Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V: tagraxofusp (blastic plasmacytoid dendritic cell neoplasm, first-line)

of 2 December 2021

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of a rare disease (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a paragraph 1, sentence 11, 1st half of the sentence of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a paragraph 1 sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation, the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the marketing authorisation studies by the G-BA, indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of € 50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). According to Section 35a paragraph 2 SGB V, the assessment by the G-BA must be

completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the active ingredient tagraxofusp in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 June 2021. 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 14 June 2021.

Tagraxofusp indicated for the treatment of blastic plasmacytoid dendritic cell neoplasm is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the marketing authorisation studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 15 September 2021 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G12-01) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of tagraxofusp.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of tagraxofusp (Elzonris) in accordance with the product information

Elzonris is indicated as monotherapy for the first-line treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN).

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Therapeutic indication of the resolution (resolution from 02.12.2021):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

Adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN)

In summary, the additional benefit of tagraxofusp is assessed as follows:

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Justification:

The STML-401-0114 study submitted for the benefit assessment is a completed multicentre, open-label, single-arm phase I/II study (dose escalation and expansion) for the treatment of adult patients in first-line or relapsed/refractory blastic plasmacytoid dendritic cell neoplasm (BPDCN) and for the treatment of adult patients with acute myeloid leukemia with tagraxofusp.

The study is divided into four stages: dose escalation (stage 1), extension stage (stage 2), pivotal study (stage 3), and open-label extension (stage 4). In step 1 (dose escalation), the maximum tolerated dose or the maximum tested dose without the occurrence of multiple dose-limiting toxicities was determined. In stage 2 (extension stage), the efficacy as well as the safety of the maximum tolerated dose or maximum tested dose determined in stage 1 was investigated. Stage 3 comprises the pivotal cohort to investigate efficacy and safety. In stage 4 (open-label extension), further efficacy and safety studies were conducted. Stages 1, 2 and 4 included patients with unrelated diagnoses such as relapsed/refractory blastic plasmacytoid dendritic cell neoplasm and acute myeloid leukaemia.

Patients with known active or suspected CNS leukaemia were not included in the study. It is not known whether tagraxofusp passes the blood-brain barrier.

The treatment of patients in stages 1-3 was carried out in compliance with the marketing authorisation with a tagraxofusp dosage of 12 µg/kg/day in liquid dosage form. In stage 4, patients were treated with a lyophilised dosage form that is not compliant with the marketing authorisation.

A total of 29 patients with first-line blastic plasmacytoid dendritic cell neoplasm treated with a dose of 12 µg/kg/day in liquid dosage form in compliance with the marketing authorisation were included in the study: three patients in stage 1, 13 patients in stage 2, and 13 patients in stage 3.

Prior to the preparation of the SAP, 3 interim analyses (data cut-offs: 16 July 2015, 30 October 2015 and 29 August 2016) were conducted. Subsequently, 5 data cut-offs were performed, two of which were for FDA (25.09.2017 and 13.03.2020) and three for EMA (31.01.2018, 03.10.2018, and 30.06.2019) according to the pharmaceutical company.

Primary efficacy endpoint for stage 3 (pivotal cohort) was complete remission–CR/CRc), defined as both complete remission (CR) and complete remission with minimal residual skin abnormality (CRc). For stages 1 and 2, secondary and exploratory efficacy endpoints were, among others, complete remission (CR/CRc) and duration of complete remission rate, and for stage 3, the rate of stem cell transplants (SCT), among others. Pooled endpoint analyses of all stages were planned for the endpoints of overall survival, progression-free survival, rate SCT, and the safety endpoints.

Mortality

The endpoint of overall survival was operationalised in the STML-401-0114 study as time from the first tagraxofusp infusion until death from any cause.

No conclusions on the extent of the additional benefit could be derived due to the absence of comparative data.

Morbidity

On the assessment of skin changes by means of mSWAT

The clinical picture of BPDCN is accompanied by externally clearly visible, often painful and/or itchy skin changes, which represent a burden for the affected patient. Depending on the definition and operationalisation of corresponding endpoints, changes in the skin may, in principle, represent patient-relevant results.

Both the assessment of complete remission and progression-free survival include the assessment of disease progression in the skin compartment. This was done in the STML-401-0114 study using the Modified Severity Weighted Assessment Tool (mSWAT). For the assessment of skin changes, a distinction was made between patches, plaques and tumours. The mSWAT was calculated in the study by multiplying the percentages of diseased skin areas (% of total body surface area) by weighting factors of 1 for patches, 2 for plaques, and 4 for tumours, and forming a common score.

