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 Ibrutinib (New Therapeutic Indication: Waldenström's Macroglobulinaemia, Combination with Rituximab)

of 20 February 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 evidence 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 evidence 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 ibrutinib (IMBRUVICA®) was first placed on the German market on 1 November 2014.

Ibrutinib is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

In its previously approved therapeutic indications, ibrutinib's sales within the German statutory health insurance system at pharmacy sales prices including VAT exceeded 50 million euros, necessitating the submission of evidence for ibrutinib in accordance with Section 5 paragraphs 1 to 6 of the Rules of Procedure (VerfO) of the G-BA to demonstrate its additional benefit compared to the appropriate comparator therapy.

On 2 August 2019, ibrutinib received marketing authorisation for a new therapeutic indication:

"IMBRUVICA in combination with rituximab is indicated for the treatment of adult patients with WM."

On 30 August 2019, 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 ibrutinib 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 the website of the G-BA (www.g-ba.de) on 2 December 2019, 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 ibrutinib 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 evaluated 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 ibrutinib.

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 ibrutinib (Imbruvica®) in accordance with the product information

IMBRUVICA in combination with rituximab is indicated for the treatment of adult patients with Waldenström's macroglobulinaemia.

2.1.2 Appropriate comparator therapy

Adult patients with Waldenström's macroglobulinaemia

- A patient-individual therapy taking into account the general condition of patients and, if appropriate, previous therapies.

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.

[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.

3. As comparator therapy, medicinal products 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.

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

On 1. Medicinal products with the following active ingredients are approved for the present therapeutic indication:

bendamustine, chlorambucil, cyclophosphamide, cytarabine, dexamethasone, doxorubicin, ibrutinib, prednisolone, prednisone, trofosfamide, vinblastine and vincristine.

Some of the above-mentioned medicinal products are approved for the superordinate therapeutic indication "non-Hodgkin lymphomas".

On 2. In the therapeutic indication under consideration, in principle, both allogenic and autologous stem cell transplantation are therapeutic non-medicinal options. However, it is assumed that neither option is appropriate at the time of treatment with ibrutinib in combination with rituximab. In addition, plasmapheresis is a relevant non-medicinal therapy option in the present therapeutic indication. However, this is usually only employed for a short period of time and as a supportive measure in cases of hyperviscosity syndrome independent of antineoplastic therapy and is therefore not considered to be part of a appropriate comparator therapy.

On 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Ibrutinib – resolution of 21 July 2016

Annex VI to Section K of the Pharmaceuticals Directive (last revised: 17 October 2019) – Prescribability of authorised medicinal products in non-approved therapeutic indications (off-label use):

- Use of fludarabine, other than for the market authorisation's stated use of treating lymphatic leukaemia (CLL), to treat low or intermediate grade non-Hodgkin lymphoma (NHL)

On 4. The general state of medical knowledge for the indication was established by means of a search for guidelines and systematic reviews of clinical studies.

Guidelines recommend various treatment regimens to treat adult patients with Waldenström's macroglobulinaemia, taking into account, in particular, general condition and, as required, previous therapy. The available evidence, on balance limited, indicates that a combination of chemotherapy and immunotherapy, the latter in the form of the anti-CD20 antibody rituximab, is more effective than chemotherapy alone. Specifically, the recommended therapeutic regimes are chlorambucil in combination with rituximab, bendamustine in combination with rituximab, rituximab in combination with cyclophosphamide, doxorubicin, vincristine and predniso(lo)ne (R-CHOP), cladribine in combination with rituximab, bortezomib in combination with rituximab, if appropriate, dexamethasone, and dexamethasone in combination with cyclophosphamide and rituximab. Only in patients who are not eligible for such therapy is monotherapy with rituximab a treatment option. However, rituximab, bortezomib and cladribine are not approved for the therapeutic indication under consideration. Ibrutinib as monotherapy is another approved treatment option, but only for patients who are not eligible for chemo-immunotherapy and for pretreated patients. In the relevant benefit assessment, no additional benefit was established for ibrutinib (resolution of 21 July 2016), as, taking into account the available evidence, no data has been presented to

support an additional benefit for ibrutinib compared to the appropriate comparator therapy. Furthermore, for suitable patients with resistance to R-CHOP or CHOP (cyclophosphamide in combination with doxorubicin, vincristine and predniso(lo)ne), the combination of fludarabine, cyclophosphamide, mitoxantrone and rituximab may be prescribed in accordance with Annex VI to Section K of the German Pharmaceuticals Directive.

