Gemeinsamer Bundesausschuss

# Justification

of the Resolution of the Federal Joint Committee (G-BA) 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

**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 all 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 the 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 is part of the Pharmaceuticals Directive.

## 2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient sotatercept on 15 September 2024 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. 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 13 September 2024.

The active ingredient sotatercept (Winrevair) was approved by the European Commission (EC) on 22 August 2024 as a medicinal product for the treatment of rare diseases (orphan drugs) under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 for the treatment of pulmonary arterial hypertension (PAH). The

pharmaceutical company has irrevocably notified the Federal Joint Committee that, despite the orphan drug status for sotatercept, a benefit assessment is to be carried out with the submission of evidence in accordance with Section 35a, paragraph 1, sentence 3, numbers 2 and 3 SGB V.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 16 December 2024 on the G-BA website (www.g-ba.de), 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 sotatercept 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, as well of the addendum drawn up by the IQWiG on the benefit assessment. 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 sotatercept.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to 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 Sotatercept (Winrevair) in accordance with the product information

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 the approved therapeutic indication

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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)

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with 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 G-BA 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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

On 1. In addition to the activin receptor signalling pathway inhibitor sotatercept to be assessed, active ingredients from the following product classes are approved in the therapeutic indication:

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

On 2. As a non-medicinal treatment option, a lung or heart-lung transplant in this therapeutic indication can generally be covered by statutory health insurance.

Furthermore, physiotherapeutic measures within the meaning of the Remedies Directive (physical therapy, e.g. physiotherapy, exercise therapy, respiratory therapy) are generally considered as non-medicinal therapy options for pulmonary arterial hypertension.

On 3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.

The following resolutions from the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the therapeutic indication of PAH of the WHO-FC II to III are available:

- selexipag (resolution of 15 December 2016),
- macitentan (resolution of 6 April 2017),
- riociguat (resolution of 3 September 2020; resolution of 21 December 2023).

In these resolutions on the benefit assessment, no additional benefit of the medicinal products assessed in each case was identified.

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present therapeutic indication. The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

Based on the available evidence, no standard therapy can be defined for the intended treatment setting. Instead, patients should be treated on a patient-individual basis, depending on their previous therapies and respective health status. Various medicinal treatment options are approved for the treatment of PAH. The individual treatment decision is made in particular taking into account previous therapies and

the patient's health status. If indicated, the treatment options may also include dose optimisation of the existing therapy, a change of the active ingredient or even combination therapies of the various active ingredients.

The recommendations of the guideline[2] state that treatment with calcium antagonists alone is indicated if the patients have a positive vasoreactivity test. However, targeted PAH therapy (e.g. with endothelin receptor antagonists, phosphodiesterase-type-5 inhibitors) is recommended for subjects with a negative vasoreactivity test and for vasoreactive subjects who no longer respond to treatment with calcium antagonists alone. It is therefore assumed that patients in the therapeutic indication under assessment are ineligible for treatment with calcium channel antagonists alone.

The prostacyclin analogues treprostinil and epoprostenol to be parenterally administered are approved for the treatment of PAH of WHO/NYHA classes III or III-IV. The clinical experts emphasised the importance of these active ingredients in healthcare as part of the written statement procedure. According to the aforementioned guideline, parenteral prostacyclin analogues can already be used in treatment-naïve PAH patients of WHO functional class III if rapid disease progression is expected. The active ingredients treprostinil and epoprostenol are therefore also considered appropriate in the context of individualised therapy.

Furthermore, there are recommendations for non-medicinal physiotherapeutic measures to improve symptomatology and physical performance. Physiotherapeutic interventions can be indicated both within the meaning of the Remedies Directive (physical therapy, e.g. physiotherapy, exercise therapy, respiratory therapy) and in the sense of targeted training therapy to improve performance (e.g. after surgical treatment). Only subjects without significant limitations in their ability to exercise are eligible for targeted training therapy to improve performance, while physiotherapeutic interventions within the meaning of the Remedies Directive (physical therapy, e.g. physiotherapy, exercise treatment, respiratory therapy) may be suitable for all patients.

Furthermore, it is assumed that patients in the therapeutic indication are ineligible for lung transplantation or heart-lung transplantation.

