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) and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Sotatercept (pulmonary arterial hypertension)

of 6 March 2025

At its session on 6 March 2025, 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 Sotatercept as follows:

Sotatercept

Resolution of: 6 March 2025
Entry into force on: 6 March 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 22 August 2024):

Winrevair, in combination with other pulmonary arterial hypertension (PAH) therapies, is indicated for the treatment of PAH in adult patients with WHO Functional Class (FC) II to III, to improve exercise capacity.

Therapeutic indication of the resolution (resolution of 6 March 2025):

See therapeutic indication according to marketing authorisation.

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

Adults with pulmonary arterial hypertension (PAH) of WHO Functional Class (WHO FC) II to III

Appropriate comparator therapy for sotatercept in combination with other PAH therapies:

Individualised therapy with selection of:

- endothelin receptor antagonists (ambrisentan, bosentan, macitentan)
- phosphodiesterase-type-5 inhibitors (sildenafil, tadalafil)
- prostacyclin analogues (iloprost, epoprostenol, treprostinil)
- selective prostacyclin receptor agonists (selexipag) and
- stimulator of soluble guanylate cyclase (riociguat)

Extent and probability of the additional benefit of sotatercept in combination with other PAH therapies compared to the appropriate comparator therapy:

Hint for a minor additional benefit

Study results according to endpoints:[1]

Adults with pulmonary arterial hypertension (PAH) of WHO Functional Class (WHO FC) II to III

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	↑	Advantages for the endpoints of walking ability and cardiovascular symptomatology. Advantage for the endpoint of health status for subjects in WHO functional class II.
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↔	No relevant differences for the benefit assessment. In detail, disadvantages in the specific adverse events of eye disorders and nosebleeds.
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 ∅: No data available. n.a.: not assessable		

STELLAR study: RCT over 24 weeks; sotatercept versus placebo (in each case in addition to a PAH background therapy)

[1] Data from the dossier assessment of the IQWiG (A24-96) and from the addendum (A25-14), unless otherwise indicated.

Mortality

Endpoint	Sotatercept + PAH background therapy		Placebo + PAH background therapy		Sotatercept + PAH background therapy vs placebo + PAH background therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Overall mortality[b]	163	2 (1.2)	160	7 (4.4)	0.28 [0.06; 1.33]; 0.097[c]

Morbidity

Endpoint	Sotatercept + PAH background therapy		Placebo + PAH background therapy		Sotatercept + PAH background therapy vs placebo + PAH background therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Symptomatology (PAH-SYMPACT – improvement at week 24[d])					
Cardiopulmonary symptoms	115	47 (40.9)	117	35 (29.9)	1.35 [0.95; 1.93]; 0.095
Cardiovascular symptoms	115	49 (42.6)	117	34 (29.1)	1.48 [1.04; 2.11]; 0.030
Dyspnoea					
Borg CR10 scale – improvement at week 24[e]	160	38 (23.8)	159	37 (23.3)	1.02 [0.69; 1.51]; 0.918
Health status					
EQ-5D VAS – improvement at week 24[f]	124	29 (23.4)	126	20 (15.9)	1.49 [0.89; 2.49]; 0.131
Subgroup analysis by disease severity					
WHO-FC II	65	16 (24.6)	65	5 (7.7)	3.20 [1.24; 8.26][g]; 0.016
WHO-FC III	59	13 (22.0)	61	15 (24.6)	0.91 [0.48; 1.73][g]; 0.764
Total					Interaction: 0.026[h]

Endpoint	Sotatercept + PAH background therapy			Placebo + PAH background therapy			Sotatercept + PAH background therapy vs placebo + PAH background therapy
	N[i]	Values at the start of the study [m] Median (Q1; Q3)	Median change at week 24 [m] MV (min; max)[j]	N[i]	Values at the start of the study [m] Median (Q1; Q3)	Median change at week 24 [m] MV (min; max)[j]	Hodges-Lehmann location shift [95% CI]; p value
Walking ability							
6-minute walk test (6MWT) at week 24	163	417.0 (348.0; 464.5)	34.3 [33.0; 35.5]	160	427.1 (365.0; 465.0)	1.0 [-1.0; 3.5]	40.40 [27.28; 53.53]; < 0.001
Subgroup analysis by disease severity							
WHO-FC II	79	n.d.	n.d.	78	n.d.	n.d.	21.6 [6.67; 36.60]; n.d.
WHO-FC III	84	n.d.	n.d.	82	n.d.	n.d.	60.9 [40.46; 81.35]; n.d.
Total							Interaction: 0.002[k]

Health-related quality of life

Endpoint	Sotatercept + PAH background therapy		Placebo + PAH background therapy		Sotatercept + PAH background therapy vs placebo + PAH background therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
PAH-SYMPACT – improvement at week 24[e]					
Physical impairments	117	39 (33.3)	123	31 (25.2)	1.31 [0.87; 1.96]; 0.193
Cognitive/ emotional impairment	117	30 (25.6)	123	30 (24.4)	1.04 [0.67; 1.60]; 0.866

