphoma post BTK inhibitor therapy; Br J Haematol. 2020 May;189(4):684-688. doi: 10.1111/bjh.16416. Epub 2020 Feb 3.

[10] Bauwens D, Maerevoet M, Michaux L, Théate I, Hagemeijer A, Stul M, Danse E, Costantini S, Vannuffel P, Straetmans N, Vekemans MC, Deneys V, Ferrant A, Van Den Neste E. Activity and safety of combined rituximab with chlorambucil in patients with mantle cell lymphoma. Br J Haematol. 2005 Nov;131(3):338-40. doi: 10.1111/j.1365-2141.2005.05777.x. PMID: 16225653.

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- Venetoclax[11,12]

In accordance with the generally recognised state of medical knowledge, it can be concluded in the overall assessment that the off-label use of the above-mentioned therapy options for relevant patient groups in the present therapeutic indication as part of a patient-individual therapy, taking into account the response and duration of remission of the previous therapies and the general condition, is generally preferable to the medicinal products previously approved in the therapeutic indication.

Mantle cell lymphoma is a very rare type of lymphoma. The number of patients is further reduced by considering the advanced relapsed or refractory treatment setting after at least two previous therapies. Accordingly, the evidence for therapy recommendations is extremely limited. Taking into account the severity of the disease of relapsed or refractory mantle cell lymphoma and the present advanced treatment setting after 2 or more prior systemic therapies, it is therefore appropriate to determine the above-mentioned therapy options in the off-label use as part of the patient-individual comparator therapy; Section 6, paragraph 2, sentence 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV).

Autologous or allogeneic stem cell transplant is primarily performed in the first or second line of therapy. However, for patients who have not yet received a stem cell transplant, this can also be considered in the present treatment setting if there is a good response and an appropriate general condition. If autologous stem cell transplant was previously performed, allogeneic stem cell transplant should be considered in relapse if suitable. High-dose therapy with autologous or allogeneic stem cell transplantation is therefore considered a relevant therapy option in the context of patient-individual therapy.

The resolution of 21 July 2022 on the requirement of routine practice data collection for brexucabtagene autoleucel in the indication mantle cell lymphoma does not mention venetoclax as a therapy option as part of the comparator's patient-individual therapy. However, as part of the expert exchange on the above-mentioned resolution, the clinical experts listed venetoclax as an off-label therapy option. Further study evidence on the long-term effects of venetoclax monotherapy is now available in addition to the guideline recommendations.[11] This leads to the interpretation that venetoclax represents a relevant therapy option in the present therapeutic indication, including for patients for whom other treatment options are no longer an option or as a treatment prior to stem cell transplantation. In addition, further literature on the specific treatment setting after BTK inhibitor prior therapy indicates a corresponding significance of venetoclax monotherapy.[3] The G-BA therefore considers venetoclax to be a relevant comparator in the context of patient-

[11] Davids, M.S. et al. Long-term Follow-up of Patients with Relapsed or Refractory Non-Hodgkin Lymphoma Treated with Venetoclax in a Phase 1, First-in-Human Study. Clin. Cancer Res. 2021, 27, 4690–4695.

[12] Eyre, T.A. et al. Efficacy of venetoclax monotherapy in patients with relapsed, refractory mantle cell lymphoma after Bruton tyrosine kinase inhibitor therapy. Haematologica 2018, 104, 68–71.

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individual therapy for the requirement of routine practice data collection, which is why the addition of this therapy option to the comparator is considered appropriate and necessary.

The therapy option R-CHOP/R-DHAP is only considered for very few patients in the present, late treatment setting after at least two prior therapies, as this therapy option is primarily used in earlier lines of therapy as induction therapy prior to stem cell transplantation. Repeat immunochemotherapy is only a suitable treatment option for patients with a late relapse of the previous therapy who are in good general condition and in whom toxicities (e.g. cumulative anthracycline toxicity) do not prevent its use. The significance of R-CHOP/R-DHAP in the context of a patient-individual therapy for the present treatment setting after at least 2 prior therapies is therefore considered to be very low. Against the background of the above-described addition of the venetoclax therapy option, which can be considered as a therapy option for a broader patient population and can also be used prior to stem cell transplantation, the G-BA considers it appropriate to delete the R-CHOP/R-DHAP therapy option from the patient-individual therapy specified in the comparator.

In addition, against the background of the provisions in Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), this amendment resolution adjusts the presentation of the designation of comparators for the routine practice data collection, which has no impact on the therapy options considered suitable and the implementation of the routine practice data collection.

For the present requirement of routine practice data collection, the comparator is therefore summarised as follows:

Patient-individual therapy with selection of:

- Bendamustine + rituximab
- Bortezomib ± rituximab
- Lenalidomide ± rituximab
- R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
- VRCAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone)
- Ibrutinib
- R-BAC (rituximab + bendamustine + cytarabine)
- Temsirolimus
- R-FCM (fludarabine + cyclophosphamide + mitoxantrone + rituximab)
- R-Cb (rituximab + chlorambucil)
- Venetoclax
- High-dose therapy with allogeneic stem cell transplantation
- High-dose therapy with autologous stem cell transplantation

taking into account the response and duration of remission of previous therapies and the general condition.

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The G-BA determines the above-described comparator for the routine practice study taking into account the required duration of the routine practice data collection, during which a new situation may arise with regard to the generally accepted state of medical knowledge in the therapeutic indication in question. In principle, this is to be considered separately from the determination of the appropriate comparator therapy, which only becomes legally binding with the resolution on the benefit assessment according to Section 35a, paragraph 3 SGB V.

3. Submission according to Section 35a, paragraph 3b, sentences 7 and 8 SGB V

A new submission procedure was not required.

The treatment options addressed by the present amendments were already the subject of the submission procedure carried out as part of the resolution on the requirement of routine practice data collection and evaluations of 21 July 2022 and were proposed by the parties entitled to make a statement, see Chapter 1 Section 14, paragraph 1, sentence 2 VerfO.

The adjustment of the description of comparators does not represent any significant change compared to the resolution on the requirement of routine practice data collection and evaluations of 21 July 2022, cf. Chapter 1 Section 14, paragraph 1 sentence 1 Rules of Procedure of the G-BA.

4. Bureaucratic costs calculation

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.

5. Process sequence

Subsequent to the resolution of 21 July 2022 on an amendment to the Pharmaceuticals Directive (AM-RL) Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V – Autologous anti-CD19-transduced CD3+ cells, an amendment to the resolution is necessary due to the further development of the generally recognised state of medical knowledge.

The issue was discussed in the working group WG RPDC and in the Subcommittee on Medicinal Products.

At its session on 16 November 2023, the plenum adopted by consensus a resolution to amend the AM-RL.

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Chronological course of consultation

Session	Date	Subject of consultation
WG RPDC	16 October 2023 2 November 2023	Consultation on the issue
Subcommittee Medicinal products	7 November 2023	Consultation on the amendment to the resolution of 21 July 2022
Plenum	16 November 2023	Resolution on the amendment to the resolution of 21 July 2022

Berlin, 16 November 2023

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken

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