Gemeinsamer Bundesausschuss

Resolution

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

of 2 December 2021

At its session on 2 December 2021, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No 49a of 31 March 2009), as last amended by the publication of the resolution of DD. Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

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

Tagraxofusp

Resolution of: 2 December 2021
Entry into force on: 2 December 2021
BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 7 January 2021):

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

Therapeutic indication of the resolution (resolution of 2 December 2021):

see therapeutic indication according to marketing authorisation

1. Extent of the additional benefit and significance of the evidence

Tagraxofusp is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan drugs. In accordance with section 35a, paragraph 1, sentence 11, 1st half 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.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

<u>Adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN)</u>

Extent of the additional benefit and significance of the evidence of tagraxofusp:

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

Study results according to endpoints:[1]

Adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN)

Summary of results for relevant clinical endpoints

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

STML-401-0114 study: multicentre, open-label, single-arm phase I/II study

Data cut-offs used:

- final data cut-off from 13 March 2020 (mortality, morbidity endpoint (complete remission) and safety)
- Data cut-off of 30 June 2019 (safety and progression-free survival)
- Data cut-off of 31.01.2018 (endpoint of morbidity (rate of stem cell transplant), study characteristics, and study medication)

Mortality

Endpoint	Tagraxofusp Phase 3		Tagraxofusp Phase 1-3	
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*
Overall survival				
Data cut-off: 13 March 2020	13	18.9 [5.2; n.a.] *8 (61.5)*	29	25.8 [9.7; 53.9] *18 (62.1)*

[1] Data from the dossier assessment of the G-BA (published on the 15. September 2021), unless otherwise indicated.

Morbidity

Endpoint	Tagraxofusp Phase 3		Tagraxofusp Phase 1-3	
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*
Progression-free survival[a] (presented additionally)				
Data cut-off: 30.06.2019	13	7.3 [2.8; not assessable] *9 (69.2)*	29	7.3 [4.3; not assessable] *19 (65.5)*

Endpoint	Tagraxofusp Phase 3		Tagraxofusp Phase 1-3	
	N	*Patients with event n (%)* [95% CI]	N	*Patients with event n (%)* [95% CI]
Complete remission (CR/CRc)[b] (presented additionally)				
Data cut-off: 13 March 2020	13	*7 (53.8)*	29	*21 (72.4)*

Endpoint	Tagraxofusp Phase 1-3	
	N	*Patients with event n (%)* [95% CI]
Rate of stem cell transplant (presented additionally)		
Data cut-off: 31 January 2018	29	*13 (44.8)* [26.4; 64.3]

Health-related quality of life

No data available.

Side effects

Endpoint	Data cut-off 30 June 2019		Data cut-off 13 March 2020	
	Tagraxofusp Phase 3 N = 13	**Tagraxofusp Phase 1-3 N = 29**	**Tagraxofusp Phase 3 N = 13**	**Tagraxofusp Phase 1-3 N = 32[c]**
	Patients with event n (%)	*Patients with event n (%)*	*Patients with event n (%)*	*Patients with event n (%)*
Total adverse events (AE) (presented additionally)				
	13 (100)	*29 (100)*	*n.d.*	*32 (100)*
Adverse events (CTCAE grade ≥ 3)				
	9 (69.2)	*22 (75.9)*	*n.d.*	*25 (87.1)*
Serious adverse events (SAE)				
	4 (30.8)	*12 (41.4)*	*n.d.*	*13 (40.6)*
Adverse event, which led to the discontinuation of the study medication				
	1 (7.7)	*1 (3.4)*	*n.d.*	*3 (9.4)*
AE with incidence ≥ 10% after SOC				
Blood and lymphatic system disorders	*8 (61.5)*	*19 (65.5)*	*n.d.*	*22 (68.8)*
Cardiac disorders	*5 (38.5)*	*8 (27.6)*	*n.d.*	*11 (34.4)*
Eye disorders	*3 (23.1)*	*8 (27.6)*	*n.d.*	*8 (25.0)*
Gastrointestinal disorders	*9 (69.2)*	*22 (75.9)*	*n.d.*	*23 (71.9)*
General disorders and administration site conditions	*12 (92.3)*	*27 (93.1)*	*n.d.*	*30 (93.8)*
Infections and infestations	*3 (23.1)*	*11 (37.9)*	*n.d.*	*12 (37.5)*
Injury, poisoning and procedural complications	*1 (7.7)*	*5 (17.2)*	*n.d.*	*5 (15.6)*
Investigations	*12 (92.3)*	*28 (96.6)*	*n.d.*	*31 (96.9)*
Metabolism and nutrition disorders	*11 (84.6)*	*23 (79.3)*	*n.d.*	*26 (81.3)*

