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 Ropeginterferon alfa-2b

of 5 March 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 relevant date for first placing on the market of the active ingredient ropeginterferon alfa-2b in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 September 2019. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 28 August 2019.

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 16 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 ropeginterferon alfa-2b 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 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 ropeginterferon alfa-2b.

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 ropeginterferon alfa-2b (Besremi®) in accordance with the product information

Besremi is indicated as monotherapy in adults for the treatment of polycythaemia vera without symptomatic splenomegaly.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with polycythaemia vera without symptomatic splenomegaly not pretreated with hydroxyurea or pretreated with hydroxyurea who are not resistant or intolerant to hydroxyurea

   Hydroxyurea

b) Adult patients with polycythaemia vera without symptomatic splenomegaly pre-treated with hydroxyurea who are resistant or intolerant to hydroxyurea

   Ruxolitinib

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 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.

[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. Hydroxyurea and ruxolitinib have been approved for the indication polycythaemia vera.

On 2. Phlebotomy and, in principle, allogenic stem cell transplantation may be considered as non-medicinal treatment. In the therapeutic scenario under consideration, allogeneic stem cell transplantation is not considered to be an appropriate comparator therapy. In addition, the G-BA does not consider splenectomy and spleen irradiation to be relevant in the therapeutic indication under consideration of "polycythaemia vera without symptomatic splenomegaly."

On 3. The following resolutions and guidelines of the G-BA have been issued for medicinal therapies in the present therapeutic indication:

Resolutions on the Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V:

- Ruxolitinib – Resolution of 15 October 2015

On 4. The generally accepted state of medical knowledge for the indication was established by means of a search for guidelines as well as systematic reviews of clinical studies.

Evidence regarding treatment of polycythaemia vera is limited. No methodologically adequate guidelines could be identified. Based on supplementary evidence (British Committee for Standards in Haematology, 2005; Marchioli R *et al.*, 2014), it can be concluded that phlebotomy and hydroxyurea treatment in patients with polycythaemia that reduce haematocrit to < 45% result in a significantly decreased incidence of severe thrombosis and cardiovascular mortality compared to such treatment that reduce haematocrit to 45–50%. The most common treatment to lower an elevated haematocrit is blood-letting (phlebotomy) and, in particular if there is a high risk of thromboembolic events, cytoreductive therapy with hydroxyurea or interferons. With the exception of ropeginterferon alfa-2b, interferons are not approved for the treatment of polycythaemia vera. On the basis of the marketing authorisation and the available evidence, the G-BA has accordingly determined hydroxyurea as an appropriate comparator therapy for patients who have not been pre-treated or have been pre-treated with hydroxyurea, but who are not resistant or intolerant to hydroxyurea. This patient group also includes patients who have not yet responded adequately to hydroxyurea.

Another patient population covered by the therapeutic indication under consideration is that of pre-treated patients who are resistant or intolerant to hydroxyurea. Two systematic reviews of the active ingredient ruxolitinib were identified for this treatment option. Both reviews reveal a clinical benefit for ruxolitinib in patients with proven intolerance or resistance to hydroxyurea based on the pivotal study. Evidence is provided for improved haematocrit control and a reduction in the incidence of thromboembolic events compared to standard therapy. The resolution of the G-BA of 15 October 2015 concluded there is a hint for a considerable additional benefit, based on the advantages in the endpoint categories morbidity and quality of life, for ruxolitinib compared to patient-individual therapy according to the doctor's instructions. Based on the marketing authorisation, the evidence and the existing G-BA resolution, the G-BA has, therefore, determined ruxolitinib as an appropriate comparator therapy for patients who are resistant or intolerant to hydroxyurea.

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 ropeginterferon alfa-2b is assessed as follows:

a) Adult patients with polycythaemia vera without symptomatic splenomegaly not pretreated with hydroxyurea or pretreated with hydroxyurea who are not resistant or intolerant to hydroxyurea

An additional benefit is not proven.

Justification:

To demonstrate the benefit of ropeginterferon alfa-2b, the pharmaceutical company has submitted data from the completed, open, randomised study PROUD-PV and the extension study CONTINUATION-PV.

