Gemeinsamer Bundesausschuss

Imlifidase (desensitisation in kidney transplantation)

Resolution of: 02.09.2021 Valid until: 01 04 2026
Entry into force on: 02.09.2021
BAnz AT 26 10 2021 B2

Therapeutic indication (according to the marketing authorisation of 25 August 2020):

Idefirix is indicated for desensitisation treatment of highly sensitised adult kidney transplant patients with positive crossmatch against an available deceased donor.

The use of idefirix should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritisation programmes for highly sensitised patients.

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

see therapeutic indication according to marketing authorisation.

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

Imlifidase 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 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 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).

Adult kidney transplant patients who have antibodies that result in a positive crossmatch against an available deceased donor.

Extend of the additional benefit and significance of the evidence of imlifidase:

In conclusion, there is a hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Study results according to endpoints:[1]

Adult kidney transplant patients who have antibodies that result in a positive crossmatch against an available deceased donor.

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	n.a.	The data are not assessable. KDQOL-SF was only collected in the 17-HMedIde-S-14 follow-up study.
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		

Single-arm studies 13-HMedIdeS-03, 14-HMedIdeS-04, 15-HMedIdeS-06

Endpoint category **Endpoint**	**13-HMedIdeS-03** **N = 5**[a, b] n (%)	**14-HMedIdeS-04**[b, c] **N = 17** n (%)	**15-HMedIdeS-06**[b] **N = 19** n (%)
Mortality			
Day 180			
n	5	17	19
Alive	5 (100.0)	17 (100.0)	19 (100.0)
Deceased	0 (0.0)	0 (0.0)	0 (0.0)
Morbidity			
Graft survival[d]			
Day 180			
n	5	n.d.	n.d.
No graft loss	5 (100.0)	n.d.	n.d.
Graft loss	0 (0.0)	1 (5.9)	2 (10.5)
Renal function measured as eGFR-MDRD[e]			
Day 180			

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

Endpoint category Endpoint	13-HMedIdeS-03 N = 5[a, b] n (%)	14-HMedIdeS-04[b, c] N = 17 n (%)	15-HMedIdeS-06[b] N = 19 n (%)
n eGFR < 30 ml/min/1.73 m^2 eGFR 30–59 ml/min/1.73 m^2 (presented additionally) eGFR ≥ 60 ml/min/1.73 m^2 (presented additionally)	5 1 (20.0) 3 (60.0) 1 (20.0)	n.d.[g]	17[f] 2 (10.5) 11 (57.9) 4 (21.1)

Health-related quality of life

Quality of life was not assessed in studies 13-HMedIdeS-03, 14-HMedIdeS-04, and 15-HMedIdeS-06.

Side effects

	13-HMedIdeS-03 N = 5[a, b] n (%)	14-HMedIdeS-04 N = 17[b, c] n (%)		15-HMedIdeS-06 N = 19[b] n (%)	
		Within 30 days[h]	Total[i]	Within 30 days[h]	Total[i]
AE	5 (100.0)	17 (100.0)	17 (100.0)	19 (100.0)	19 (100.0)
AE of CTCAE grade ≥ 3	n.d.[j]	4 (23.5)	4 (23.5)	15 (78.9)	18 (94.7)
SAE	3 (60.0)	7 (41.2)	11 (64.7)	13 (68.4)	15 (78.9)
AE, which led to the discontinuation of the study medication	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	n.d.
AE of special interest[k] Infections Infusion-associated reactions	n.d. n.d.	6 (35.3)[l] 0 (0.0)	n.d.[l] 0 (0.0)	n.a.[m] n. a.	n.a.[m] n.a.

a) Dose group 1, which received a single dose of 0.25 mg/kg.
b) The study duration should be 180 days according to the study protocol. The actual duration of the study was not reported.
c) A dosage (ED 0.24 mg/kg) was used, which differs slightly from the dosage compliant with the marketing authorisation (ED 0.25 mg/kg)).
d) Graft survival was not defined a priori as an endpoint. Graft function was continuously monitored. The endpoint was presented in the context of safety.
e) Captured via security.
f) Information is provided on 17 participants (89.5%) at day 180, although only 16 participants (84.2%) completed the study. It remains unclear why more data is provided for 1 subject
g) Information is provided on the end of the study. However, it remains unclear to what extent this is information on day 180. According to Module 4, data were available at the end of the study from 16 of the 17 participants, although 2 participants discontinued the study prematurely. In 1 subject

