Resolution

Gemeinsamer Bundesausschuss

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 Osilodrostat (Endogenous Cushing's Syndrome)

of 7 January 2021

On 7 January 2021, the Federal Joint Committee (G-BA) resolved by written statement to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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 on 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 osilodrostat as follows:

Osilodrostat

Resolution of: 7 January 2021
Entry into force on: 7 January 2021
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 9 January 2020):

Isturisa is indicated for the treatment of endogenous Cushing's syndrome in adults.

Therapeutic indication of the resolution (resolution of 7 January 2021):

See therapeutic indication according to marketing authorisation

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

Osilodrostat is approved as a medicinal product for the treatment of a rare disease according to 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 patients with endogenous Cushing's syndrome

Extent of the additional benefit and significance of the evidence for osilodrostat:

Hint for a non-quantifiable additional benefit.

Study results according to endpoints:[1]

Adult patients with endogenous Cushing's syndrome

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No differences relevant for the benefit assessment.
Morbidity	↔	Overall, no differences relevant for the benefit assessment; advantage in normalisation of mean urinary free cortisol (mUFC, complete response).
Health-related quality of life	↔	No differences relevant for the benefit assessment.
Side effects	↔	Overall, no differences relevant for the benefit assessment; disadvantages for individual specific AE
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		

Study C2301[2]: Osilodrostat vs placebo (Randomised withdrawal period)

Mortality

Study C2301 Endpoint	Osilodrostat[a]		Placebo[b]		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference (AD)[c]
Overall mortality	36	0 (0)	34	0 (0)	-

(Continuation)

[1] Data from the dossier assessment by the G-BA (published on 15 October 2020) and from the amendment (from 9 December 2020) to the dossier assessment unless indicated otherwise.
[2] Results of the randomised withdrawal period of Study C2301: 8-week comparison of osilodrostat vs placebo.

Morbidity

Study C2301 Endpoint	Osilodrostat[a]		Placebo[b]		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference (AD)[c,f]
mUFC response					
Complete response[c] at Week 34	36	33 (91.7)	34	16 (47.1)	RR = 1.95 [1.35; 2.82]; p < 0.001 AD = 44.6%
EQ-5D-VAS					
No data[g]					
BDI-II					
No data[g]					

(Continuation)

Health-related quality of life

Study C2301 Endpoint	Osilodrostat[a]		Placebo[b]		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference (AD)[c,f]
CushingQoL					
No data[g]					

(Continuation)

Side effects

Study C2301 Endpoint	Osilodrostat[a]		Placebo[b]		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference (AD)[c]
Adverse events in total					
	36	26 (72.2)	34	23 (67.6)	-
Serious adverse events (SAE)					

Study C2301 Endpoint	Osilodrostat[a]		Placebo[b]		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference (AD)[c]
	36	2 (5.6)	34	1 (2.9)	RR = 1.89 [0.18; 19.89]; p = 0.609
Severe adverse events (CTCAE grade 3 or 4)					
	36	2 (5.6)	34	3 (8.8)	RR = 0.63 [0.11; 3.54]; p = 0.612
Therapy discontinuations because of adverse events					
	36	0 (0)	34	2 (5.9)	n.c.
AE with an incidence ≥ 10%[i] **MedDRA System Organ Class** Preferred Term					
Gastrointestinal disorders	36	8 (22.2)	34	5 (14.7)	RR = 1.51 [0.55; 4.17]; p = 0.433[h]
Nausea	36	4 (11.1)	34	0 (0)	n.c.
General disorders and administration site conditions	36	6 (16.7)	34	5 (14.7)	RR = 1.13 [0.38; 3.37]; p = 0.833[h]
Infections and infestations	36	5 (13.9)	34	7 (20.6)	RR = 0.67 [0.24; 1.92]; p = 0.471[h]
Investigations	36	7 (19.4)	34	3 (8.8)	RR = 2.20 [0.62; 7.84]; p = 0.224[h]
AE of special interest[j]					
AE associated with hypocortisolism	36	3 (8.3)	34	1 (2.9)	RR = 2.83 [0.31; 25.93]; p = 0.363
AE associated with accumulation of adrenal hormone precursor(s).	36	2 (5.6)	34	1 (2.9)	RR = 1.89 [0.18; 19.89]; p = 0.609