However, to assess validity and reliability in the present assessment situation, information is lacking on the (evidence-based) basis of the weighting factors used for the type of skin alteration (patches, plaques, tumours) as well as on interrater reliability, so that questions about the reliable estimation of the intensity of the alteration and the percentage of the body region affected remain open. In addition, quantification of skin alterations using the mSWAT for each skin measurement was only specified during the course of the study, so it is unclear to what extent the measurement procedure is comparable between all stages or throughout the course of the study.

Thus, there is doubt whether the measurement tool mSWAT used for the assessment of skin response is sufficiently valid and reliable to represent the cutaneous disease burden and whether stringent objective measurements were available in this study.

Overall, there are no adequate aggregated results on mSWAT in the dossier, so no results on mSWAT can be presented.

Progression-free survival

PFS was assessed as a secondary endpoint in the STML-401-0114study and was defined as the time from the start of treatment with tagraxofusp until the occurrence of a progression and/or death from any cause, whichever occurs first. For patients, who received stem cell transplant, progression-free survival included the time to progression or death after transplantation.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The "mortality" endpoint component was assessed as an independent endpoint in the present study via the "overall survival" endpoint.

The assessment of the "disease progression" morbidity component in the compartments of bone marrow, peripheral blood, lymph nodes as well as spleen and liver was not made symptom-related, but by means of imaging procedures and laboratory parameters, in accordance with the operationalisation. Therefore, the assessment of disease progression of these areas is not assessed as directly relevant to patients.

Disease progression in the skin compartment was assessed using the Modified Severity Weighted Assessment Tool (mSWAT). However, in view of the present operationalisation, there are doubts, as outlined above, as to whether the assessment of skin alterations using the mSWAT measurement tool is sufficiently valid and reliable to depict relevant skin alterations.

For the reasons stated above, the PFS endpoint is presented but not used in this assessment.

Notwithstanding this, no conclusions can be drawn on the extent of additional benefit due to the absence of comparative data.

Complete remission (CR/CRc)

The endpoint of complete remission (CR/CRc) was the primary efficacy endpoint for stage 3 in first-line therapy in the STML-401-0114 study and included patients with complete remission (CR) and complete remission with minimal residual skin abnormality (CRc). The CRc endpoint and the primary endpoint of complete remission (CR/CRc) were defined in this form only during the course of the study.

A complete remission (CR), defined as the disappearance of all signs of the disease in all compartments, can principally be an important prognostic factor in relation to the present therapeutic indication and relevant for treatment decisions. A CR associated with a noticeable disappearance of disease symptoms is patient-relevant.

The assessment of complete remission (CR) in the study was mainly based on imaging and laboratory tests. The assessment of disease symptoms in the compartments of bone marrow, peripheral blood, lymph nodes and spleen and liver was based on the criteria of Cheson[2]. An indirect assessment of disease symptoms potentially noticeable to patients was carried out by means of the mSWAT only for the skin compartment.

[2] Cheson et al. 2007. Revised response criteria for malignant lymphoma. Journal of Clinical Oncology, 25, 579-86.

It should be taken into account that there are considerable uncertainties regarding the operationalisation of the endpoint of complete remission, in particular with regard to the standardisation of the survey time points as well as the uniform evaluation. Overall, survey time points varied both between the five different compartments and between stages. Thus, it does not appear certain in which time frame all compartments had to meet the criteria of a CR or a CRc in order to be assessed as a CR or CRc, respectively. In addition, it is unclear by which survey time point CR or CR/CRc should be included in the respective endpoint.

CRc is defined as the disappearance of all signs of the disease in all compartments except for a minimal residual skin abnormality. This is determined, among other things, by percentage changes and percentage values of the mSWAT. It is unclear whether a CRc, which includes partial or incomplete skin recovery, has comparable clinical relevance as achievement of a CR.

Overall, there are doubts about the significance of the endpoint for the evaluation of patient-relevant therapeutic effects; the endpoint of complete remission (CR/CRc) is only presented additionally.

Notwithstanding this, no conclusions can be drawn on the extent of additional benefit due to the absence of comparative data.