In the overall assessment, the G-BA therefore considers it appropriate in the present therapeutic indication to determine the appropriate comparator therapy for sotatercept in combination with other PAH therapies to be an individualised therapy by selecting endothelin receptor antagonists (ambrisentan, bosentan, macitentan), phosphodiesterase type 5 inhibitors (sildenafil, tadalafil), prostacyclin analogues (iloprost, epoprostenol, treprostinil), selective prostacyclin receptor agonists (selexipag) and stimulators of soluble guanylate cyclase (riociguat).

Individualised therapy is based on the assumption that the treating physicians can choose from the various therapy options. The treatment decision is made individually for each subject in this therapeutic indication, in particular taking into account the

[2] Therapy for Pulmonary Arterial Hypertension in Adults, Update of the CHEST Guideline and Expert Panel Report, CHEST 2019; 155(3):565-586; https://doi.org/10.1016/j.chest.2018.11.030

previous therapies and the respective health status. The requirements in the respective product information are to be taken into account here.

Editorial note: The term "individualised therapy" is used instead of previously used terms such as "patient-individual therapy" or "therapy according to doctor's instructions". This harmonises the terms used in the European assessment procedures (EU-HTA).

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

*Change of the appropriate comparator therapy*

The adjustment of the appropriate comparator therapy takes account of the current significance of parenteral prostacyclin analogues in healthcare. These were not part of the appropriate comparator therapy until now.

According to the statements of the scientific-medical societies, the parenteral prostacylin analogues epoprostenol and treprostinil are now regularly used in clinical practice for the treatment of PAH patients of WHO functional class III. Therapy recommendations for these active ingredients can also be derived on the basis of the above-mentioned guideline.

For this reason, the G-BA considers it appropriate to include the active ingredients epoprostenol and treprostinil in the appropriate comparator therapy and thus to adapt it to the generally recognised state of medical knowledge.

### 2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of sotatercept in combination with other PAH therapies is assessed as follows:

For adults with pulmonary arterial hypertension of WHO functional class II to III, there is a hint for a minor additional benefit of sotatercept compared with the appropriate comparator therapy.

Justification:

For assessment of the additional benefit of sotatercept, the pharmaceutical company presented the results of a double-blind, randomised, controlled phase III study. A total of 323 patients aged 18 to 82 years with pulmonary arterial hypertension of WHO functional class II or III were enrolled in the STELLAR study. The study examined subjects with idiopathic PAH, hereditary PAH, drug/toxin-induced PAH, PAH associated with connective tissue disease and PAH associated with simple, congenital systemic-pulmonary shunts.

The study participants were randomised in a 1:1 ratio to the two study arms sotatercept (N = 163) and placebo (N = 160). In both study arms, the study medication was administered in

combination with PAH background therapy. This background therapy included mono- or combination therapies of endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, stimulators of soluble guanylate cyclase, prostacyclin analogues and/or selective prostacyclin receptor agonists. As part of the background therapy, around 40 per cent of patients in both treatment groups were treated with intravenous prostacyclin therapy.

The background therapy had to have been administered at a stable dose for at least 90 days prior to screening and should be continued stably during the study. For all PAH therapy options, the specific dose target for each study participant had to have already been reached at the time of enrolment in the study. Treatment with the study medication was discontinued if clinical deterioration that required emergency therapy with approved PAH treatment options or an increase in the prostacyclin infusion by at least 10% occurred in the course of the study. While dose adjustments of oral diuretics were possible during the study, the addition of a diuretic or switching from an oral to a parenteral diuretic was not permitted.

It was also possible to take concomitant medication for chronic concomitant diseases and to continue physiotherapy rehabilitation measures. It was not allowed to restart physiotherapeutic measures 90 days before the start of the study and during the study.

The design of the study comprised two consecutive treatment phases. The 24-week primary treatment phase was followed by a likewise blinded, long-term treatment phase of up to 72 weeks, with continuation of the initially assigned study medication. After completion of the controlled treatment phases or in the event of clinical deterioration, all study participants were able to receive treatment with sotatercept as part of the uncontrolled extension study SOTERIA.

The primary endpoint of the study was the improvement in the 6-minute walking distance at week 24. Furthermore, endpoints in the categories of morbidity, health-related quality of life and side effects were collected. Subgroup analyses were presented by age, sex and WHO functional class for all endpoints listed in the dossier with the exception of the endpoint of overall mortality. Interaction tests were not possible for the endpoint of overall mortality due to a sample size below the threshold of 10 events.

