

Resolution
by the Federal Joint Committee
on an amendment to the Pharmaceutical Directive (AM-RL):
Appendix XII – Resolutions on the benefit assessment of pharmaceuticals
with new active ingredients, in accordance with the German Social Code,
Book Five (SGB V), section 35a
Belatacept

from 5 July 2012

In its session on 5 July 2012, the Federal Joint Committee resolved to amend the Pharmaceutical Directive (AM-RL), version published 18 December 2008/22 January 2009 (Federal Gazette, number 49a of 31 March 2009), last amended on 21 June 2012 (Federal Gazette, AT 10.08.2012 B5) as follows:

I.

Appendix XII shall be amended in alphabetical order to include the active ingredient belatacept:

Belatacept

Therapeutic indication:

Nulojix, in combination with corticosteroids and a mycophenolic acid (MPA), is indicated for prophylaxis of graft rejection in adults receiving a renal transplant (see section 5.1 for data on renal function). It is recommended to add an interleukin (IL)-2-receptor antagonist for induction therapy to this belatacept-based regimen.

1. Additional benefit of the pharmaceutical over appropriate comparator

a) Patients who have received a transplant from a standard criteria donor (SCD).

Appropriate comparator: ciclosporin in combination with corticosteroids and mycophenolate mofetil.

Extent and probability of additional benefit over ciclosporin in combination with corticosteroids and mycophenolate mofetil:

Indication of a minor additional benefit.

a) Patients who have received a transplant from an expanded criteria donor (ECD).

Appropriate comparator: ciclosporin in combination with corticosteroids and mycophenolate mofetil.

Extent and probability of additional benefit over ciclosporin in combination with corticosteroids and mycophenolate mofetil:

Indication of a minor additional benefit.

Study results according to endpoints:

a) Patients who have received a transplant from a standard criteria donor (SCD).

Endpoint	Effect estimates [95% CI]	Incident rate [absolute risk reduction (ARR)] ¹	p-value
	Belatacept vs. ciclosporin A		
Mortality			
Overall mortality	RR 0.65 [0.30; 1.42]	4.4% vs. 6.8%	0.289
Morbidity			
Loss of transplant	RR 0.88 [0.37; 2.12]	4.0% vs. 4.5%	0.826
Aggregate endpoint: patient and transplant survival	RR 0.70 [0.40; 1.25]	8.0% vs. 11.3%	0.245
Cardiovascular morbidity and mortality	RR 0.90 [0.40; 1.99]	4.9% vs. 5.4%	0.826
Aggregate endpoint: cardio-renal diseases	RR 0.90 [0.54; 1.52]	10.6% vs. 11.8%	0.769

Endpoint	Effect estimates [95% CI]	Incident rate [absolute risk reduction (ARR)] ¹	p-value
	Belatacept vs. ciclosporin A		
Chronic kidney disease in CKD stage 4/5	RR 0.49 [0.29; 0.82] ²	10.0% vs. 20.5% ARR = 10.5% ²	0.005 ²
Kidney function (cGFR)	Difference of means 21.40 ml/min/ 1.73 m ² [16.18; 26.62] ³		
Health-related quality of life			
Physical health aggregate score (SF 36)	Hedges'g 0.18 [- 0.01; 0.38] ⁴		0.070 ²
Mental health aggregate score (SF 36)	Hedges'g 0.22 [0.03; 0.42] ⁴		0.027 ²
Side effects			
Overall rate AE	RR 1.00 [0.99; 1.02]	99.6% vs. 99.1%	0.577
Overall rate SAE	RR 0.85 [0.74; 0.99]	58.0% vs. 67.9% ARR = 9.9%	0.031
Terminations due to AE	RR 0.51 [0.28; 0.90]	7.1% vs. 14.0% ARR = 6.9%	0.018
Post-transplant lymphoproliferative disorder	RR 1.91 [0.20; 18.46]	0.9% vs. 0.5%	0.639
Post-transplant diabetes mellitus	RR 0.59 [0.29; 1.21]	6.5% vs. 11.1%	0.154
Malignancies	RR 0.81 [0.36; 1.85]	4.4% vs. 5.4%	0.647
Infections	RR 1.03 [0.94; 1.13]	81.9% vs. 79.6%	0.583

¹ Figures shown for significant differences only

² Own calculation

³ Data from dossier

⁴ Standardized difference of means as Hedges'g to assess relevance of statistically significant group difference.

Abbreviations used:

CI = confidence interval, RR = relative risk, ARR = absolute risk reduction, AE = adverse event, SAE = serious adverse event, CKD = chronic kidney disease

a) Patients who have received a transplant from an expanded criteria donor (ECD).

Endpoint	Effect estimates [95% CI]	Incident rate [absolute risk reduction (ARR)] ¹	p-value
	Belatacept vs. ciclosporin A		
Mortality			
Overall mortality	RR 0.93 [0.48; 1.80]	8.6% vs. 9.2%	0.839
Morbidity			
Loss of transplant	RR 0.96 [0.55; 1.67]	12.0% vs. 12.5%	0.916
Aggregate endpoint: patient and transplant survival	RR 0.88 [0.57; 1.35]	17.7% vs. 20.1%	0.583
Cardiovascular morbidity and mortality	RR 0.67 [0.27; 1.69]	4.0% vs. 6.0%	0.476