Study C2301 Endpoint	Osilodrostat[a]		Placebo[b]		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference (AD)[c]

a. Patients who met the randomisation criteria at Week 26 and were randomised to the osilodrostat arm in which osilodrostat was administered in a controlled manner through Week 34 and received at least one dose of study medication during the RW period.

b. Patients who met the randomization criteria at Week 26 and were randomised to the placebo arm by Week 34 and received at least one dose of study medication during the RW period.

c. Absolute difference (AD) given only in the case of a statistically significant difference; own calculation

d. Complete response is defined as mUFC ≤ ULN with no therapy discontinuation in the RW period. A dose increase in the randomised period did not result in classification as a non-responder. Missing values were classified as non-response. However, no information is available on the proportion of missing values (see Table 8 of the benefit assessment).

e. Data source: Module 4

f. 95% CIs are based on the Clopper-Pearson exact method; p values are based on Fisher's exact test.

g. Because of a lack of traceability of the evaluations and inconsistencies between the study report and Module 4, no results can be used for the comparative study phase.

h. Data source: Module 4 No information is available on the static methods used.

i. AE with an incidence ≥ 10% during the randomised withdrawal period.

Abbreviations used:

AD: absolute difference; BDI-II: Beck Depression Inventory-II; CTCAE = Common Terminology Criteria for Adverse Events; CushingQoL: Cushing's Disease Health-Related Quality of Life; EQ-5D-VAS: visual analogue scale of the European Quality of Life 5 Dimensions; HR: Hazard Ratio; CI: confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; mUFC: mean free cortisol in urine; MV: mean value; N: number of patients evaluated; n: number of patients with (at least one) event; n.c. : not calculable; n. a.: not achieved; RAS: Randomised Analysis Set; RR: relative risk; RW: Randomised Withdrawal; SASR: Safety Analysis Set Randomised; SD: standard deviation; (S)AE: (serious) adverse event(s); ULN: upper limit of the normal range; vs: versus.

Study C2301[3]: Osilodrostat treatment (non-comparative evaluation over the entire course of the study)

Mortality

Study C2301 Endpoint	Osilodrostat[a]	
	N	Patients with event n (%)
Overall mortality	137	2 (1.5)

(Continuation)

Morbidity

Study C2301 Endpoint	Osilodrostat[a]	
	N	Patients with event n (%)
Complete mUFC response[g,h] at Week 48	137	91 (66.4)
	N	MV (SD)
EQ-5D-VAS[b] at Week 48 Absolute value at Week 48 Absolute change compared with baseline	109	 72.7 (17.90) 9.8 (17.24)
BDI-II[c] at Week 48 Absolute value at Week 48 Absolute change compared with baseline	110	 10.7 (10.66) −5.8 (9.45)

(Continuation)

Health-related quality of life

Study C2301 Endpoint	Osilodrostat[a]	
	N	MV (SD)
CushingQoL[d] at Week 48		
Total score Absolute value at Week 48 Absolute change compared with baseline	110	 58.3 (21.28) 14.1 (16.86)
"Psychosocial issues" sub-scale Absolute value at Week 48 Absolute change compared with baseline	110	 57.9 (22.35) 12.7 (17.39)
"Physical problems" sub-scale Absolute value at Week 48 Absolute change compared with baseline	110	 59.5 (24.28) 18.3 (21.99)

(Continuation)

Side effects

[3] Non-comparative evaluation over the entire course of Study C2301. All patients included in the study with at least one dose of osilodrostat. Patients who received placebo during the RW period are included at the respective time points with all their data – regardless of whether they received osilodrostat or placebo at that time point. The median treatment duration with osilodrostat was 130 weeks.