As part of the randomisation process, in addition to stratification according to WHO-FC at the start of the study (class II vs III), stratification was also carried out according to the type of PAH background therapy (mono/double therapy vs triple therapy).

Extent and probability of the additional benefit

Mortality

For the endpoint of overall mortality, there was no statistically significant difference between the treatment groups at the end of the STELLAR study.

Morbidity

Morbidity is presented in the present assessment on the basis of walking ability (6MWT), cardiopulmonary and cardiovascular symptomatology (PAH-SYMPACT), dyspnoea (Borg CR10 scale) and health status (EQ-5D VAS).

*Walking ability – using the 6-minute walk test (6MWT)*

Walking ability and physical resilience were assessed using the 6-minute walk test. At study week 24, there was a statistically significant advantage of sotatercept over the appropriate comparator therapy. The median difference at week 24 calculated as Hodges-Lehmann location shift was 40.4 metres.

For this endpoint, there was an effect modification due to the WHO functional class characteristic. For PAH patients of WHO functional class II, there was a statistically significant advantage of sotatercept over placebo in each case in combination with other PAH therapies. However, the lower limit of the 95% confidence interval was only 6.7 m. Against this background, it is not possible to estimate with sufficient certainty to what extent the effect is clinically relevant.

For subjects of WHO-functional class III, there was also a statistically significant advantage of sotatercept over the appropriate comparator therapy. This effect is considered clinically relevant as the lower limit of the 95% confidence interval here was 40.5 m.

The result of the total population of the STELLAR study is used for the benefit assessment. The extent of the improvement in the 6-minute walking distance is rated as low.

*Symptomatology – using Pulmonary Arterial Hypertension – Symptoms and Impact Questionnaire (PAH-SYMPACT) – Cardiopulmonary and cardiovascular symptoms*

The disease symptomatology was assessed using the Pulmonary Arterial Hypertension – Symptoms and Impact questionnaire at study week 24. For the endpoint of cardiopulmonary symptoms, there was no statistically significant difference between the treatment groups. In contrast, there was a statistically significant advantage of sotatercept compared to placebo, in each case in combination with other PAH therapies, for the endpoint of cardiovascular symptoms.

*Dyspnoea – using the Borg 10 Point Category Ratio Scale (Borg CR10 Scale)*

Dyspnoea was assessed using the CR10 scale according to Borg at week 24. For the endpoint, there was no statistically significant difference between the treatment groups.

*Health status – using the visual analogue scale of the EQ-5D questionnaire (EQ-5D VAS)*

The health status was assessed using the visual analogue scale of EQ-5D. At study week 24, there was no statistically significant difference between sotatercept and the appropriate comparator therapy in the total population for this endpoint.

However, an effect modification by the WHO functional class characteristic was observed for the endpoint of health status. For subjects with PAH of WHO functional class II, a statistically significant advantage of sotatercept over placebo in combination with other PAH therapies was observed. In contrast, there was no statistically significant difference between the treatment groups for PAH patients of the WHO functional class III.

Thus, there was an advantage of sotatercept over placebo, in each case in combination with other PAH therapies, for the endpoint of health status for subjects with PAH of WHO functional class II.

Quality of life

*Health-related quality of life – using PAH-SYMPACT – physical impairments and cognitive/ emotional impairments*

The endpoint of health-related quality of life was assessed using the PAH-SYMPACT domains of physical impairment and cognitive/ emotional impairment. In both domains, no statistically significant difference between sotatercept and the appropriate comparator therapy could be identified at week 24.

Side effects

*SAEs*

In the STELLAR study, there was no statistically significant difference between the treatment groups in the evaluation of the endpoint of SAEs.

*Therapy discontinuation due to AEs*

The results of the endpoint of therapy discontinuation due to AEs showed no statistically significant difference between sotatercept and placebo, in each case in combination with other PAH therapies.

*Specific AEs – eye disorders (AEs) and nosebleeds (AEs)*

In detail, there was a statistically significant difference between the treatment groups to the disadvantage of sotatercept for the endpoints of eye disorders (AEs) and nosebleeds (AEs).