Endpoint	Effect estimates [95% CI]	Incident rate [absolute risk reduction (ARR)] ¹	p-value
	Belatacept vs. ciclosporin A		
Aggregate endpoint: cardio-renal diseases	RR 0.91 [0.60; 1.39]	18.9% vs. 20.7%	0.720
Chronic kidney disease in CKD stage 4/5	RR 0.62 [0.45; 0.84] ²	27.1% vs. 44.1% ARR = 17.0% ³	0.0022 ³
Kidney function (cGFR)	Difference of means 10.70 ml/min/ 1.73 m ² [5.32; 16.08] ⁴		
Health-related quality of life			
Physical health aggregate score (SF 36)	Hedges'g 0.25 [0.02; 0.48] ⁵		0.034 ²
Mental health aggregate score (SF 36)	Hedges'g 0.04 [- 0.19; 0.27] ⁵		0.716 ²
Side effects			
Overall rate AE	RR 0.99 [0.98; 1.01]	99.4% vs. 100%	0.356
Overall rate SAE	RR 1.00 [0.90; 1.11]	79.4% vs. 79.3%	1.000
Terminations due to AE	RR 0.86 [0.58; 1.27]	20.6% vs. 23.9%	0.500
Post-transplant lymphoproliferative disorder	RR 4.78 [0.67; 34.21]	1.7% vs. 0.0%	0.079
Post-transplant diabetes mellitus	RR 1.03 [0.48; 2.20]	9.6% vs. 9.3%	0.994
Malignancies	RR 0.83 [0.44; 1.58]	8.6% vs. 10.3%	0.588
Infections	RR 1.00 [0.91; 1.10]	82.3% vs. 82.1%	1.000

¹ Figures shown for significant differences only

² Own calculation

³ Data from the hearing procedure by the pharmaceutical company

⁴ Data from dossier

⁵ Standardized difference of means as Hedges'g to assess relevance of statistically significant group difference.

Abbreviations used:

CI = confidence interval, RR = relative risk, ARR = absolute risk reduction, AE = adverse event, SAE = serious adverse event, CKD = chronic kidney disease

2. Number of patients or inclusion criteria for patients eligible for treatment

a) Patients who have received a transplant from a standard criteria donor (SCD).

Number: 1,847 – 2,123 patients

a) Patients who have received a transplant from an expanded criteria donor (ECD).

Number: 1,098 – 1,262 patients

3. Requirements for quality-assured administration

The specifications outlined in the product information are to be followed. The use of belatacept is limited to patients with de novo kidney transplants. Its use does not include a change in therapy from another immunosuppressive agent in patients with kidney transplants.

4. Costs of treatment

Costs of treatment are calculated based on the maintenance dosage.

Duration of treatment:

Description of therapy	Mode of treatment	Number of treatments per patient per year	Duration per treatment (days)	Number of treatment days per patient per year
Pharmaceutical evaluated				
Belatacept	every 4 weeks	ongoing	13	13
Mycophenolate mofetil	ongoing 2 x daily	ongoing	365	365
Prednisolone	ongoing 2 x daily	ongoing	365	365
Appropriate comparator				
Ciclosporin A	ongoing 2 x daily	ongoing	365	365
Mycophenolate mofetil	ongoing 2 x daily	ongoing	365	365
Prednisolone	ongoing 2 x daily	ongoing	365	365

Consumption:

Description of therapy	Strength (mg)	Number/amount per pack (bottles/tablets) ¹	Average annual consumption (bottles/tablets) ²
Pharmaceutical evaluated			
Belatacept	250 mg	2	26
Mycophenolate mofetil	500 mg	250	1,460
Prednisolone	5 mg	100	365
Appropriate comparator			
Ciclosporin A	50 mg	100	365
	100 mg	100	730
Mycophenolate mofetil	500 mg	250	1,460
Prednisolone	5 mg	100	365

Costs:

Cost of pharmaceutical:

Description of therapy	Strength (mg)	Cost (pharmacy retail price ¹)	Cost after legally mandated rebates
Pharmaceutical evaluated			
Belatacept	250 mg	€1,598.77	€1,395.44 [€2.05 ³ ; €201.28 ⁴]
Mycophenolate mofetil	500 mg	€527.99	€460.45 [€2.05 € ³ ; €65.49 ⁴]
Prednisolone	5 mg	€14.61 ²	€12.23 [€2.05 ³ ; €0.33 ⁴]
Appropriate comparator			
Ciclosporin A	50 mg	€236.89 ²	€216.93 [€2.05 ³ ; €17.91 ⁴]
	100 mg	€471.99 ²	€433.44 [€2.05 ³ ; €36.50 ⁴]
Mycophenolate mofetil	500 mg	€527.99	€460.45 [€2.05 € ³ ; €65.49 ⁴]

Description of therapy	Strength (mg)	Cost (pharmacy retail price ¹)	Cost after legally mandated rebates
Prednisolone	5 mg	€14.61 ²	€12.23 [€2.05 ³ ; €0.33 ⁴]

¹ Largest pack

² Reference price

³ Rebate in accordance with SGB V, section 130

⁴ Rebate in accordance with SGB V, section 130a

"Lauer-Taxe", effective 1 June 2012

Costs for additional, necessary statutory health insurance (SHI) benefits:

None

Annual treatment costs:

Description of therapy	Annual treatment costs per patient
Pharmaceutical evaluated	
Belatacept	€18,140.72
Mycophenolate mofetil	€2,689.03
Prednisolone	€44.64
Appropriate comparator	
Ciclosporin A	€3,955.91
Mycophenolate mofetil	€2,689.03
Prednisolone	€44.64

II.

Validity

1. This resolution takes effect on the day of its publication in the internet on the website of the Federal Joint Committee on 5 July 2012.

2. This resolution remains valid until 5 July 2015.

The justification for this resolution will be published on the website of the Federal Joint Committee at www.g-ba.de.

Berlin, 5 July 2012

The Federal Joint Committee in
accordance with SGB V, section 91

The Chair
Hecken