In summary, in the therapeutic indication under consideration there is a discrepancy between medicinal products approved for the indication and those used in health care or recommended in guidelines and that, according to the generally recognised state of medical knowledge, no therapeutic option is generally preferable to all other therapeutic options. In this context, the G-BA, therefore, considers patient-individual therapy, taking into account the general condition of patients and, if appropriate, previous therapies, to constitute appropriate comparator therapy. Such individual comparator therapy may include the active ingredients or combinations of active ingredients discussed in the justification above.

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 ibrutinib is assessed as follows.

No additional benefit has been proven to treat Waldenström's macroglobulinaemia in adult patients with ibrutinib in combination with rituximab compared to the appropriate comparator therapy.

Justification:

In its dossier, the pharmaceutical company initially presents the results of the iNNOVATE pivotal study. This study is a randomised, controlled trial comparing ibrutinib in combination with rituximab (arm A) to placebo and rituximab (arm B). The study included a total of 150 adult patients with untreated or pretreated Waldenström's macroglobulinaemia and an EGOC-PS of 0 to 2. In addition, in a further non-randomised study arm (arm C), 31 patients who were refractory to a prior rituximab-containing therapy and were thus excluded from the randomised main study were further treated with ibrutinib monotherapy. Thus, in the iNNOVATE study all patients in arm B received rituximab monotherapy. However, this was only considered as a treatment option for patients ineligible for chemo-immunotherapy. Hence, it cannot be assumed that rituximab monotherapy constitutes an adequate patient-individual therapy for all patients included in the comparator arm of the iNNOVATE study. In this regard, in its dossier the pharmaceutical company did not name or identify a sub-population suitable for rituximab monotherapy. Hence, in this case it could not be proven that, in the context of patient-individual therapy, rituximab monotherapy is a suitable intervention for a specific sub-population. And thus it remains unclear, taken as a whole, whether, or to what extent, patients in the iNNOVATE study were provided with an appropriate comparator therapy. Based on the available data, deriving an additional benefit from ibrutinib in combination with rituximab compared to the appropriate comparator therapy is, therefore, neither possible for the total population nor for a specific sub-population.

In the dossier, the pharmaceutical company goes on to present comparisons of individual arms from various studies, comparing arm A of the iNNOVATE study (i.e., ibrutinib in combination with rituximab) with patient-individual therapy or ibrutinib monotherapy. To make a comparison with a patient-individual therapy, the pharmaceutical company presents data from the retrospective cohort studies Castillo *et al.* (2018), Castillo *et al.* (2019) and the retrospective

secondary database PHEDRA, while to make a comparison with ibrutinib monotherapy it presents data from the single-arm open-label study PCYC-1118E and arm C of the iNNOVATE study.

In doing so, the comparisons presented are each subject to limitations. It remains, for instance, unclear in the comparisons made with ibrutinib monotherapy whether this is the most appropriate therapy for all patients included in the PCYC-1118E study and in arm C of the iNNOVATE study. Regarding the comparison with a patient-individual therapy, no data on the side effects endpoint category are presented for the appropriate comparator therapy. Irrespective of this, the effect estimates presented for patient-relevant outcomes are not so large that they could not be solely due to systematic bias. Rather, no statistically significant results are demonstrated for patient-relevant outcomes.

Summary

Overall, no suitable data have been presented to evaluate ibrutinib in combination with rituximab compared to the appropriate comparator therapy for the treatment of adult patients with Waldenström's macroglobulinaemia. The pharmaceutical company was unable, in particular, to provide evidence that rituximab monotherapy represents an adequate patient-individual therapy for all, or a subset, of patients included in the study. The additional benefit of ibrutinib in combination with rituximab is therefore not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of a new therapeutic indication for ibrutinib.

The therapeutic indication assessed here is as follows: "IMBRUVICA in combination with rituximab is indicated for the treatment of adult patients with Waldenström's macroglobulinaemia."

Ibrutinib has received marketing authorisation as an orphan drug.

As an appropriate comparator therapy, the G-BA designated a patient-individual therapy taking into account the general condition of patients and, if appropriate, previous therapies.

In its dossier, the pharmaceutical company presents results from the randomised, controlled authorisation study iNNOVATE, in which ibrutinib in combination with rituximab was compared to rituximab monotherapy. In the iNNOVATE study all patients in the comparator arm received rituximab monotherapy. The pharmaceutical company can neither demonstrate that rituximab monotherapy represents a suitable patient-individual therapy for all patients included in the comparator arm, nor can it identify a sub-population to which this applies. It is thus unclear, taken as a whole, whether, or to what extent, the iNNOVATE study provided patients with an appropriate comparator therapy. The other comparisons with ibrutinib monotherapy or patient-individual therapy from individual arms of various studies presented are either limited in value due to inadequate implementation of the appropriate comparator therapy or due to a lack of data in the side effects endpoint category. Regardless of this, these comparisons do not reveal statistically significant results for patient-relevant outcomes.