Overall assessment

Evaluations of the double-blind, randomised, placebo-controlled phase III STELLAR study (in each case in addition to other PAH therapies) are available for the assessment of the additional benefit of sotatercept. In principle, the entire observation period up to the end of the study is used for the present benefit assessment. However, for the endpoints in the morbidity and health-related quality of life categories, evaluations are only available at week 24 due to a lack of surveys after week 24 or low return rates at later survey time points.

In the endpoint category of mortality, there was no statistically significant difference between the treatment groups at the end of the STELLAR study.

In the morbidity category, there was a statistically significant advantage of sotatercept over the appropriate comparator therapy at study week 24 for the endpoint of walking ability (assessed using 6MWT). The improvement by 40.4 metres achieved in the walking ability is classified as minor in magnitude.

In the endpoint of symptomatology, the PAH-SYMPACT domain of cardiovascular symptoms showed a statistically significant advantage of sotatercept compared to placebo, in each case in combination with other PAH therapies, which is also classified as minor in magnitude. There were no statistically significant differences between the treatment groups in the domain of cardiopulmonary symptoms or in the endpoint of dyspnoea which was measured using the CR10 scale according to Borg.

There were no statistically significant differences in the total population for the health status endpoint collected using the EQ-5D VAS. However, a statistically significant advantage of

sotatercept over the appropriate comparator therapy was shown for the subgroup of patients of functional class II.

In the category of health-related quality of life (assessed using the PAH-SYMPACT domains of physical impairment and cognitive/ emotional impairment), no statistically significant differences were identified for sotatercept compared to placebo, in each case in combination with other PAH therapies.

In the side effects category, statistically significant differences between the two treatment arms at the end of the study were observed neither for serious adverse events nor therapy discontinuation due to adverse events. In detail, there were statistically significant differences in the specific adverse events of eye disorders and nosebleeds to the disadvantage of sotatercept compared to placebo, in each case in combination with other PAH therapies.

In the overall assessment, there were thus statistically significant and clinically relevant advantages of sotatercept over the appropriate comparator therapy in the endpoint category of morbidity. There were no relevant differences for the benefit assessment for quality of life and side effects. Overall, the positive effects of sotatercept are classified as minor in magnitude.

As a result, the G-BA therefore identified a minor additional benefit of sotatercept in combination with other PAH therapies for the treatment of adults with pulmonary arterial hypertension of WHO functional class II to III.

Reliability of data (probability of additional benefit)

This assessment is based on the results of the STELLAR study – a randomised, double-blind, direct comparator phase III study.

In addition to the cross-endpoint risk of bias at study level, the risk of bias for the endpoints of walking ability and dyspnoea is also classified as low. Incomplete observations, potentially due to informative reasons, lead to a high risk of bias at the level of the endpoints of overall mortality, SAEs and the specific AEs of eye disorders and nosebleeds. Even taking into account the data subsequently submitted in the written statement procedure, it remains unclear, for example, how many study participants switched to the SOTERIA extension study at what point in time due to a clinical deterioration. The risk of bias of the patient-reported endpoints of symptomatology, health status and health-related quality of life is also considered to be high. The reasons for this lie in the high percentage of study participants who were not included in the evaluation of the results. For the endpoint of therapy discontinuation due to AEs, despite a low risk of bias due to unclear demarcation from the endpoint of therapy discontinuation for other reasons, the reliability of data is limited.

Uncertainties regarding the validity of the results for the total population also result from the described effect modification by the WHO functional class characteristic, which was shown for the endpoints of walking ability and health status.

There is also lack of clarity regarding the optimal setting of PAH background therapy at the start of the study. On the one hand, it is not known to what extent physiotherapeutic measures (e.g. physiotherapy, exercise treatment, respiratory therapy) were available to patients to a sufficient extent. Moreover, 4.9% of subjects in the intervention arm and 9.4% of participants in the comparator arm would have been eligible for additional medicinal

therapy at the start of the study. Furthermore, the use of PAH background therapies in accordance with the marketing authorisation could not be fully verified, as only limited information was available on the dosage used. Thus, there are uncertainties overall as to whether the individualised therapy was implemented appropriately for all study participants in the comparator arm.

In the overall assessment, the reliability of data of the results is classified in the "hint" category.

### 2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Winrevair with the active ingredient sotatercept. Sotatercept, in combination with other pulmonary arterial hypertension therapies, is approved for the treatment of pulmonary arterial hypertension in adults with WHO functional class II to III to improve exercise capacity.