PROUD-PV

In PROUD-PV, ropeginterferon alfa-2b was compared to hydroxyurea, the appropriate comparator therapy. The study lasted for 12 weeks. Both therapy-naïve and pre-treated patients were included in the study. The study was conducted at a total of 48 sites in Europe. Recruitment took place between October 2013 and April 2016.

Therapy-naïve patients had to meet at least one of the following criteria: > 60 years, at least one prior cardiovascular event (associated with polycythaemia vera), poor tolerance of phlebotomies. Patients pre-treated with hydroxyurea had to be primary endpoint non-responders (haematocrit < 45% without phlebotomy within the last 3 months, platelet count < 400 x 10^9/l, leucocyte count < 10 x 10^9/l, normal spleen size). Additionally, they had to have been pre-treated with hydroxyurea for no longer than three years and had to show no resistance or intolerance to hydroxyurea.

Patients in PROUD-PV had a mean age of 59 and 58 years, respectively, and the majority were therapy-naïve (approximately 65 % and 70 %, respectively). Patients pre-treated with hydroxyurea had received treatment for a mean of approximately 12 months. All but one of the patients had a JAK2 mutation.

A total of 257 patients were randomised at ration of 1:1 to the two study arms (N = 127 ropeginterferon alfa-2b, N = 130 hydroxyurea). Randomisation was stratified based on previous hydroxyurea treatment (yes / no), age (≤ 60 / > 60 years) and history of a thromboembolic event (yes / no). Of the randomized patients, 254 received the study medication (N = 127 ropeginterferon alfa-2b, N = 127 hydroxyurea). Patients were treated with ropeginterferon alfa-2b and hydroxyurea as specified by the respective product information documents. Provided there were no contraindications, patients in both study arms received 100 mg acetylsalicylic acid daily as concomitant medication. In addition, if haematocrit was > 45 %, a phlebotomy was to be performed. Patients pre-treated with hydroxyurea who were not resistant or intolerant to hydroxyurea were initially treated with an unchanged, patient-individual hydroxyurea dose regimen. As these patients had not responded adequately to hydroxyurea, the study aimed to perform a response-guided dose adjustment of hydroxyurea in a two-week interval. Information on the dose adjustment actually performed in these patients is not available in the study documentation.

CONTINUATION-PV

The CONTINUATION-PV study is an open-label phase IIIb extension study to evaluate the long-term efficacy and safety of ropeginterferon alfa-2b in patients with polycythaemia vera who had previously participated in the PROUD-PV study. The pharmaceutical company has

submitted data from a 24 month data cut-off for this study. As such, the data analysed was collected over a period of 36 months. In light of the chronic and gradual progression of polycythaemia vera, the G-BA considers long-term data to be highly relevant. However, the CONTINUATION-PV findings are not considered relevant for the benefit assessment for the following reasons.

The study was initially solely intended as a non-comparative extension study of the ropeginterferon alfa-2b arm of the PROUD-PV study. The study design was modified to integrate the comparator arm (hydroxyurea or a therapy according to the doctor's instructions) only after approximately nine months after the first patient had completed the PROUD-PV study. Due to the delayed transition of patients into the comparator arm, less than 40% of patients treated with hydroxyurea were under observation in the first year of the CONTINUATION-PV study. In addition, only 171 of the 254 patients (approx. 67 %) from the PROUD-PV study moved over to the extension study. Of these, 95 patients switched from the ropeginterferon-alfa-2b arm (approx. 75%) and 76 patients switched from the hydroxyurea arm (60%). This means that there was a 15 percentage difference in the number of patients from the two study arms switching to the extension study. As a result, the structural equivalence of the study's treatment arms can no longer be guaranteed.

The data submitted by the pharmaceutical company for the patients enrolled in the extension study's comparator arm show evidence of a potential selection effect with regards to which patients did or did not move over into the CONTINUATION-PV study. For example, a significantly higher percentage of patients in the hydroxyurea arm of the PROUD-PV study were found to have been hypertensive at the time of screening of the PROUD-PV study (56.6% vs 34.3%), to have received phlebotomies (42.1% vs 22.9%), or to have a higher median haematocrit (49.9% vs 46%).

