Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
/Lusutrombopag (Thrombocytopenia with chronic liver disease)

of 19 May 2022

At its session on 19 May 2022, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient Lusutrombopag as follows:

Lusutrombopag

Resolution of: 19 May 2022
Entry into force on: 19 May 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 18 February 2019):

Mulpleo is indicated for the treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures.

Therapeutic indication of the resolution (resolution of 19 May 2022):

See therapeutic indication according to marketing authorisation.

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

Adults with severe thrombocytopenia due to chronic liver disease who are scheduled to undergo invasive procedures

Appropriate comparator therapy:

Monitoring wait-and-see approach

Extent and probability of the additional benefit of Lusutrombopag compared to a monitoring wait-and-see approach:

An additional benefit is not proven.

Study results according to endpoints:[1]

Adults with severe thrombocytopenia due to chronic liver disease who are scheduled to undergo invasive procedures

Summary of results for relevant clinical endpoints

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

- Randomised, double-blind phase III study L-PLUS 2: lusutrombopag vs placebo
- Randomised, double-blind phase III study L-PLUS 1: lusutrombopag vs placebo
- Randomised, double-blind phase IIb study M0626: lusutrombopag vs placebo

Mortality

Endpoint	Lusutrombopag		Placebo		Lusutrombopag vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value
Overall survival					
L-PLUS 2	107	3 (2.8)	107	0 (0)	7.00 [0.37; 133.90] 0.095[a]
L-PLUS 1	48	0 (0)	48	0 (0)	-
M0626	16	0 (0)	15	0 (0)	-
Meta-analysis					-[b]

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A21-157) unless otherwise indicated.

Morbidity

Endpoint	Lusutrombopag		Placebo		Lusutrombopag vs Placebo
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value
Patients without transfusion[c]					
L-PLUS 2	108	68 (63.0)	107	31 (29.0)	2.20 [1.60; 3.04] < 0.001
L-PLUS 1	48	38 (79.2)	48	6 (12.5)	6.16 [2.92; 13.00] < 0.001
M0626	16	13 (81.3)	15	3 (20.0)	4.08 [1.25; 13.34] 0.001
Meta-analysis	Heterogeneity: p = 0.035; I^2 = 70.2%				-[d]
Bleeding WHO grade ≥ 2[e]					
L-PLUS 2	107	1 (0.9)	107	1 (0.9)	1.00 [0.06; 15.78] > 0.999[a]
L-PLUS 1		n.d.		n.d.	-
M0626		n.d.		n.d.	-
Meta-analysis					-[f]

Health-related quality of life

Was not collected in the studies L-PLUS 1, L-PLUS 2 and M0626.

Side effects

Endpoint	Lusutrombopag		Placebo		Lusutrombopag vs Placebo
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value
Adverse events (AEs; presented additionally)					
L-PLUS 2	107	51 (47.7)	107	52 (48.6)	-
L-PLUS 1	48	45 (93.8)	48	48 (100)	-
M0626	16	16 (100)	15	15 (100)	-

Endpoint	Lusutrombopag		Placebo		Lusutrombopag vs Placebo
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value
Serious adverse events (SAE)					
L-PLUS 2	107	7 (6.5)	107	7 (6.5)	1.02 [0.37; 2.80] 0.971[g]
L-PLUS 1	48	1 (2.1)	48	4 (8.3)	0.48 [0.11; 2.05] 0.195[g]
M0626	16	1 (6.3)	15	1 (6.7)	0.76 [0.11; 5.42] 0.819[g]
Meta-analysis					0.79 [0.30; 2.13] 0.419[h]
Therapy discontinuation due to adverse events					
L-PLUS 2	107	0 (0)	107	1 (0.9)	0.33 [0.01; 8.09] 0.529[a]
L-PLUS 1	48	0 (0)	48	0 (0)	-
M0626	16	0 (0)	15	0 (0)	-
Meta-analysis					-[b]
Thromboembolic events (SMQ[i], AEs)					
L-PLUS 2	107	2 (1.9)	107	2 (1.9)	1.02 [0.15; 6.99] 0.988[g]
L-PLUS 1	48	1 (2.1)	48	1 (2.1)	0.91 [0.10; 8.05] 0.950[g]
M0626	16	0 (0)	15	1 (6.7)	0.25 [0.01; 4.23] 0.221[g]
Meta-analysis					0.75 [0.15; 3.79] 0.530[h]

a. IQWiG calculation, unconditional exact test (CSZ method)
b. A meta-analysis was not performed because no event occurred in 2 of 3 studies.
c. The primary endpoint of the L-PLUS 2 study was the percentage of patients who did not require platelet transfusions before the invasive procedure nor emergency procedures due to bleeding after randomisation and up to 7 days after a scheduled procedure. The primary endpoint of the L-PLUS 1 and M0626 studies was the percentage of study participants who did not receive a platelet transfusion before the invasive procedure. Based on the results of the endpoint "patients without transfusion", no additional benefit is derived.
d. Due to heterogeneity, there is no separate calculation according to a random effects model. A qualitative evidence synthesis of the three statistically significant results shows clearly correlated effects.
e. In Module 4 A, the results for severe bleeding (SAE) are available for all 3 studies. In total, 1 patient in each of the studies L-PLUS 1 and M0626 experienced such events. In addition, 1 patient in study L-PLUS 2 and 2 patients in study L-PLUS 1 each received emergency therapy for the treatment of acute bleeding during the entire duration of the study.

f. A meta-analysis was not performed because in 2 of 3 studies the events were not according to WHO severity classification.

g. Calculation according to the pharmaceutical company: Effect and CI: CMH method, stratified for M0626 by platelet count and Child-Pugh classification, for L-PLUS 1 and L-PLUS 2 by platelet count and invasive procedure; null cell correction of 0.5, if applicable; p-value: for L-PLUS 1 and M0626 studies using the CMH test, for L-PLUS 2 study using the Wald test; no data available, whether p-values for RR or other effect measure were determined

h. Meta-analysis by random effects model using the method of Knapp and Hartung; IQWiG calculation from the effect estimates reported by the pharmaceutical company, calculated under stratification.

i. Summarised from the following SMQs: "Embolism and thrombosis events, arterial", "Embolism and thrombosis events, without vessel specification and mixed arterial / venous" and "Embolism and thrombosis events, venous"

Abbreviations used:
CMH = Cochran-Mantel-Haenszel; n.d. = no data available; CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients evaluated; n = number of patients with (at least one) event; RR = relative risk; SMQ: standardised MedDRA query; SAE = serious adverse event; AE = adverse event; vs = versus; WHO = World Health Organization

2. Number of patients or demarcation of patient groups eligible for treatment

Adults with severe thrombocytopenia due to chronic liver disease who are scheduled to undergo invasive procedures

approx. 1,790 – 24,130 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 Mulpleo (active ingredient: lusutrombopag) at the following publicly accessible link (last access: 12 May 2022):

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

4. Treatment costs

Annual treatment costs:

Adults with severe thrombocytopenia due to chronic liver disease who are scheduled to undergo invasive procedures

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Lusutrombopag[2]	€ 1,442.69 - € 4,328.07
Appropriate comparator therapy:	
Monitoring wait-and-see approach	Different from patient to patient[3]

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 May 2022)

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 19 May 2022.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 19 May 2022

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

Prof. Hecken

[2] Platelet transfusions may be indicated in addition to lusutrombopag.
[3] Platelet transfusions may be indicated patient-individual as part of the appropriate comparator therapy.