Overall, therefore, no suitable data have been presented that would allow an assessment of additional benefit for ibrutinib in combination with rituximab compared to the appropriate comparator therapy. The additional benefit of ibrutinib in combination with rituximab is therefore 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 bases its resolution on the information provided by the pharmaceutical company. The calculation used to derive patient numbers is comprehensible, and the magnitude of the figures arrived at are plausible. The stated range takes into account uncertainties in the available data and reflects the minimum and maximum values obtained when deriving the patient numbers.

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 Imbruvica® (active ingredient: ibrutinib) at the following publicly accessible link (last access: 18 December 2019):

https://www.ema.europa.eu/en/documents/product-information/imbruvica-epar-product-information_en.pdf

Treatment with ibrutinib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology who are experienced in the treatment of patients with Waldenström's macroglobulinaemia.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 February 2020).

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 Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

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 patient-individual and/or is shorter on average. The time unit "days" is employed in calculating the "number of treatments/patient/year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

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				
Ibrutinib	continuously, 1 × daily	365	1	365
Rituximab	1 every 7 days in weeks 1–4 and weeks 17–20	2 cycles	4	8
Appropriate comparator therapy				
Patient-individual therapy taking into account the general condition of patients and, if appropriate, previous therapies.	Different for each individual patient			

Usage and consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis (average height: 1.72 m, average body weight: 77 kg). From this, a body surface area of 1.90 m² is calculated (calculation according to Du Bois 1916)[2].

Designation of the therapy	Dosage/ application	Dosage/ patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Ibrutinib	420 mg	420 mg	1 × 420 mg	365	365 × 420 mg
Rituximab	375 mg/m²	712.5 mg	3 × 100 mg 1 × 500 mg	8	24 × 100 mg 8 × 500 mg
Appropriate comparator therapy					

[2] Federal health reporting. Average body measurements of the population (2017, both sexes), www.gbe-bund.de

Designation of the therapy	Dosage/ application	Dosage/ patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Patient-individual therapy taking into account the general condition of patients and, if appropriate, previous therapies.	Different for each individual patient				

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					
Ibrutinib 420 mg	28 FCT	€ 5,978.75	€ 1.77	€ 0.00	€ 5,976.98
Rituximab 100 mg	2 CIS	€ 716.94	€ 1.77	€ 39.08	€ 676.09
Rituximab 500 mg	1 CIS	€ 1,777.06	€ 1.77	€ 98.21	€ 1,677.08
Appropriate comparator therapy					
Patient-individual therapy taking into account the general condition of patients and, if appropriate, previous therapies.	Different for each individual patient				
Acronyms: FCT = film-coated tablets, CIS = concentrate for infusion solution					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 February 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 evaluated 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.

Designation of the therapy	Type of service	Cost per package or service	Treatment days per year	Annual costs per patient
Ibrutinib or rituximab	HBV test Hepatitis B surface antigen status (fee schedule number 32781)	€ 5.50	1	€ 5.50
	Hepatitis B antibody status (fee schedule number 32614)	€ 5.90	1	€ 5.90
Rituximab	Pre-medication Antihistamines e.g. dimetindene i.v. Antipyretics e.g. paracetamol	 € 14.88 € 1.36[3]	 8 8	 € 59.52 € 1.36

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: arbitral award to determine the mg prices for parenteral preparations from proprietary medicinal products in oncology in the Hilfstaxe according to Section 129, paragraph 5c, sentences 2–5 SGB V of 19 January 2018), surcharges for the production of parenteral preparations containing cytostatic drugs of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall be payable. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

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

On 30 August 2019, the pharmaceutical company submitted a dossier for the benefit assessment of ibrutinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA.

[3] Non-prescription medicinal products that are reimbursable at the expense of the SHI in accordance with Section 12, paragraph 7 AM-RL (information as accompanying medication in the product information of the prescription medicinal product) are not subject to the current medicinal product price regulation. Instead, for these, in accordance with Section 129, paragraph 5a SGB V when a non-prescription medicinal product is sold and invoiced in accordance with Section 300, for the insured person, a pharmaceutical selling price in the amount of the selling price of the pharmaceutical company – plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the 31 December 2003 version – shall apply.

By letter dated 2 September 2019 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 ibrutinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 November 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 2 December 2019. The deadline for submitting written statements was 23 December 2019.

The oral hearing was held on 6 January 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 11 February 2020, and the proposed resolution was approved.

At its session on 20 February 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	26 February 2019	Determination of the appropriate comparator therapy
Subcommittee Medicinal Products	6 January 2020	Conduct of the oral hearing
Working group Section 35a	15 January 2020 22 January 2020 5 February 2020	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	11 February 2020	Concluding discussion of the draft resolution
Plenum	20 February 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 20 February 2020

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

Prof. Hecken