The inclusion criteria of the CONTINUATION-PV study are such that further selection effects cannot be excluded. For example, in the study only patients were enrolled who had benefited from ropeginterferon alfa-2b as evidenced by normalisation or reduction of relevant blood levels (haematocrit, leucocytes, thrombocytes), normalisation of spleen size or any other clear medical benefit (such as normalisation of disease-associated microvascular symptoms or relevant reduction of JAK-2 allelic load).

In addition, the treatment guidelines in the CONTINUATION-PV study differ between the intervention arm and the comparator arm. For example, in the comparator arm (hydroxyurea/therapy according to the doctor's instructions) there is no information on how doses should be adapted if required. Moreover, as per treatment guidelines, patients in the intervention arm of the study administered with ropeginterferon alfa-2b every two weeks by their doctor had blood samples taken at the same time. In contrast, those patients in the comparator and ropeginterferon alfa-2b arms who self-administered using prefabricated pens were only required to attend a consultation every three months. As haematocrit was one of the parameters evaluated in the blood samples, if a dose adjustment was necessary this could be done more rapidly in the group of patients administered ropeginterferon alfa-2b by their doctor.

Overall, the G-BA finds that the described methodological deficiencies of the CONTINATION-PV study make interpretation of its findings sufficiently unreliable to support a claim of additional benefit. Consequently, only the data from the PROUD-PV study, covering an observation period of 12 months, have been considered in the present benefit assessment.

Extent and probability of the additional benefit

Mortality

With regards to the overall survival endpoint, only one event occurred in the intervention arm and none in the comparator arm. Presenting an effect estimator would, as such, be meaningless. Overall, the difference is not statistically significant. An additional benefit of ropeginterferon alfa-2b for the mortality endpoint has, thus, not been proven.

Morbidity

Haematological response

The haematological response endpoint is defined as a haematocrit of < 45% combined with a phlebotomy-free period of at least three months and a platelet count of < 400 × 10^9/l and a leucocyte count of < 10 × 10^9/l. This endpoint was defined *post-hoc* by the pharmaceutical company as the primary endpoint. In the PROUD-PV study, the primary endpoint was pre-specified as the both haematological response, as per the definition above, and also normalisation of spleen size. The reason for this amendment can be found in the EMA assessment report, which states that only a small proportion of patients were found to have a significant splenomegaly at baseline and spleen sizes in the study differed only minimally.

The frequency with which patients are administered a phlebotomy is based directly on their haematocrit; reducing haematocrit to below 45 % is considered critical. Phlebotomies are usually associated with a loss of quality of life for patients and an increased risk of treatment-related side effects. Controlling haematocrit and, therefore, the need for phlebotomies is considered to be patient-relevant in the therapeutic indication under consideration. The haematological response endpoint is therefore assessed as patient-relevant in the present operationalisation of "a haematocrit of < 45% combined with a phlebotomy-free period of at least three months".

For this *post-hoc* defined endpoint disregarding spleen size, no statistically significant difference was found between the study arms (relative risk = 0.82 [0.64; 1.05]). An additional benefit of ropeginterferon alfa-2b for the haematological response endpoint has, thus, not been proven.

Phlebotomies

With regard to the frequency of phlebotomies performed based on a haematocrit of > 45%, no statistically significant differences were found between the study arms for the entire study period of 12 months or for the titration phase (weeks 1–12). A statistically significant difference to the detriment of ropeginterferon alfa-2b was observed during the maintenance phase (week 13–52) (relative risk: 1.55 [1.19; 2.02]).

Health status (EQ-5D VAS)

No statistically significant difference was found between the study arms for the health status endpoint, as evaluated by the EQ-5D visual analogue scale (VAS). An additional benefit of ropeginterferon alfa-2b for the health status endpoint has, thus, not been proven.

Quality of life

Data on health-related quality of life were not collected in the PROUD-PV study.

Side effects

Adverse events (AEs) occurred at least once in > 80 % of patients in both study arms. The results for the “combined adverse events” endpoint are presented only on a supplementary basis.

No statistically significant differences were found between the study arms for the endpoints serious adverse events (SAEs), severe AEs (CTCAE grade 3) and discontinuation due to AE.