Side effects

Endpoint	Sotatercept + PAH background therapy		Placebo + PAH background therapy		Sotatercept + PAH background therapy vs placebo + PAH background therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Total adverse events (AEs) *(presented additionally)*	163	151 (92.6)	160	149 (93.1)	–
Serious adverse events (SAE)	163	40 (24.5)	160	47 (29.4)	0.84 [0.58; 1.20] 0.529[c]
Therapy discontinuation due to adverse events	163	6 (3.7)	160	11 (6.7)	0.54 [0.20; 1.41]; 0.246[c]
Eye disorders (SOC, AEs)[l]	163	21 (12.9)	160	7 (4.4)	2.94 [1.29; 6.73]; 0.007[c]
Nosebleeds (PT, AEs)	163	36 (22.1)	160	3 (1.9)	11.78 [3.70; 37.48]; < 0.001[c]

a. Unless otherwise stated: Mantel-Haenszel estimate, stratified by WHO functional class (class II vs III) and PAH background therapy (mono/double vs triple therapy); p value of the Wald test
b. The results on overall mortality are based on the data on fatal AEs over the entire course of the study.
c. Own calculation of RR, 95% CI (asymptotic) and p value (unconditional exact test, CSZ method according to *Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://doi.org/10.1016/0167-9473(94)90148-1*)
d. A decrease by ≥ 0.6 points compared to the start of the study is considered a clinically relevant improvement (scale range: 0 to 4).
e. A decrease by ≥ 1.5 points compared to the start of the study is considered a clinically relevant improvement (scale range: 0 to 10).
f. An increase by ≥ 15 points compared to the start of the study is considered a clinically relevant improvement (scale range: 0 to 100).
g. RR: Mantel-Haenszel estimate, stratified by WHO functional class (class II vs III) and PAH background therapy (mono/ double vs triple therapy); p value: Wald test
h. p value of the likelihood ratio test, based on a linear model (according to the pharmaceutical company) with the covariates of treatment and subgroup as well as the interaction between treatment and subgroup, which is stratified according to WHO functional class (class II vs III) and PAH background therapy (mono/double vs triple therapy)
i. Number of patients who were taken into account in the effect estimate; the values at the start of the study (and at week 24) can be based on other patient numbers.
j. Mean, minimum and maximum of the median changes at week 24 resulting from the imputation data records generated by multiple imputation
k. p value of the Cochran's Q-test
l. Frequent events occurred in the intervention vs control arm were blurred vision (4 vs 0) and cataract (4 vs 0)

Abbreviations used: 6MWT: 6-minute walk test; CR10: 10 points category ratio scale; n.d.: no data available; CI: confidence interval; m: metre; max: maximum; min: minimum; MV: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; PAH: pulmonary arterial hypertension; PT: preferred term; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomised controlled trial; RR: relative risk; SOC: system organ class; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale; WHO: World Health Organization; WHO-FC: WHO Functional Class

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

Adults with pulmonary arterial hypertension (PAH) of WHO Functional Class (WHO FC) II to III

Approx. 580 – 7,850 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 Winrevair (active ingredient: sotatercept) at the following publicly accessible link (last access: 21 January 2025):

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

Treatment with sotatercept should only be initiated and monitored by doctors experienced in the therapy of pulmonary arterial hypertension.

4. Treatment costs

Annual treatment costs:

Adults with pulmonary arterial hypertension (PAH) of WHO Functional Class (WHO FC) II to III

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Sotatercept	€ 172,387.02
Sotatercept in combination with an endothelin receptor antagonist (ERA)	
Endothelin receptor antagonists (ERA)	€ 16,818.84 – € 19,118.34
Total:	**€ 189,205.86 – € 191,505.36**
Sotatercept in combination with a phosphodiesterase type 5 inhibitor (PDE5i)	
Phosphodiesterase type 5 inhibitors	€ 2,066.51 – € 2,395.86
Total:	**€ 174,453.53 – € 174,782.88**
Sotatercept in combination with an endothelin receptor antagonist (ERA) and a phosphodiesterase type 5 inhibitor (PDE5i)	
Endothelin receptor antagonists (ERA)	€ 16,818.84 – € 19,118.34
Phosphodiesterase type 5 inhibitors	€ 2,066.51 – € 2,395.86
Total:	**€ 191,272.37 – € 193,901.22**
Sotatercept in combination with an endothelin receptor antagonist (ERA), a phosphodiesterase type 5 inhibitor (PDE5i) and prostacyclin analogues	