Rate of stem cell transplant

In the STML-401-0114 study, the stem cell transplant (SCT) rate was defined as the number and percentage of patients who were eligible for SCT and received the same.

The rate of SCT can be assumed to be a patient-relevant endpoint in the present therapeutic indication, depending on the operationalisation. However, the assessment of the endpoint in the present study is subject to uncertainty. The survey time points of SCT were not clear either before the endpoint was specified or thereafter. Therefore, it seems unclear whether all SCTs or which SCTs were collected from when individually (for example, from time of enrolment) and overall (from which study time point) and evaluated in the rate of SCTs. Furthermore, it was not assessed during the study as to why a patient did not receive a transplant. The endpoint of rate of stem cell transplant is therefore only presented additionally.

No conclusions on the extent of the additional benefit could be derived due to the absence of comparative data.

No conclusions on the extent of additional benefit can be derived from the overall analysis of the data on morbidity.

Quality of life

No data on quality of life were assessed.

Side effects

Adverse events were defined as those adverse medical events which occur after the first administration of tagraxofusp up to 30 days after the last infusion, regardless of their association with study medication.

Adverse events in total

One adverse event occurred in all patients included in the study. The results were presented additionally.

Severe adverse events CTCAE grade ≥ 3

An adverse event with CTCAE grade ≥ 3 occurred in 22 (75.9%) patients in stage 1-3 and in 9 (69.2%) patients in stage 3 of the STML-401-0114 study. The most frequent AEs of CTCAE grade ≥ 3 included "Blood and lymphatic system disorders", "Cardiac disorders", "Infections and infestations", "Investigations", "Metabolism and nutrition disorders", "Musculoskeletal and connective tissue disorders" and "Vascular disorders".

Serious adverse events (SAE)

A serious adverse event occurred in 12 (41.4%) patients in stage 1-3 and in 4 (30.8%) patients in stage 3.

The most frequent SAEs are "Blood and lymphatic system disorders", "Cardiac disorders", "General disorders and administration site conditions", "Infections and infestations", "Metabolism and nutrition disorders", "Nervous system disorders", and "Vascular disorders".

Discontinuation because of AEs

One patient (3.4%) in stage 1-3 and one patient (7.7%) in stage 3 experienced an adverse event that led to discontinuation of study medication

AE of special interest

AEs of special clinical interest occurred in nearly 80% of the study participants in the SMQ "Medicinal product-related diseases of the liver". Other adverse events of special interest include: "Hypersensitivity", "Capillary leak syndrome", "Visual acuity", and "Venocclusive disorders following stem cell transplant".

In the overall analysis of the results on side effects, no statements on the extent of additional benefit can be derived due to the absence of comparative data.

<u>Overall assessment</u>

The benefit assessment of tagraxofusp for the first-line treatment of patients with blastic plasmacytoid dendritic cell neoplasm is based on the STML-401-0114 study, from which results on mortality, morbidity and side effects are available

No data are available for comparative assessment due to the single-arm design of the STML-401-0114 study.

Thus, quantification of the additional benefit is not possible on the basis of the data presented.

In the overall assessment, a non-quantifiable additional benefit is determined for tagraxofusp for the treatment of patients with blastic plasmacytoid dendritic cell neoplasm as the scientific data basis does not allow quantification.

Significance of the evidence

The STML-401-0114 study is a single-arm study so that a comparative assessment is not possible.

In the overall assessment, the result is a hint for a non-quantifiable additional benefit concerning the significance of the evidence.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Elzonris with the active ingredient tagraxofusp.

Tagraxofusp was approved as an orphan drug under exceptional circumstances for the first-line treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN).

The benefit assessment of tagraxofusp is based on the STML-401-0114 study, from which results on mortality, morbidity and side effects are available.

No data are available for comparative assessment due to the single-arm design of the STML-401-0114 study.

Thus, quantification of the additional benefit is not possible on the basis of the data presented.

In the overall assessment, a non-quantifiable additional benefit is determined for tagraxofusp for the treatment of patients with blastic plasmacytoid dendritic cell neoplasm as the scientific data basis does not allow quantification.

Overall, a hint for a non-quantifiable additional benefit is identified for tagraxofusp because the scientific data basis does not allow quantification.

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 G-BA bases its resolution on the information from the dossier of the pharmaceutical company. Overall, the information is subject to uncertainties, in particular due to uncertainties in the incidence rates used for the calculation. In addition, the required restriction to adults was not applied.