A statistically significant advantage of ropeginterferon alfa-2b over hydroxyurea was identified for the specific AEs Gastrointestinal disorders (SOC) and for the PT Nausea and the PT Influenza within this SOC.

Taking into account the clinical symptomatology and severity of the disease as well as the type and incidence of the AEs, the advantages regarding the specific AEs are considered to constitute a non-relevant reduction of side effects.

Thus, in the side effects endpoint category no differences between the study arms relevant for assessment have been established.

Overall assessment

To assess the additional benefit for ropeginterferon alfa-2b, the pharmaceutical company presented the open, randomised phase III study PROUD-PV, lasting 12 months, comparing ropeginterferon alfa-2b with hydroxyurea. The pharmaceutical company also presented data from the phase IIIb extension study CONTINUATION-PV, covering a total observation period of 36 months. Patients in this study had previously participated in the PROUD-PV study.

The G-BA finds that methodological deficiencies of the extension study (e.g. dissimilar provisions on how patients of the the two study arms should be treated, possible selection effects due to specific inclusion criteria, relevant differences in the percentage of patients who transitioned from the two study arms of the PROUD-PV study to the extension study) make interpretation of its findings sufficiently unreliable to assess the additional benefit. Consequently, only the data from the PROUD-PV study, covering an observation period of 12 months, have been considered in the present benefit assessment.

No statistically significant difference between ropeginterferon alfa-2b and hydroxyurea has been established for the endpoint overall survival.

A statistically significant difference between the study arms for the endpoint category morbidity has not been established for the endpoints haematological response and health status (EQ-5D VAS). A statistically significant difference to the detriment of ropeginterferon alfa-2b compared to hydroxyurea for the endpoint phlebotomies was found during the maintenance phase. This difference is not deemed sufficiently significant to establish an overall detriment in the morbidity endpoint category.

Data on health-related quality of life were not collected in the PROUD-PV study.

No statistically significant differences were found between the study arms for the endpoints serious adverse events (SAEs), severe AEs (CTCAE grade 3) and discontinuation due to AE. Advantages for ropeginterferon alfa-2b were observed in several specific AEs. Taking into account the clinical symptomatology and the severity of the disease as well as the type and frequency of occurrence of the AEs, these specific AE advantages are not considered to

constitute a relevant reduction of side effects and are therefore not grounds for deriving an additional benefit.

In summary, in consideration of the combined findings on mortality, morbidity, and side effects, an additional benefit has not been proven for ropeginterferon alfa-2b over hydroxyurea in adult patients with polycythaemia vera without symptomatic splenomegaly not pretreated with hydroxyurea or pretreated with hydroxyurea who are not resistant or intolerant to hydroxyurea.

Ropeginterferon alfa-2b may be a relevant therapeutic option in individual cases.

b) Adult patients with polycythaemia vera without symptomatic splenomegaly pre-treated with hydroxyurea who are resistant or intolerant to hydroxyurea

An additional benefit is not proven.

Justification:

No data were submitted to establish an additional benefit for ropeginterferon alfa-2b compared to the appropriate comparator therapy (ruxolitinib) for the group adult with polycythaemia vera without symptomatic splenomegaly pre-treated with hydroxyurea who are resistant or intolerant to hydroxyurea.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Besremi® " with the active ingredient ropeginterferon alfa-2b. The active ingredient ropeginterferon alfa-2b is indicated as monotherapy in adults for the treatment of polycythaemia vera without symptomatic splenomegaly.

In the therapeutic indication to be considered, two patient populations were distinguished:

a) Adult patients with polycythaemia vera without symptomatic splenomegaly not pretreated with hydroxyurea or pretreated with hydroxyurea who are not resistant or intolerant to hydroxyurea
b) Adult patients with polycythaemia vera without symptomatic splenomegaly pre-treated with hydroxyurea who are resistant or intolerant to hydroxyurea

a) Adult patients with polycythaemia vera without symptomatic splenomegaly not pretreated with hydroxyurea or pretreated with hydroxyurea who are not resistant or intolerant to hydroxyurea

Hydroxyurea was determined as an appropriate comparator therapy by the G-BA. For this patient group, the pharmaceutical company has submitted data from the 12-month phase III study PROUD-PV and the associated extension study CONTINUATION-PV. The G-BA finds that methodological deficiencies of the extension study make interpretation of its findings sufficiently unreliable to assess the additional benefit. Thus, the present benefit assessment only draws on findings from the PROUD-PV study.

