Gemeinsamer Bundesausschuss

Ropeginterferon alfa-2b

Resolution of: 5 March 2020 valid until: unlimited
Entry into force on: 5 March 2020
Federal Gazette, BAnz AT 04 06 2020 B3

Resolution of: 16 July 2020
Entry into force on: 16 July 2020
Federal Gazette, BAnz AT 21 August 2020 B3

Therapeutic indication (according to the marketing authorisation of 15 February 2019):

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

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

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

Appropriate comparator therapy:

Hydroxyurea

Extent and probability of the additional benefit of ropeginterferon alfa-2b compared with hydroxyurea:

An additional benefit is not proven.

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

Appropriate comparator therapy:

Ruxolitinib

Extent and probability of additional benefit of ropeginterferon alfa-2b compared with the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

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

Open phase III study PROUD-PV: Ropeginterferon alfa-2b vs hydroxyurea

Mortality

Endpoint	**Ropeginterferon alfa-2b**		**Hydroxyurea**		Intervention vs control
	N	Patients with event n *(%)*	N	Patients with event n *(%)*	Effect estimator[a] [95% CI] p value[b] Absolute difference (AD)[c]
Overall survival					
	127	1 *(0.8)*	127	0 *(0)*	- 0.408

Morbidity

Endpoint	**Ropeginterferon alfa-2b**		**Hydroxyurea**		Intervention vs control
	N	Patients with event n *(%)*	N	Patients with event n *(%)*	Relative risk [95% CI] p value[b]
Haematological response[d]					
	124	56 *(45.2)*	127	70 *(55.1)*	0.82 [0.64; 1.05]

Endpoint	**Ropeginterferon alfa-2b**			**Hydroxyurea**			Intervention vs control
	N	Patients with event n *(%)*	Mean number of events per patient per visit[j] MV [min; max]	N	Patients with event n *(%)*	Mean number of events per patient per visit[j] MV [min; max]	Relative risk[i] [95% CI]
Phlebotomies[e]							
Total[f]	127	94 *(74.0)*	0.13 [0; 3]	127	81 *(63.8)*	0.09 [0; 2]	1.16 [0.98; 1.37]
Titration phase[g]	127	62 *(48.8)*	0.17 [0; 2]	126	68 *(54.0)*	0.21 [0; 2]	0.90 [0.71; 1.15]
Maintenance phase[h]	123	74 *(60.2)*	0.12 [0; 3]	121	47 *(38.8)*	0.05 [0; 2]	1.55 [1.19; 2.02]

[1] Data from the dossier evaluation of the IQWiG (A19-72) unless otherwise indicated.

Endpoint	Ropeginterferon alfa-2b			Hydroxyurea			Intervention vs control
	N[l]	Median baseline values [Q1; Q3]	Median change to end of study[n] [Q1; Q3]	N[l]	Median baseline values [Q1; Q3]	Median change to end of study[n] [Q1; Q3]	Median differences [95% CI] p value[m]
EQ-5D VAS[k]							
	105	80.0 [70.0; 90.0]	0.0 [-4.0; 7.0]	109	84.5 [70.0; 90.0]	0.0 [-5.0; 7.0]	0.0 [-2.0; 3.0] 0.733

Health-related quality of life

Was not collected.

Side effects

Endpoint	Ropeginterferon alfa-2b		Hydroxyurea		Intervention vs control
	N	Patients with event n *(%)*	N	Patients with event n *(%)*	Relative risk [95% CI] p value[b]
Total adverse events (AE) (presented additionally)					
	127	104 (81.9)	127	111 (87.4)	-
Serious adverse events (SAEs)					
	127	14 (11.0)	127	11 (8.7)	1.27 [0.60; 2.70] 0.561
Severe adverse events (CTCAE grade ≥ 3)					
	127	21 (16.5)	127	26 (20.5)	0.81 [0.48; 1.36] 0.532
Discontinuation due to AEs					
	127	7 (5.5)	127	2 (1.6)	3.5 [0.74; 16.5] 0.098
Specific adverse events (SOC, *PT*)					
Gastrointestinal disorders (SOC)					
	127	23 (18.1)	127	42 (33.1)	0.55 [0.35; 0.85] 0.007
Nausea (PT)	127	3 (2.4)	127	15 (11.8)	0.20 [0.06; 0.67] 0.003
Endpoint	**Ropeginterferon alfa-2b**		**Hydroxyurea**		Intervention vs

					control
	N	Patients with event n *(%)*	N	Patients with event n *(%)*	Relative risk [95% CI] p value[b]
Influenza (PT)					
	127	2 (1.6)	127	10 (7.9)	0.20 [0.04; 0.89] 0.020

a) No representation of effect estimation and confidence interval because not informative.
b) Relative risk and confidence interval: asymptotic, p value: unconditional exact test, CSZ method as per Andrés *et al.* If there were no events in one study arm, a correction factor of 0.5 was used to calculate effect and confidence interval in both study arms.
c) Absolute difference (AD) given only in the case of a statistically significant difference; own calculation.
d) Operationalised by means of haematocrit < 45% and at least 3 months since last phlebotomy. Patients who terminated the study were rated as non-responders (> 10%).
e) Phlebotomies due to a haematocrit > 45 %
f) Without phlebotomies on day 1
g) Weeks 1–12
h) Weeks 13–52
i) Relative risk and confidence interval: asymptotic
j) Consultations took place every 2 weeks. The event rates presented occurred in the period between two consultations.
k) A positive change over the course of the study indicates an improvement; a positive median difference indicates an advantage for the intervention.
l) Number of patients who were taken into account in the evaluation for the calculation of the estimation of the effect; the values at the start of study can be based on other patient figures.
m) Effect and CI: Hodges-Lehmann estimator; p value: Wilcoxon rank-sum test
n) Analysis without replacing missing value

Acronyms used:
AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EQ-5D = European Quality of Life – 5 Dimensions; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; max. = maximum; min. = minimum; MV = mean value; PT = Preferred Term; Q1 = 1st quartile; Q3 = 3rd quartile; SOC = System Organ Class; VAS = visual analogue scale; vs = versus.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No difference relevant for the benefit assessment.
Morbidity	↔	No differences relevant for the benefit assessment.
Health-related quality of life	∅	No data available.
Side effects	↔	No differences relevant for the benefit assessment.

Explanations:
↑, ↓: statistically significant and relevant positive or negative effect with high or unclear risk of bias
↑↑, ↓↓: statistically significant and relevant positive or negative effect with low risk of bias
↔: no relevant difference
∅: no data available
n.a.: not assessable

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

There is no data that would allow for the assessment of the additional benefit.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.
Explanations: ↑, ↓: statistically significant and relevant positive or negative effect with high or unclear risk of bias ↑↑, ↓↓: statistically significant and relevant positive or negative effect with low risk of bias ↔: no relevant difference ∅: no data available n.a.: not assessable		

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

approx. 1,560–16,440 patients

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

approx. 300–3,360 patients

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.

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ropeginterferon alfa-2b	€ 34,337.20–136,824.55
Appropriate comparator therapy:	
Hydroxyurea	€ 283.68–567.36

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 February 2020

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

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ropeginterferon alfa-2b	€ 34,337.20–136,824.55
Appropriate comparator therapy:	
Ruxolitinib	€ 24,669.44–73,283.79

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 February 2020

Costs for additionally required SHI services: not applicable