Endpoint	Data cut-off 30 June 2019		Data cut-off 13 March 2020	
	Tagraxofusp Phase 3 N = 13	**Tagraxofusp Phase 1-3 N = 29**	**Tagraxofusp Phase 3 N = 13**	**Tagraxofusp Phase 1-3 N = 32[c]**
	Patients with event n (%)	*Patients with event n (%)*	*Patients with event n (%)*	*Patients with event n (%)*
Musculoskeletal and connective tissue disorders	*8 (61.5)*	*16 (55.2)*	*n.d.*	*17 (53.1)*
Neoplasms benign, malignant and unspecified (including cysts and polyps)	*0*	*4 (13.8)*	*n.d.*	*4 (12.5)*
Nervous system disorders	*7 (53.8)*	*17 (58.6)*	*n.d.*	*17 (53.1)*
Psychiatric disorders	*5 (38.5)*	*12 (41.4)*	*n.d.*	*12 (37.5)*
Renal and urinary disorders	*4 (30.8)*	*5 (17.2)*	*n.d.*	*7 (21.9)*
Respiratory, thoracic and mediastinal disorders	*6 (46.2)*	*12 (41.4)*	*n.d.*	*14 (43.8)*
Skin and subcutaneous tissue disorders	*6 (46.2)*	*14 (48.3)*	*n.d.*	*15 (46.9)*
Vascular disorders	*7 (53.8)*	*15 (51.7)*	*n.d.*	*16 (50.0)*

AE of CTCAE grade ≥ 3 with incidence ≥ 5 %				
Blood and lymphatic system disorders	*4 (30.8)*	*12 (41.4)*	*n.d.*	*14 (43.8)*
Cardiac disorders	*1 (7.7)*	*1 (3.4)*	*n.d.*	*2 (6.3)*
Infections and infestations	*1 (7.7)*	*2 (6.9)*	*n.d.*	*3 (9.4)*
Investigations	*3 (23.1)*	*14 (48.3)*	*n.d.*	*16 (50.0)*
Metabolism and nutrition disorders	*6 (46.2)*	*12 (41.4)*	*n.d.*	*14 (43.8)*
Musculoskeletal and connective tissue disorders	*1 (7.7)*	*3 (10.3)*	*n.d.*	*3 (9.4)*
Vascular disorders	*5 (38.5)*	*6 (20.7)*	*n.d.*	*7 (21.9)*
SAE with incidence ≥ 5% after SOC				
Blood and lymphatic system disorders	*1 (7.7)*	*1 (3.4)*	*n.d.*	*1 (3.1)*
Cardiac disorders	*1 (7.7)*	*1 (3.4)*	*n.d.*	*1 (3.1)*
General disorders and administration site conditions	*0*	*2 (6.9)*	*n.d.*	*2 (6.3)*
Infections and infestations	*0*	*1 (3.4)*	*n.d.*	*2 (6.3)*
Metabolism and nutrition disorders	*1 (7.7)*	*1 (3.4)*	*n.d.*	*1 (3.1)*
Nervous system disorders	*1 (7.7)*	*1 (3.4)*	*n.d.*	*1 (3.1)*
Vascular disorders	*2 (15.4)*	*4 (13.8)*	*n.d.*	*5 (15.6)*
AE of special interest				
	Total	**CTCAE grade ≥ 3**	**Total**	**CTCAE grade ≥ 3**
Hypersensitivity	*14 (48.3)*	*1 (3.4)*	*n.d.*	*1 (3.1)*
Capillary leak syndrome	*4 (13.8)*	*1 (3.4)*	*n.d.*	*2 (6.3)*
Visual acuity	*1 (3.4)*	*0*	*n.d.*	*0*
Liver diseases caused by medicinal products	*23 (79.3)*	*14 (48.3)*	*n.d.*	*17 (53.1)*

Veno-occlusive diseases as a result of stem cell transplant	*2 (6.9)*	*0*	*n.d.*	*n.d.*

[a] Data from the tagraxofusp module 4A dossier of 15 June 2021.
[b] Data from the written statement of the pharmaceutical company dated 6 October 2021.
[c] 3/32 subjects received an off-label dosage of 7 µg/kg/day of tagraxofusp in phase 1.

Abbreviations used:
CTCAE = Common Terminology Criteria for Adverse Events; n.d. = no data available; CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PT = preferred term; SAE = serious adverse event(s); SOC = System Organ Class; AE = adverse event(s).

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

Adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN)

approx. 30 – 90 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for 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.

4. Treatment costs

Annual treatment costs:

Adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN)

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Tagraxofusp	€ 2,478,338.48 - € 2,546,838.00
Additionally required SHI costs[2]:	Incalculable

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 15 October 2021)

Other SHI services[3]:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Tagraxofusp	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	5	82	€ 6,642

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 2 December 2021.

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

Berlin, 2 December 2021

[2] Includes the inpatient stay as well as any additional outpatient costs for premedication.
[3] For outpatient use

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

Prof. Hecken