Study C2301 **Endpoint**	Osilodrostat[a]		
	N	Patients with event n[e,f] (%)	
Adverse events			
AE CTCAE grade ≥ 3	137	83 (60.6)	
Serious adverse events (SAE)			
SAE	137	55 (40.1)	
Therapy discontinuations because of adverse events			
AE leading to therapy discontinuation	137	25 (18.2)	
AE of any severity with incidence ≥ 10% and severe AE with incidence ≥ 5%.			
MedDRA System Organ Class Preferred Term	N	**All severities** n (%)	**Severity ≥ 3** n (%)
Blood and lymphatic system disorders	137	**22 (16.1)**	**-**
Anaemia	137	15 (10.9)	**-**
Cardiac disorders	137	26 (19.0)	**-**
Endocrine disorders	137	**74 (54.0)**	**17 (12.4)**
Adrenal insufficiency	137	40 (29.2)	**-**
Glucocorticoid deficiency	137	28 (20.4)	**-**
Gastrointestinal disorders	137	**99 (72.3)**	**15 (10.9)**
Nausea	137	62 (45.3)	**-**
Vomiting	137	34 (24.8)	**-**
Diarrhoea	137	27 (19.7)	**-**
Abdominal pain	137	18 (13.1)	**-**
Dyspepsia	137	15 (10.9)	**-**
General disorders and administration site conditions	137	**95 (69.3)**	**-**
Fatigue	137	45 (32.8)	**-**
Asthenia	137	27 (19.7)	**-**
Peripheral oedema	137	22 (16.1)	**-**
Pyrexia	137	21 (15.3)	**-**
Infections and infestations	137	**100 (73.0)**	**13 (9.5)**
Nasopharyngitis	137	33 (24.1)	**-**
Influenza	137	26 (19.0)	**-**
Urinary tract infection	137	25 (18.2)	**-**

Study C2301 **Endpoint**	Osilodrostat[a]		
	N	Patients with event n[e,f] (%)	
Upper respiratory tract infections	137	14 (10.2)	-
Injury, poisoning, and procedural complications	137	**42 (30.7)**	**8 (5.8)**
Investigations	137	**86 (62.8)**	**18 (13.1)**
Blood corticotropin increased	137	28 (20.4)	-
Hormone level abnormal	137	18 (13.1)	-
Blood testosterone increased	137	16 (11.7)	-
Metabolism and nutrition disorders	137	**65 (47.4)**	**15 (10.9)**
Reduced appetite	137	22 (16.1)	-
Hypocalcaemia	137	18 (13.1)	-
Benign, malignant, and non-specific neoplasms	137	**30 (21.9)**	**12 (8.8)**
Nervous system disorders	137	**81 (59.1)**	**12 (8.8)**
Headaches	137	50 (36.5)	-
Dizziness	137	26 (19.0)	-
Psychiatric disorders	137	**45 (32.8)**	-
Renal and urinary disorders	137	**14 (10.2)**	-
Reproductive system and breast disorders	137	**29 (21.2)**	-
Respiratory, thoracic and mediastinal disorders	137	**52 (38.0)**	-
Coughing	137	20 (14.6)	-
Oropharyngeal pain	137	14 (10.2)	-
Skin and subcutaneous tissue disorders	137	**77 (56.2)**	-
Rash	137	21 (15.3)	-
Vascular disorders	137	**44 (32.1)**	**17 (12.4)**
High blood pressure	137	24 (17.5)	16 (11.7)
SAE with incidence ≥ 5% Preferred Term			
Adrenal insufficiency	137	8 (5.8)	
AE of special interest Preferred Term			
AE associated with hypocortisolism	137	74 (54.0)	