Endpoint category Endpoint	13-HMedIdeS-03 N = 5[a, b] n (%)	14-HMedIdeS-04[b, c] N = 17 n (%)	15-HMedIdeS-06[b] N = 19 n (%)

(5.9%), an eGFR < 30 ml/min/1.73 m² was observed, in 6 subjects (35.3%) an eGFR 30-59ml/min/1.73 m² and in 9 subjects (52.9 %) an eGFR ≥ 60 ml/min/1.73 m² was observed.

h) AEs that occurred within 30 days after application of the study medication.

i) AEs that occurred within 30 days of study medication application and post-treatment (> 30 days after receiving imlifidase) until the follow-up visit.

j) No summary presentation of severe AEs according to CTCAE grade ≥ 3 was made. A separate presentation was made according to CTCAE grades 3 and 4.

k) Post hoc defined.

l) In study 14-HMedIdeS-04 the following AEs were defined as AEs of special interest post hoc: antibody-mediated rejections, infections, infusion-associated reactions. As an overlap with efficacy endpoints is evident in antibody-mediated rejection reactions, a presentation is omitted. According to the study report, a total of 6 subjects experienced AEs as TEAE within the corresponding efficacy window (infections < 30 days after imlifidase administration in 6 participants). The proportion of subjects with AEs by SOC and PT could not be identified.

m) In study 15-HMedIdeS-06 , post hoc specific AEs were defined as delayed graft function, graft rejection and end-of-study renal biopsies, and biopsy-confirmed rejection. Since an overlap with efficacy endpoints is evident, no presentation is made.

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; SD: Single dose; GFR: Glomerular filtration rate; n. d.: no data; MDRD: Modification of Diet in Renal Disease; n. a.: not applicable; PT: Preferred Terms; SOC: System organ class/s; (S)AEs: (Serious) adverse event: TEAE: Treatment emergent adverse events

Follow-up study 17-HMedIdeS-14:

Endpoint category Endpoint Study 17-H-MedIdeS-14	17-HMedIdeS-14[a]			
	13-HMedIdeS-03[b, c] **N = 5** n (%)[d]	**14-HMedIdeS-04[e]** **N = 11** n (%)[d]	**15-HMedIdeS-06** **N = 13** n (%)[d]	**Total[f]** **N = n. d.[g]** n (%)[d]
Mortality				
Last study visit Visit n Alive Deceased	n.d.	Year 3 6 6 (54.5) 0 (0.0)	Year 2 10 10 (76.9) 0 (0.0)	n.d.
Subjects not actively participating in the 17-HMedIdeS-14 study[h] n Alive Deceased	n.d.	4 3 (27.3) 1 (9.1)	1 0 (0.0) 1 (7.7)	n.d.
Morbidity				
Graft survival[h]				
Last study visit Visit n No graft loss Graft loss	n.d.	Year 3 6 6 (54.5) 0 (0.0)	Year 2 10 10 (76.9) 0 (0.0)	n.d.
Subjects not actively participating in the 17-HMedIdeS-14 study[i] n No graft loss Graft loss	n.d.	4 1 (9.9) 3 (27.8)	1 1 (7.7) 0 (0.0)	n.d.
Renal function (e-GFR-MDRD)				
Last study visit Visit n eGFR < 30 ml/min/1.73 m^{2} [b] eGFR 30–59 ml/min/1.73 m^{2} [b] (presented additionally) eGFR ≥ 60 ml/min/1.73 m^{2} [b] (presented additionally)	n.d.	Year 3 6 1 (9.1) 2 (18.2) 3 (27.3)	Year 2 9 1 (7.7) 6 (46.2) 2 (15.4)	n.d.

Endpoint category Endpoint Study 17-H-MedIdeS-14	17-HMedIdeS-14[a]			
	13-HMedIdeS-03[b, c] **N = 5** n (%)[d]	**14-HMedIdeS-04[e]** **N = 11** n (%)[d]	**15-HMedIdeS-06** **N = 13** n (%)[d]	**Total[f]** **N = n. d.[g]** n (%)[d]
Health status (EQ-5D-VAS)	no suitable data			
Quality of life				
KDQOL-SF	no suitable data			
Security				
AE	n.d.	n.d.	n.d.	n.d.
AE of CTCAE grade ≥ 3	n.d.	n.d.	n.d.	n.d.
SAE	n.d.	n.d.	n.d.	n.d.
AE, which led to the discontinuation of the study medication	n.d.	n.d.	n.d.	n.d.
AE of special interest	n.d.	n.d.	n.d.	n.d.

a) 46 subjects (including participants with non-compliant dosages) from studies 13-HMedIdeS-02/03, 14-HMedIdeS-04, and 15-HMedIdeS-06 were able to cross over into the follow-up study 17-HMedIdeS-14. No observation period data could be identified for the study. It also remains unclear how long the period was between the end of the preceding studies and inclusion in study 17-HMedIdeS-14.
b) Dose group 1, which received a single dose of 0.25 mg/kg.
c) Only data for all subjects (dose group 1: ED 0.25 mg/kg and dose group 2: ED 0,5 mg/kg). A separate presentation of the results for dosage group 1 relevant to the approval could not be identified.
d) Percentages refer to the number of subjects who participated in study 17-HMedIdeS-14.
e) A dosage (ED 0.24 mg/kg) was used, which differs slightly from the dosage compliant with marketing authorisation (ED 0.25 mg/kg).
f) Data from all subjects at the end of the "feeder studies" (13-HMedIdeS-03, 14-HMedIdeS-04, 15-HMedIdeS-06).
g) No evaluation was performed for the sub-population with the dosage compliant with marketing authorisation (ED 0.25 mg/kg).
h) Graft survival was defined as the time from transplantation to graft loss. Graft loss was defined as a permanent return to dialysis for at least 6 weeks, re-transplantation, or graftectomy.
i) After the end of the "feeder studies" but before inclusion in the 17-HMedIdeS-14 study, 3 subjects with functioning grafts died, and 3 subjects experienced graft loss. The results of these 6 subjects were included in the study after permission from the local ethics committees in study 17-HMedIdeS-14.

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; ED: Single dose; eGFR: estimated glomerular filtration rate; n. d.: no data; KDQOL-SF: Kidney Disease Quality of Life Questionnaire - short form; MDRD: Modification of Diet in Renal Disease; (S)AE: (Serious) adverse event

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

Adult kidney transplant patients who have antibodies that result in a positive crossmatch against an available deceased donor.

approx. 3 – 69 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 Idefirix (active ingredient: imlifidase) at the following publicly accessible link (last access: 2 July 2021):

https://www.ema.europa.eu/documents/product-information/idefirix-epar-product-information_de.pdf

Treatment should only be prescribed and supervised by a healthcare professional experienced in the immunosuppressive treatment and the care of sensitised kidney transplant patients.

This medicinal product has been authorised under a so-called "conditional approval" scheme. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency (EMA) will assess new information on this medicinal product at least annually and update the product information for healthcare professionals as necessary.

4. Treatment costs

Treatment costs:

Adult kidney transplant patients who have antibodies that result in a positive crossmatch against an available deceased donor.

Designation of the therapy	Treatment costs/ subject[2]
Medicinal product to be assessed:	
Imlifidase[3]	€ 426,020 – 852,040

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

Costs for additionally required SHI services: not applicable

[2] Imlifidase is administered as a single dose (0.25 mg/kg) preferably within 24 hours prior to transplantation. One dose is sufficient for crossmatch conversion in the majority of patients, but a second dose may be administered within 24 hours of the first dose if necessary.

[3] Imlifidase is currently only available as a clinic pack. Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung) and no rebates according to Section 130 or Section 130a SGB V apply. The calculation is based on the purchase price of the clinic package (information from the pharmaceutical company) including 19 % value added tax.