No statistically significant difference between the study arms has been established for the endpoint overall survival (mortality) and for the endpoints haematological response and health status (EQ-5D VAS) in the morbidity category. A statistically significant difference to the detriment of ropeginterferon alfa-2b compared to hydroxyurea for the endpoint phlebotomies was found during the maintenance phase. This difference is not deemed

sufficiently significant to establish an overall detriment in the morbidity endpoint category. There was no survey of health-related quality of life.

No statistically significant differences were found between the study arms for the endpoints serious adverse events (SAEs), severe AEs (CTCAE grade 3) and discontinuation due to AE. Advantages for ropeginterferon alfa-2b were observed in several specific AEs. Taking into account the clinical symptomatology and the severity of the disease as well as the type and frequency of occurrence of the AEs, these specific AE advantages are not considered to constitute a relevant reduction of side effects and are therefore not grounds for deriving an additional benefit.

In summary, no additional benefit of ropeginterferon alfa-2b compared with hydroxyurea has been established.

Ropeginterferon alfa-2b may be a relevant therapeutic option in individual cases.

b) Adult patients with polycythaemia vera without symptomatic splenomegaly pre-treated with hydroxyurea who are resistant or intolerant to hydroxyurea

For this patient population, the pharmaceutical company did not present a study that would have been suitable to assess the additional benefit of ropeginterferon alfa-2b compared to the appropriate comparator therapy.

In summary, an additional benefit of ropeginterferon alfa-2b for the patient population under consideration has not been proven.

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

a) Adult patients with polycythaemia vera without symptomatic splenomegaly not pretreated with hydroxyurea or pretreated with hydroxyurea who are not resistant or intolerant to hydroxyurea

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

The resolution will be based on the information from the dossier of the pharmaceutical company. These numbers are subject to uncertainties. On the one hand, the data in the sources on the prevalence of polycythaemia vera are associated with uncertainties due to the lack of studies on the prevalence of polycythaemia vera in Germany and the fact that studies in other European countries often refer to myeloproliferative disorders in general rather than specifically to polycythaemia vera. On the other, some of the studies drawn on are outdated. In its calculations, the pharmaceutical company continues to disregard the fact that ropeginterferon alfa-2b is only approved for adult patients, instead basing its calculations on prevalence data for the entire population of Germany. This step in the calculation therefore tends to lead to an overestimation. In subsequent calculations, the pharmaceutical company subtracts the percentage figure for all patients with splenomegaly, even though ropeginterferon alfa-2b is not solely indicated only for patients with symptomatic splenomegaly. This tends to lead to an underestimation. Furthermore, information on patients with contraindications has not been taken into account. Finally, when calculating the percentage of patients who are resistant or intolerant to hydroxyurea, the pharmaceutical company disregards the fact that not all patients with polycythaemia vera receive first-line therapy with hydroxyurea. This tends to lead to an overestimation.

b) Adult patients with polycythaemia vera without symptomatic splenomegaly pre-treated with hydroxyurea who are resistant or intolerant to hydroxyureaa

The resolution is based on the patient numbers from the previous resolution on ruxolitinib for the therapeutic indication polycythaemia (of 15 October 2015).

Justification: The G-BA considers that the patient figures presented by the pharmaceutical company do not represent a clearly better estimate than the patient figures from the previous resolution on ruxolitinib for the therapeutic indication polycythaemia vera. The patient numbers presented in the previous case are indeed subject to uncertainties due to the limited epidemiological data on the incidence and prevalence of polycythaemia vera and their unclear transferability to the context of the German health care system. However, this is equally applicable to the patient numbers submitted in the present case. In addition, the percentage of patients with resistance or intolerance to hydroxyurea is overestimated based on the available patient numbers, since the pharmaceutical company disregards the fact that not all patients with polycythaemia vera receive first-line therapy with hydroxyurea. This is also reflected in the fact that the patient numbers determined for the ruxolitinib assessment are lower, even though the therapeutic indication of ruxolitinib is not limited to patients without symptomatic splenomegaly and has, therefore, been made on the basis of a larger patient population with resistance or intolerance to hydroxyurea.