Designation of the therapy	Annual treatment costs/ patient
Endothelin receptor antagonists (ERA)	€ 16,818.84 – € 19,118.34
Phosphodiesterase type 5 inhibitors	€ 2,066.51 – € 2,395.86
Iloprost[2] Additionally required SHI services (first year)	€ 42,076.81 – € 63,115.21 € 3,500
Total: Additionally required SHI services (first year)	**€ 233,349.18 – € 257,016.43** € 3,500
Sotatercept in combination with an endothelin receptor antagonist (ERA), a phosphodiesterase type 5 inhibitor (PDE5i) and a selective prostacyclin receptor agonist	
Endothelin receptor antagonists (ERA)	€ 16,818.84 – € 19,118.34
Phosphodiesterase type 5 inhibitors	€ 2,066.51 – € 2,395.86
Selexipag	€ 32,342.29 - € 38,102.11
Total:	**€ 223,614.66 – € 232,003.33**
Sotatercept in combination with an endothelin receptor antagonist (ERA) and stimulators of soluble guanylate cyclase	
Endothelin receptor antagonists (ERA)	€ 16,818.84 – € 19,118.34
Riociguat	€ 18,989.39 – € 19,509.77
Total:	**€ 208,195.25 – € 211,015.13**
Appropriate comparator therapy:	
Active ingredients of the appropriate comparator therapy, if applicable as monotherapy	
Endothelin receptor antagonists	
Ambrisentan	€ 16,818.84 – € 17,530.83
Bosentan	€ 17,530.83
Macitentan	€ 19,118.34
Phosphodiesterase type 5 inhibitors	
Sildenafil	€ 2,395.86
Tadalafil	€ 2,066.51
Prostacyclin analogues	
Iloprost Additionally required SHI services (first year)	€ 42,076.81 – € 63,115.21 € 3,500

[2] Epoprostenol and treprostinil doses are different from patient to patient; the annual treatment costs of these active ingredients cannot be quantified in general terms. For this reason, only the costs of the active ingredient iloprost are taken into account as a representative of the prostacyclin analogues when calculating the total costs of the combination therapy.

Designation of the therapy	Annual treatment costs/ patient
Epoprostenol	Different from patient to patient
Treprostinil	Different from patient to patient
Selective prostacyclin receptor agonists	
Selexipag	€ 32,342.29 – € 38,102.11
Stimulators of soluble guanylate cyclase	
Riociguat	€ 18,989.39 – € 19,509.77
Combination therapies	
Combination of an endothelin receptor antagonist (ERA) and a phosphodiesterase type 5 inhibitor (PDE5i)	
Endothelin receptor antagonists (ERA)	€ 16,818.84 – € 19,118.34
Phosphodiesterase type 5 inhibitors	€ 2,066.51 – € 2,395.86
Total:	**€ 18,885.35 – € 21,514.20**
Combination of an endothelin receptor antagonist (ERA), a phosphodiesterase type 5 inhibitor (PDE5i) with prostacyclin analogues	
Endothelin receptor antagonists (ERA)	€ 16,818.84 – € 19,118.34
Phosphodiesterase type 5 inhibitors	€ 2,066.51 – € 2,395.86
Iloprost[2] Additionally required SHI services (first year)	€ 42,076.81 – € 63,115.21 € 3,500
Total: Additionally required SHI services (first year)	**€ 60,962.16 – € 84,629.41** € 3,500
Combination of an endothelin receptor antagonist (ERA), a phosphodiesterase type 5 inhibitor (PDE5i) and a selective prostacyclin receptor agonist	
Endothelin receptor antagonists (ERA)	€ 16,818.84 – € 19,118.34
Phosphodiesterase type 5 inhibitors	€ 2,066.51 – € 2,395.86
Selexipag	€ 32,342.29 - € 38,102.11
Total:	**€ 51,227.64 – € 59,616.31**
Combination of an endothelin receptor antagonist (ERA) and stimulators of soluble guanylate cyclase	
Endothelin receptor antagonists (ERA)	€ 16,818.84 – € 19,118.34
Riociguat	€ 18,989.39 – € 19,509.77
Total:	**€ 35,808.23 – € 38,628.11**

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 February 2025)

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Adults with pulmonary arterial hypertension (PAH) of WHO Functional Class (WHO FC) II to III

The following medicinal products with new active ingredients that can be used in a combination therapy with sotatercept in the therapeutic indication of the resolution on the basis of the marketing authorisation under Medicinal Products Act are named (active ingredients and invented names) in accordance with Section 35a, paragraph 3, sentence 4 SGB V:

- Selexipag (Uptravi)

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

II. In Annex XIIa of the Pharmaceuticals Directive, the following information shall be added in alphabetical order:

"Active ingredient of the assessed medicinal product

Sotatercept

Resolution according to Section 35a paragraph 3 SGB V from

6 March 2025

Therapeutic indication of the resolution

Winrevair, in combination with other pulmonary arterial hypertension (PAH) therapies, is indicated for the treatment of PAH in adult patients with WHO Functional Class (FC) II to III, to improve exercise capacity.

Patient group a

Adults with pulmonary arterial hypertension (PAH) of WHO Functional Class (WHO FC) II to III

Naming of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V (active ingredients and invented names[2])

Selexipag (Uptravi)

Period of validity of the designation (since... or from... to)

Since 6 March 2025

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

III. The resolution will enter into force on the day of its publication on the website of the G-BA on 6 March 2025.

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

Berlin, 6 March 2025

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

Prof. Hecken