Study C2301 **Endpoint**	Osilodrostat[a]	
	N	Patients with event n[e,f] (%)
AE associated with accumulation of adrenal hormone precursors.	137	80 (58.4)
AE associated with enlargement of the pituitary tumour	137	22 (16.1)
AE associated with QT prolongation/ AE with arrhythmogenic potential	137	6 (4.4)

a. All patients included in the study with at least one dose of osilodrostat. The median treatment duration with osilodrostat was 130 weeks.
b. EQ-5D-VAS: Scale from 0 to 100. The higher the value, the better the health status.
c. BDI-II: Scale from 0 to 63. Higher values indicate more severe depression.
d. CushingQoL: Scale from 0 to 100 in each case. The higher the value, the better the quality of life.
e. All patients included with at least one dose of osilodrostat and an assessment of safety/tolerability at post-baseline.
f. AE that occurred during the RW period on placebo were not included in the analysis.
g. Complete response is defined as mUFC ≤ ULN.
h. All patients included in the study with at least one dose of osilodrostat (FAS). Patients randomised to placebo during the RW period had all their data included in the analysis regardless of whether they were treated with osilodrostat or placebo at the time point.

Abbreviations used:
AD: absolute difference; BDI-II: Beck Depression Inventory-II; CTCAE = Common Terminology Criteria for Adverse Events; CushingQoL: Cushing's Disease Health-Related Quality of Life; EQ-5D-VAS: visual analogue scale of the European Quality of Life 5 Dimensions; FAS: Full Analysis Set; HR = Hazard Ratio; CI = confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; mUFC: mean free cortisol in urine; MV: mean value; N: number of patients evaluated; n: number of patients with (at least one) event; n.c. : not calculable; n. a.: not achieved; RAS: Randomised Analysis Set; RR: relative risk; RW: Randomised Withdrawal; SASR: Safety Analysis Set Randomised; SD: standard deviation; (S)AE: (serious) adverse event(s); ULN: upper limit of the normal range; vs: versus.

Study C2302[4]: Osilodrostat vs placebo (12-week comparison)

Mortality

Study C2302 Endpoint	Osilodrostat[a]		Placebo[a]		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference (AD)[b]
Overall mortality	48	0 (0)	25	0 (0)	-

(Continuation)

Morbidity

Study C2302 Endpoint	Osilodrostat[a]		Placebo[a]		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference (AD)[b]
mUFC response					
Complete response[c] at Week 12	48	37 (77.1)	25	2 (8.0)	RR = 9.64 [2.53; 36.73]; p < 0.0001[d] AD = 69.1%
C-SSRS[k]					
Suicidal tendency (completed suicide)	48	0 (0.0)	25	0 (0.0)	-
Suicide attempts	48	0 (0.0)	25	0 (0.0)	-
Preparatory acts or preparatory behaviour for suicidal acts	48	1 (2.1)	25	0 (0.0)	-
Suicidal thoughts[l]	48	4 (8.3)	25	0 (0.0)	-
Self-harming behaviour without suicidal intent	48	1 (2.1)	25	0 (0.0)	-

[4] Results of the 12-week randomised, double-blind, placebo-controlled period of Study C2302.

	N	Absolute value MV (SD)	N	Absolute value MV (SD)	Adjusted mean difference [95% CI]
EQ-5D-VAS[f]					
Baseline	48	70.3 (17.3)	23	76.7 (17.9)	
Week 12	45	71.0 (18.5)	23	76.4 (16.7)	
Change compared with baseline					
MV (SD)		0.5 (13.6)		−0.3 (10.5)	
LS mean [95% CI]		−0.84 [−4.61; 2.93][e]		0.83 [−4.54; 6.20][e]	−1.67 [−8.26; 4.92][e]
BDI-II[g]					
Baseline	48	12.2 (10.2)	25	8.4 (7.8)	
Week 12	46	10.3 (8.5)	24	4.7 (6.1)	
Change compared with baseline					
MV (SD)		−1.4 (8.0)		−3.9 (5.4)	
LS mean [95% CI]		−1.10 [−2.68; 0.49][h]		−4.74 [−6.94; −2.54][h]	3.64 [0.92; 6.37][h]

(Continuation)