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 Besremi® (active ingredient: ropeginterferon alfa-2b) at the following publicly accessible link (last access: 7 January 2020):
https://www.ema.europa.eu/en/documents/product-information/besremi-epar-product-information_en.pdf

Treatment with ropeginterferon alfa-2b should only be initiated and monitored by specialists in internal medicine, haematology, and oncology experienced in the treatment of patients with polycythaemia vera.

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: 15 February 2020).

Treatment duration:

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 used to calculate the "number of treatments/patient/year", time between individual treatments and for maximum treatment duration, if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Ropeginterferon	1 × every 14	26.1	1	26.1

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
alfa-2b	days			
Appropriate comparator therapy				
Patient population a)				
Hydroxyurea	continuously, 1 × daily	365	1	365

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Patient population b)				
Ruxolitinib	continuously, 2 × daily	365	1	365

Usage and consumption:

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

According to the product information, the dose of ropeginterferon alfa-2b should be increased individually every 14 days by 50 µg with an initial dose of 100 µg. The maximum recommended single dose is 500 µg every 14 days. A dose range of 100–500 µg is therefore assumed for the cost calculation. As the prefabricated pen is stable for 30 days after initial opening and there is a 14-day interval between doses, for the lowest dose in this range (100 µg) it is assumed that a single prefabricated pen can be used twice.

According to the respective product information, a mean continuous dose of 500–1000 mg / day is assumed for hydroxyurea and a range of 2 x 5 mg to 2 x 25 mg for ruxolitinib.

Designation of the therapy	Dosage/ application	Dosage/patient /treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Ropeginterferon alfa-2b	100–500 µg	50–500 µg	0.5–2 x 250 µg	26.1	13.1–52.2 x 250 µg
Appropriate comparator therapy					
Patient population a)					
Hydroxyurea	500–1000 mg	500–1000 mg	1–2 x 500 mg	365	365–730 × 500 mg
Patient population b)					
Ruxolitinib	5–25 mg	2 × 5 mg – 2 × 25 mg	2 × 5 mg – 2 × 20 mg + 2 × 5 mg	365	730 × 5 mg – 730 × 5 mg + 730 × 20 mg

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					
Ropeginterferon alfa-2b, 250 µg	1 PEN	€ 2,778.32	€ 1.77	€ 155.39	€ 2,621.16
Appropriate comparator therapy					
Patient population a)					
Hydroxyurea, 500 mg	100 HC	€ 82.90	€ 1.77	€ 3.41	€ 77.72
Patient population b)					
Ruxolitinib, 5 mg	56 TAB	€ 2,005.48	€ 1.77	€ 111.26	€ 1,892.45
Ruxolitinib, 20 mg	56 TAB	€ 3,953.60	€ 1.77	€ 222.51	€ 3,729.32
PEN = prefabricated pens, HC = hard capsules, TAB = tablets					

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

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.

Other services covered by SHI funds: not applicable

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 26 September 2017.

On 28 August 2019, the pharmaceutical company submitted a dossier for the benefit assessment of ropeginterferon alfa-2b to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 29 August 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 ropeginterferon alfa-2b.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 December 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 16 December 2019. The deadline for submitting written statements was 6 January 2020.

The oral hearing was held on 28 January 2020.

On 27 February 2020, the IQWiG submitted a new version of the IQWiG dossier evaluation to the G-BA. Version 1.1 of 27 February 2020 replaces version 1.0 of the dossier evaluation of 12 December 2019. The evaluation result was not affected by the changes in version 1.1 compared with version 1.0.

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 25 February 2020, and the proposed resolution was approved.

At its session on 5 March 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	26 September 2017	Determination of the appropriate comparator therapy
Working group Section 35a	22 January 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	28 January 2020	Conduct of the oral hearing
Working group Section 35a	5 February 2020 19 February 2020	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	25 February 2020	Concluding discussion of the draft resolution
Plenum	5 March 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 5 March 2020

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

Prof. Hecken