The G-BA determined the appropriate comparator therapy to be an individualised therapy by selecting endothelin receptor antagonists (ambrisentan, bosentan, macitentan), phosphodiesterase type 5 inhibitors (sildenafil, tadalafil), prostacyclin analogues (iloprost, epoprostenol, treprostinil), selective prostacyclin receptor agonists (selexipag) and stimulators of soluble guanylate cyclase (riociguat).

The double-blind, randomised, placebo-controlled phase III study STELLAR (in each case in combination with other PAH therapies) was presented for the assessment of the additional benefit of sotatercept.

For the endpoint of overall mortality, there was no statistically significant difference between the treatment groups at the end of the STELLAR study.

In the morbidity category, there were advantages of sotatercept over the appropriate comparator therapy for the endpoints of walking ability and cardiovascular symptoms in the total population. However, there was an advantage of sotatercept only for subjects of WHO functional class II for the endpoint of health status. The evaluations of the endpoint of dyspnoea showed no statistically significant difference between the treatment groups.

In the endpoint categories of health-related quality of life and side effects, no relevant differences could be identified between the treatment groups for the benefit assessment. In detail, there were negative effects for the specific AEs of eye disorders and nosebleeds.

The advantages in the morbidity category are not offset by any relevant disadvantages of other endpoint categories for the benefit assessment. In the overall assessment, the additional benefit of sotatercept compared with the appropriate comparator therapy is classified as minor overall.

The significance of the evidence is classified in the hint category. In addition to a high risk of bias at the level of some endpoints, uncertainties also remain with regard to the appropriate implementation of the individualised concomitant therapy in the comparator arm and with regard to the effect modification shown.

In summary, a hint for a minor additional benefit of sotatercept over the appropriate comparator therapy was identified.

## 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 data is based on the patient numbers which are based on the information provided by the pharmaceutical company in the dossier, taking into account the adopted resolutions for riociguat (3 September 2020 and 16 October 2014) on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the therapeutic indication "Adult patients with pulmonary arterial hypertension (PAH) of WHO functional classes (FC) II to III".

The number of patients in the SHI target population is in a plausible order of magnitude, even if these figures are subject to uncertainties as no current data on prevalence was provided by the pharmaceutical company. As the overall prevalence of this disease in the population can be assumed to be stable, it can be assumed that the number of patients in the therapeutic indication has not changed fundamentally. The stated range is considered appropriate also for reasons of consistency with the previous resolutions.

## 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 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.

## 2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 February 2025).

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

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

The prostacyclin analogues epoprostenol and treprostinil are administered as a long-term continuous infusion via a central venous catheter. It is not possible to present the treatment costs due to the dosages that are different from patient to patient.

Treatment period:

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

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Treatment days/ patient/ year |
|---|---|---|---|---|
| Medicinal product to be assessed | | | | |
| Sotatercept in combination with other PAH therapies | | | | |
| Sotatercept | Continuously, every 21 days | 17.4 | 1 | 17.4 |
| Endothelin receptor antagonists | | | | |
| Ambrisentan | Continuously, 1 x daily | 365.0 | 1 | 365.0 |
| Bosentan | Continuously, 2 x daily | 365.0 | 1 | 365.0 |
| Macitentan | Continuously, 1 x daily | 365.0 | 1 | 365.0 |
| Phosphodiesterase type 5 inhibitors | | | | |
| Sildenafil | Continuously, 3 x daily | 365.0 | 1 | 365.0 |
| Tadalafil | Continuously, 1 x daily | 365.0 | 1 | 365.0 |
| Prostacyclin analogues | | | | |
| Iloprost | Continuously, 6 - 9 x daily | 365.0 | 1 | 365.0 |
| Epoprostenol | Different from patient to patient | | | |
| Treprostinil | Different from patient to patient | | | |
| Selective prostacyclin receptor agonists | | | | |
| Selexipag | Continuously, 2 x daily | 365.0 | 1 | 365.0 |
| Stimulator of soluble guanylate cyclase | | | | |
| Riociguat | Continuously, 3 x daily | 365.0 | 1 | 365.0 |

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Treatment days/ patient/ year |
|---|---|---|---|---|
| Appropriate comparator therapy | | | | |
| Endothelin receptor antagonists | | | | |
| Ambrisentan | Continuously, 1 x daily | 365.0 | 1 | 365.0 |
| Bosentan | Continuously, 2 x daily | 365.0 | 1 | 365.0 |
| Macitentan | Continuously, 1 x daily | 365.0 | 1 | 365.0 |
| Phosphodiesterase type 5 inhibitors | | | | |
| Sildenafil | Continuously, 3 x daily | 365.0 | 1 | 365.0 |
| Tadalafil | Continuously, 1 x daily | 365.0 | 1 | 365.0 |
| Prostacyclin analogues | | | | |
| Iloprost | Continuously, 6 - 9 x daily | 365.0 | 1 | 365.0 |
| Epoprostenol | Different from patient to patient | | | |
| Treprostinil | Different from patient to patient | | | |
| Selective prostacyclin receptor agonists | | | | |
| Selexipag | Continuously, 2 x daily | 365.0 | 1 | 365.0 |
| Stimulator of soluble guanylate cyclase | | | | |
| Riociguat | Continuously, 3 x daily | 365.0 | 1 | 365.0 |

Consumption:

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

For dosages depending on body weight (BW), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population"[3] were used as a basis (average body weight 18 years and older: 77.7 kg).

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

| Designation of the therapy | Dosage/ application | Dose/ patient/ treatment days | Consumption by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Sotatercept in combination with other PAH therapies | | | | | |
| Sotatercept | 0.7 mg/ kg BW = 54.39 mg at 77.7 kg BW | 54 mg | 1 x 60 mg | 17.4 | 17.4 x 60 mg |
| Endothelin receptor antagonists | | | | | |
| Ambrisentan | 5 mg – 10 mg | 5 mg – 10 mg | 1 x 5 mg – 1 x 10 mg | 365.0 | 365 x 5 mg – 365 x 10 mg |
| Bosentan | 125 mg | 250 mg | 2 x 125 mg | 365.0 | 730 x 125 mg |
| Macitentan | 10 mg | 10 mg | 1 x 10 mg | 365.0 | 365 x 10 mg |
| Phosphodiesterase type 5 inhibitors | | | | | |
| Sildenafil | 20 mg | 60 mg | 3 x 20 mg | 365.0 | 1,095 x 20 mg |
| Tadalafil | 40 mg | 40 mg | 2 x 20 mg | 365.0 | 730 x 20 mg |
| Prostacyclin analogues | | | | | |
| Iloprost | 5 µg | 30 – 45 µg | 6 x 10 µg – 9 x 10 µg | 365.0 | 2,190 x 10 µg – 3,285 x 10 µg |
| Epoprostenol | Different from patient to patient | | | | |
| Treprostinil | Different from patient to patient | | | | |
| Selective prostacyclin receptor agonists | | | | | |
| Selexipag | 200 µg – 1,600 µg | 400 µg – 3200 µg | 2 x 200 µg – 2 x 1,600 µg | 365.0 | 730 x 200 µg – 730 x 1,600 µg |

[3] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

| Designation of the therapy | Dosage/ application | Dose/ patient/ treatment days | Consumption by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Stimulator of soluble guanylate cyclase | | | | | |
| Riociguat | 1 mg – 2.5 mg | 3 mg – 7.5 mg | 3 x 1 mg – 3 x 2.5 mg | 365.0 | 1,095 x 1 mg – 1,095 x 2.5 mg |
| Appropriate comparator therapy | | | | | |
| Endothelin receptor antagonists | | | | | |
| Ambrisentan | 5 mg – 10 mg | 5 mg – 10 mg | 1 x 5 mg – 1 x 10 mg | 365.0 | 365 x 5 mg – 365 x 10 mg |
| Bosentan | 125 mg | 250 mg | 2 x 125 mg | 365.0 | 730 x 125 mg |
| Macitentan | 10 mg | 10 mg | 1 x 10 mg | 365.0 | 365 x 10 mg |
| Phosphodiesterase type 5 inhibitors | | | | | |
| Sildenafil | 20 mg | 60 mg | 3 x 20 mg | 365.0 | 1,095 x 20 mg |
| Tadalafil | 40 mg | 40 mg | 2 x 20 mg | 365.0 | 730 x 20 mg |
| Prostacyclin analogues | | | | | |
| Iloprost | 5 µg | 30 – 45 µg | 6 x 10 µg – 9 x 10 µg | 365.0 | 2,190 x 10 µg – 3,285 x 10 µg |
| Epoprostenol | Different from patient to patient | | | | |
| Treprostinil | Different from patient to patient | | | | |
| Selective prostacyclin receptor agonists | | | | | |
| Selexipag | 200 µg – 1,600 µg | 400 µg – 3,200 µg | 2 x 200 µg – 2 x 1,600 µg | 365.0 | 730 x 200 µg – 730 x 1,600 µg |
| Stimulator of soluble guanylate cyclase | | | | | |
| Riociguat | 1 mg – 2.5 mg | 3 mg – 7.5 mg | 3 x 1 mg – 3 x 2.5 mg | 365.0 | 1,095 x 1 mg – 1,095 x 2.5 mg |

Costs:

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. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

**Costs of the medicinal products:**

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

| Designation of the therapy | Packaging 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 | | | | | |
| Sotatercept 60 mg | 1 PSI | € 10,505.76 | € 1.77 | € 596.69 | € 9,907.30 |
| Ambrisentan 5 mg[4] | 60 FCT | € 3,007.15 | € 1.77 | € 240.64 | € 2,764.74 |
| Ambrisentan 10 mg[4] | 60 FCT | € 3,134.59 | € 1.77 | € 251.04 | € 2,881.78 |
| Bosentan 125 mg[4] | 120 FCT | € 3,134.59 | € 1.77 | € 251.04 | € 2,881.78 |
| Epoprostenol 0.5 mg | 1 PIS | € 143.49 | € 1.77 | € 16.72 | € 125.00 |
| Epoprostenol 1.5 mg | 1 PIS | € 231.19 | € 1.77 | € 27.82 | € 201.60 |
| Iloprost 10 µg | 168 SON | € 3,392.84 | € 1.77 | € 163.26 | € 3,227.81 |
| Macitentan 10 mg[4] | 30 FCT | € 1,573.14 | € 1.77 | € 0.00 | € 1,571.37 |
| Riociguat 1 mg | 84 FCT | € 1,498.69 | € 1.77 | € 0.00 | € 1,496.92 |
| Riociguat 2.5 mg | 294 FCT | € 5,104.45 | € 1.77 | € 0.00 | € 5,102.68 |
| Selexipag 200 µg | 140 FCT | € 6,204.40 | € 1.77 | € 0.00 | € 6,202.63 |
| Selexipag 1600 µg | 60 FCT | € 3,133.45 | € 1.77 | € 0.00 | € 3,131.68 |
| Sildenafil 20 mg[4] | 30 FCT | € 72.23 | € 1.77 | € 4.82 | € 65.64 |
| Tadalafil 20 mg[4] | 12 FCT | € 37.84 | € 1.77 | € 2.10 | € 33.97 |
| Treprostinil 10 mg | 1 INF | € 2,103.90 | € 1.77 | € 267.12 | € 1,835.01 |
| Treprostinil 200 mg | 1 INF | € 15,555.41 | € 1.77 | € 758.64 | € 14,795.00 |
| Appropriate comparator therapy | | | | | |
| Ambrisentan 5 mg | 60 FCT | € 3,007.15 | € 1.77 | € 240.64 | € 2,764.74 |
| Ambrisentan 10 mg[4] | 60 FCT | € 3,134.59 | € 1.77 | € 251.04 | € 2,881.78 |
| Bosentan 125 mg[4] | 120 FCT | € 3,134.59 | € 1.77 | € 251.04 | € 2,881.78 |
| Epoprostenol 0.5 mg | 1 PIS | € 143.49 | € 1.77 | € 16.72 | € 125.00 |
| Epoprostenol 1.5 mg | 1 PIS | € 231.19 | € 1.77 | € 27.82 | € 201.60 |
| Iloprost 10 µg | 168 SON | € 3,392.84 | € 1.77 | € 163.26 | € 3,227.81 |
| Macitentan 10 mg[4] | 30 FCT | € 1,573.14 | € 1.77 | € 0.00 | € 1,571.37 |
| Riociguat 1 mg | 84 FCT | € 1,585.68 | € 1.77 | € 87.27 | € 1,496.64 |
| Riociguat 2.5 mg | 294 FCT | € 5,405.72 | € 1.77 | € 305.43 | € 5,098.52 |
| Selexipag 200 µg | 140 FCT | € 6,204.40 | € 1.77 | € 0.00 | € 6,202.63 |
| Selexipag 1600 µg | 60 FCT | € 3,133.45 | € 1.77 | € 0.00 | € 3,131.68 |
| Sildenafil 20 mg[4] | 30 FCT | € 72.23 | € 1.77 | € 4.82 | € 65.64 |
| Tadalafil 20 mg[4] | 12 FCT | € 37.84 | € 1.77 | € 2.10 | € 33.97 |
| Treprostinil 10 mg | 1 INF | € 2,103.90 | € 1.77 | € 267.12 | € 1,835.01 |
| Treprostinil 200 mg | 1 INF | € 15,555.41 | € 1.77 | € 758.64 | € 14,795.00 |

[4] Fixed reimbursement rate

| Designation of the therapy | Packaging size | Costs (pharmacy sales price) | Rebate Section 130 SGB V | Rebate Section 130a SGB V | Costs after deduction of statutory rebates |
|---|---|---|---|---|---|
| Abbreviations: FCT = film-coated tablets; INF = infusion solution; SON = solution for a nebuliser; PIS = powder for the preparation of an infusion solution; PSI = powder and solvent for solution for injection | | | | | |

LAUER-TAXE® last revised: 15 February 2025

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 the standard expenditure in the course of the treatment are not shown.

Because there are no 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, no costs for additionally required SHI services need to be taken into account.

An inhaler is required for the use of iloprost in accordance with the product information. The product information lists, among others, the following options for the 10 µg/ml ampoules: Breelib and the I-Neb AAD system. Breelib and the I-Neb AAD system are listed in the LAUER-TAXE®; however, price information is only available for the I-Neb AAD system, so this inhaler is listed here as an example. The inhaler priced at 3,500 euros is charged once to the patient. The contract prices of the respective health insurance funds may differ from this.

## 2.5 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

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with

the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to

Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

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.

Justification for the findings on designation in the present resolution:

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

The designated medicinal products concern in each case an active ingredient which may be used in combination therapy with the assessed medicinal product in the context of a therapeutic indication specified in the product information for the assessed medicinal product. This therapeutic indication concerns other therapies for pulmonary arterial hypertension according to the requirements in the product information.

For the designated medicinal products, the prerequisites of Section 35a, paragraph 3, sentence 4 SGB V are fulfilled and, according to the requirements in the product information, there are no reasons for exclusion that prevent a combination therapy with the assessed medicinal product.

References:

Product information for

- Sotatercept (Winrevair); Winrevair® 45 mg/ 60 mg powder and solvent for solution for injection; last revised: August 2024

- Selexipag (Uptravi); Uptravi® 100/ 200/ 400/ 600/ 800/ 1,000/ 1,200/ 1,400/ 1,600 microgram film-coated tablets; last revised: March 2024

Supplement to Annex XIIa of the Pharmaceuticals Directive

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive and provided with patient-group-related information on the period of validity of the designation.

## 3. Bureaucratic costs calculation

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 13 September 2024, the pharmaceutical company submitted a dossier for the benefit assessment of sotatercept to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

The Subcommittee on Medicinal Products determined the appropriate comparator therapy for the assessment procedure at its session on 24 September 2024.

By letter dated 17 September 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 sotatercept. The appropriate comparator therapy determined for the assessment procedure was submitted to IQWiG on 24 September 2024 in addition to the letter of 17 September 2024.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 December 2024, and the written statement procedure was initiated with publication on the G-BA website on 16 December 2024. The deadline for submitting statements was 6 January 2025.

The oral hearing was held on 27 January 2025.

By letter dated 28 January 2025, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 14 February 2025.

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 was discussed at the session of the subcommittee on 25 February 2025, and the proposed draft resolution was approved.

At its session on 6 March 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee on Medicinal Products | 24 September 2024 | Determination of the appropriate comparator therapy |
| Working group Section 35a | 15 January 2025 | Information on written statements received; preparation of the oral hearing |
| Subcommittee on Medicinal Products | 27 January 2025 | Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents |
| Working group Section 35a | 5 February 2025<br>19 February 2025 | Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure |
| Subcommittee on Medicinal Products | 25 February 2025 | Concluding discussion of the draft resolution |
| Plenum | 6 March 2025 | Adoption of the resolution on the amendment of the Pharmaceuticals Directive |

Berlin, 6 March 2025

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

Prof. Hecken