Health-related quality of life

Study C2302 Endpoint	Osilodrostat[a]		Placebo[a]		Intervention vs control
	N	Absolute value MV (SD)	N	Absolute value MV (SD)	Adjusted mean difference [95% CI]
CushingQoL[i]					
Total score					
Baseline	48	49.1 (19.6)	25	56.9 (19.0)	
Week 12	46	56.1 (22.1)	24	65.6 (17.6)	
Change compared with baseline					
MV (SD)		6.2 (14.9)		8.6 (12.1)	
LS mean [95% CI]		5.65 [2.18; 9.13][h,j]		9.42 [4.59; 14.25][h,j]	−3.77 [−9.75; 2.21][h,j]
"Psychosocial issues" sub-scale					
Baseline	48	49.9 (20.3)	25	56.7 (21.1)	
Week 12	46	56.8 (23.3)	24	66.4 (19.5)	
Change compared with baseline					
MV (SD)		6.1 (17.2)		9.6 (13.6)	
LS mean [95% CI]		no data available		no data available	no data available

Study C2302 Endpoint	Osilodrostat[a]		Placebo[a]		Intervention vs control
	N	Absolute value MV (SD)	N	Absolute value MV (SD)	Adjusted mean difference [95% CI]
"Physical problems" sub-scale					
Baseline	48	46.9 (22.3)	25	57.7 (21.9)	
Week 12	46	54.0 (23.4)	24	63.2 (18.2)	
Change compared with baseline					
MV (SD)		6.3 (13.3)		5.6 (13.4)	
LS mean [95% CI]		no data available		no data available	no data available

(Continuation)

Side effects

Study C2302 Endpoint	Osilodrostat[k]		Placebo[k]		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference (AD)[m]
Adverse events in total					
	48	46 (95.8)	25	23 (92.0)	-
Serious adverse events (SAE)					
	48	2 (4.2)	25	1 (4.0)	RR = 1.04 [0.10; 10.94]; p = 1.000
Severe adverse events (CTCAE grade 3 or 4)					
	48	10 (20.8)	25	5 (20.0)	RR = 1.04 [0.40; 2.72]; p = 1.000
Therapy discontinuations because of adverse events					
	48	1 (2.1)	25	0 (0.0)	RR = 1.59 [0.07; 37.71]; p = 0.544
AE with an incidence ≥ 10%[n] **MedDRA System Organ Class** Preferred Term					
Cardiac disorders Tachycardia	48	7 (14.6)	25	0 (0.0)	n.c.

Study C2302 Endpoint	Osilodrostat[k]		Placebo[k]		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference (AD)[m]
Endocrine disorders	48	**8 (16.7)**	25	0 (0.0)	**9.02 [0.54; 150.16]; 0.044** AD = 16.7%
Adrenal insufficiency	48	7 (14.6)	25	0 (0.0)	7.96 [0.47; 133.92]; 0.045 AD = 14.6%
Gastrointestinal disorders	48	**26 (54.2)**	25	**5 (20.0)**	**2.71 [1.19; 6.19]; 0.006** AD = 34.2%
Diarrhoea	48	10 (20.8)	25	0 (0.0)	11.14 [0.68; 182.67] 0.012 AD = 20.8%
General disorders and administration site conditions Asthenia	48	11 (22.9)	25	0 (0.0)	12.20 [0.75; 198.93] 0.006 AD = 22.9%
Musculoskeletal and connective tissue disorders	48	**24 (50.0)**	25	**5 (20.0)**	**2.50 [1.09; 5.75]; 0.022 AD = 30.0%**
Arthralgia	48	17 (35.4)	25	2 (8.0)	4.43 [1.11; 17.65] 0.012 AD = 27.4%
Myalgia	48	11 (22.9)	25	1 (4.0)	5.73 [0.78; 41.88] 0.048 AD = 18.9%
AE of CTCAE grade ≥ 3 with an incidence ≥ 5% MedDRA System Organ Class					