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 Elzonris (active ingredient: tagraxofusp) at the following publicly accessible link (last access: 17 August 2021):

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

Initiation and monitoring of treatment with tagraxofusp should be performed only by specialists in internal medicine, haematology and oncology.

According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide a guideline for health professionals and a patient pass. In particular, the information material contains indications on signs and symptoms of specific side effects associated with the capillary leak syndrome (CLS).

Tagraxofusp should only be given in a setting where a complete resuscitation equipment is immediately available.

This medicinal product was approved under “special conditions”. This means that due to the rarity of the disease, it was not possible to obtain complete information on this medicinal product. The EMA will assess any new information that becomes available on an annual basis, and, if necessary, the summary of product characteristics will be updated.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 November 2021).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

The annual treatment costs shown refer to the first year of treatment.

According to the product information, treatment with tagraxofusp should be in an inpatient setting in the first treatment cycle. In subsequent treatment cycles, tagraxofusp may be administered in an inpatient setting or in an appropriate outpatient care centre appropriately equipped for intensive monitoring of patients with haematologic cancers undergoing treatment.

For the cost calculation, the case scenarios a) purely inpatient administration and b) inpatient administration only in the first treatment cycle and subsequent outpatient treatment are considered.

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 77.0 kg).[3]

[3] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tagraxofusp	on day 1-5 of a 21 day cycle[4]	17.4	5	87

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Usage by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tagraxofusp	12 µg/kg = 924 µg	924 µg	1 x 1 mg	87	87 x 1 mg

Costs:

In the inpatient setting:

Tagraxofusp meets the criteria of the NUB agreement for 2021 according to the list of information pursuant to Section 6 para. 2 KHEntgG (Act on Charges for Fully and Partially Inpatient Hospital Services). According to Section 1 para. 1 of the NUB Agreement for 2021, the agreement of a hospital-specific fee pursuant to Section 6 para. 2 KHEntgG is permissible for these services. As an approximation, the manufacturer's sales price plus 19% value added tax is used to calculate the inpatient costs for the medicinal product. The actual costs incurred may vary from hospital to hospital.

[4] The first treatment with tagraxofusp should be in an inpatient setting according to the product information. In subsequent treatment cycles, administration may be in an inpatient setting or in an appropriate outpatient care centre appropriately equipped for intensive monitoring of patients with haematologic cancers undergoing treatment.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Value added tax (19%)	Costs of the medicinal product
Medicinal product to be assessed				
Tagraxofusp 1 mg	1 CIS	€ 24,600.00	€ 4,674.00	€ 29,274.00
Abbreviations: CIS = concentrate for the preparation of an infusion solution				

LAUER-TAXE® last revised: 15 November 2021

In the outpatient setting:

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 Section 130 and Section 130 a SGB V. The required number of packs of a particular potency was first determined based on consumption to calculate the annual treatment costs. 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.

Costs of the medicinal products:

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					
Tagraxofusp 1 mg	1 CIS	€ 30,162.41	€ 1.77	€ 1,722.00	€ 28,438.64
Abbreviations: CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 15 November 2021

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

Premedication

According to the product information, patients must receive pretreatment with an H1 histamine antagonist (e.g., diphenhydramine hydrochloride), an H2 histamine antagonist (e.g., ranitidine), a corticosteroid (e.g., 50 mg intravenous methylprednisolone or an equivalent medicinal product) and paracetamol approximately 60 minutes prior to the start of the infusion. In the inpatient treatment setting, the costs for premedication are included in the per case flat rate. The additional costs for premedication incurred in the outpatient treatment setting cannot be precisely quantified due to the largely lacking dosage data for premedication.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy sales price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

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 14 June 2021, the pharmaceutical company submitted a dossier for the benefit assessment of tagraxofusp to the G-BA in due time in accordance with Chapter 5, Section 8, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 15 September 2021 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 6 October 2021.

The oral hearing was held on 25 October 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 23 November 2021, and the draft resolution was approved.

At its session on 2 December 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	7 September 2021	Information of the benefit assessment of the G-BA
Working group Section 35a	20 October 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	25 October 2021	Conduct of the oral hearing
Working group Section 35a	3 November 2021 17 November 2021	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal product	23 November 2021	Concluding discussion of the draft resolution
Plenum	2 December 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 2 December 2021

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

Prof. Hecken