Study C2302 Endpoint	Osilodrostat[k]		Placebo[k]		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference (AD)[m]
Preferred Term					
Musculoskeletal and connective tissue disorders		**3 (6.3)**		**0**	**3.71 [0.20; 69.20]; 0.292**
Vascular disorders		**4 (8.3)**		**4 (16.0)**	0.52 [0.14; 1.91]; 0.433
High blood pressure		4 (8.3)		4 (16.0)	0.52 [0.14; 1.91]; 0.433
AE of special interest[j]					
AE associated with hypocortisolism					
All grades	48	7 (14.6)	25	0 (0.0)	RR = 7.96 [0.47; 133.92]; p = 0.045 AD = 14.6%
CTCAE grade ≥ 3	48	0 (0.0)	25	0 (0.0)	-
AE associated with accumulation of adrenal hormone precursor(s).					
All grades	48	21 (43.8)	25	9 (36.0)	RR = 1.22 [0.66; 2.24]; p = 0.619
CTCAE grade ≥ 3	48	5 (10.4)	25	4 (16.0)	n.c.

a. Full Analysis Set
b. Absolute difference (AD) given only in the case of a statistically significant difference; own calculation.
c. Complete response at Week 12 is defined as mUFC ≤ ULN (determined in the central laboratory). Study discontinuation during the randomised period and missing mUFC values for Week 12 were considered non-response. Dose reductions or temporary interruptions in administration of medication for safety reasons did not result in categorisation as non-response.
d. RR was determined by four-field table; CI was estimated by the Wald method; p values are based on Fisher's exact test.
e. Linear mixed model (change from baseline = baseline value + randomised treatment + error)
f. EQ-5D-VAS: Scale from 0 to 100. The higher the value, the better the health status.
g. BDI-II: Scale from 0 to 63. Higher values indicate more severe depression.

Study C2302 Endpoint	Osilodrostat[k]		Placebo[k]		Intervention vs control
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value Absolute difference (AD)[m]

h. Linear mixed model (change from baseline = baseline value + randomised treatment + week + randomised treatment×week + error)
i. CushingQoL: Scale from 0 to 100. Higher values mean a better quality of life.
j. It is assumed that the results of the linear mixed model on CushingQoL refer to the total score. An evaluation using the linear mixed model is available for only one scale. Information on the specification of this scale beyond "CushingQoL score" was not identified.
k. Safety analysis set
l. Study participants with suicidal thoughts assessed the "wish to be dead" item as "yes".
m. RR was determined by four-field table. If no event was observed in a study arm (null cells), a continuity correction was applied with a correction value of 0.5 for each of the cells. CI were estimated using the Wald method and p value was calculated using Fisher exact method.
n. AE with an incidence ≥ 10% in a study arm. Only results showing statistically significant differences between treatment arms were presented.

Abbreviations used:

AD: absolute difference; BDI-II: Beck Depression Inventory-II; CTCAE = Common Terminology Criteria for Adverse Events; CushingQoL: Cushing's Disease Health-Related Quality of Life; EQ-5D-VAS: visual analogue scale of the European Quality of Life 5 Dimensions; FAS: Full Analysis Set; HR = Hazard Ratio; CI = confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; mUFC: mean free cortisol in urine; MV: mean value; N: number of patients evaluated; n: number of patients with (at least one) event; n.c. : not calculable; n. a.: not achieved; RAS: Randomised Analysis Set; RR: relative risk; RW: Randomised Withdrawal; SASR: Safety Analysis Set Randomised; SD: standard deviation; (S)AE: (serious) adverse event(s); ULN: upper limit of the normal range; vs: versus.

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

Adult patients with endogenous Cushing's syndrome

approx. 1,130 to 1,550 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 Isturisa (active ingredient: osilodrostat) at the following publicly accessible link (last access: 10 December 2020):
https://www.ema.europa.eu/documents/product-information/isturisa-epar-product-information_de.pdf

4. Treatment costs

Annual treatment costs:

Adult patients with endogenous Cushing's syndrome

Designation of the therapy	Annual treatment costs/patient
Osilodrostat	€ 43,851.10 – 269,985.39

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 December 2020

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 7 January 2021.

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

Berlin, 7 January 2021

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken