Justification

Gemeinsamer Bundesausschuss

to 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 Osilodrostat (Endogenous Cushing's Syndrome)

of 7 January 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 in accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy need not 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, Nos. 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 during the last 12 calendar months. In accordance with 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 in accordance with Chapter 5, Section 5, paragraphs 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 compared 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). On the basis of the statutory requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is deemed to have been proven through the grant of 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, in the case of 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 provided is assessed exclusively on the basis of the pivotal 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 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 of 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 market of the active ingredient osilodrostat in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 July 2020. 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, number 1 VerfO on 15 July 2020.

Osilodrostat for the treatment of endogenous Cushing's syndrome 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.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half 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 by the G-BA on the basis of the pivotal studies.

The G-BA carried out the benefit assessment and commissioned the IQWiG to assess 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 October 2020 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 carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G20-14) prepared by IQWiG, and the written statements submitted in the written and oral hearing procedure as well as the amendment to the benefit assessment prepared by the G-BA.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for marketing authorisation with regard to their therapeutic relevance (qualitative) according to 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 set aside in the benefit assessment of osilodrostat.

In the light of the above and taking into account the written statements received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Osilodrostat (Isturisa) in accordance with the product information

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 General Methods, Version 6.0 dated 5 November 2020. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

2.1.2 Extent of the additional benefit and significance of the evidence

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

For osilodrostat for the treatment of endogenous Cushing's syndrome in adults, there is a hint for a non-quantifiable additional benefit.

Justification:

For the benefit assessment according to Section 35a SGB V, the pharmaceutical company submits in the dossier the pivotal Study C2301 and Study C1201 as well as an unadjusted indirect comparison against pasireotide. The pharmaceutical company also submits the results of Study C2302 in the written statement procedure; these were not yet available at the time of dossier preparation.

Study C2301

Study C2301 is a multi-centre study consisting of 4 phases with a randomised withdrawal design. The study included 137 patients with confirmed Cushing's disease (persistent or recurrent) between the ages of 18 and 75 years. Patients had *mean urinary free cortisol* (mUFC) > 1.5 × the *upper limit of normal* (ULN) at the screening time point. In addition, patients with *de novo* Cushing's syndrome were included if they were not eligible for surgery. Excluded patients included female or male patients with Cushing's syndrome resulting from ectopic ACTH secretion or ACTH-independent (adrenal) Cushing's syndrome.

At the start of study, all patients received osilodrostat. In the single-arm 1st phase, patient-individual dose titration of osilodrostat was performed over 12 weeks (2–30 mg bid based on the mean of the triple determination of mUFC). In the subsequent single-arm 2nd phase, further treatment with osilodrostat was given at the dose defined in 1st phase (Weeks 13 to 24). At the start of Phase 3, all patients who met the randomisation criteria were randomised (1:1) to receive either continued osilodrostat or placebo for 8 weeks (*randomised withdrawal* (RW) phase, Weeks 26 to 34). A total of 66 patients were not randomised. In the single-arm, open-label 4th phase, all patients received osilodrostat at doses determined by the study personnel (Week 35 to 48). Subsequently, all patients were eligible to cross over into an open-label extension study until Week 72 with osilodrostat. The primary endpoint of the study was complete response at the end of the 8-week randomised period (defined as mUFC ≤ ULN at Week 34 with no therapy discontinuation and no dose increase during the randomised period).

In study C2301, patients were on average 41 years old at the start of study, and the median time of initial diagnosis was approximately 4 years before inclusion in the study. A large proportion of the individuals was female (75%). 88% of patients had persistent or recurrent and 12% had *de novo* Cushing's syndrome. 75% of the patients included had received prior therapy for Cushing's syndrome before the start of study (31% with cabergoline, 36% with ketoconazole, 10% with metyrapone, and 31% pasireotide). Before the start of study, this had to be discontinued, and a wash-out period defined in each case had to be completed. The mean mUFC value at the start of study was 1006 nmol/24 h with a median of 476 nmol/24 h (36–9612 nmol/24 h).

Study C2302

The multi-centre Study C2302 consists of a 12-week randomised, double-blind, placebo-controlled period (Weeks 1 to 12), a subsequent 36-week open-label, uncontrolled treatment period with osilodrostat (Weeks 13 to 48), and an optional extension period to investigate the efficacy and safety of osilodrostat for CD. The inclusion criteria for Study C2302 are very similar to that of Study C2301: 74 patients with confirmed Cushing's disease (persistent or recurrent) between the ages of 18 and 75 years with an mUFC value > 1.3 × ULN at the time of screening were included. Study C2302 also allowed patients with *de novo* Cushing's syndrome to be included if they were not eligible for surgery; excluded patients included female or male patients with Cushing's syndrome resulting from ectopic ACTH secretion or ACTH-independent (adrenal) Cushing's syndrome.

At the start of the placebo-controlled period, patients were randomised at a 2:1 ratio to receive either patient-individual osilodrostat dose titration (2–20 mg bid) or placebo treatment with mock dose titration (simulated dose titration sequence) for 12 weeks. In the subsequent single-arm treatment period, all patients received osilodrostat (dose titration of 2–30 mg bid possible) for 36 weeks. Subsequently, all patients for whom continued clinical benefit was established were eligible to cross over into the open-label extension study until Week 96. The primary endpoint of the study was complete response mUFC ≤ ULN at Week 12.

Patients in Study C2302 were on average approx. 42 and 39 years old at the start of study with a median of approx. 5.8 and 5.4 years of initial diagnosis prior to inclusion in the study (in the osilodrostat and placebo arms). A large proportion of subjects were female (90% in the osilodrostat arm and 72% in the placebo arm), and almost all patients had persistent or recurrent Cushing's syndrome (94% in the osilodrostat arm and 100% in the placebo arm). Previous therapies for Cushing's syndrome included ketoconazole, cabergoline, metyrapone, pasireotide, and lanretide. Before the start of study, this had to be discontinued, and a wash-out period defined in each case had to be completed. In the osilodrostat and placebo arm, the mean mUFC value at the start of study was 421 and 452 nmol/24 h, respectively with a median of 342 nmol/24h (90–1720 nmol/24 h) and 298 nmol/24 h (21–2607 nmol/24 h), respectively.

Study C1201

Study C1201 is an open-label, single-arm, multi-centre Phase II study in 9 Japanese adults with Cushing's syndrome as a result of adrenal adenoma (n = 5), ectopic corticotropin syndrome (n = 3), or ACTH-independent macronodular hyperplasia of the adrenal glands (n = 1). However, because of the low patient numbers, the uncontrolled data from the study are not suitable for deriving the extent of the additional benefit.

Unadjusted, indirect comparison

The pharmaceutical company presented an unadjusted indirect comparison of osilodrostat with pasireotide in Cushing's disease in the dossier. For this purpose, the results of Study C2301 (osilodrostat) and Study CSOM230B2305 (pasireotide) will be used with the aim of comparatively presenting the uncontrolled results of the first 24 and 26 weeks of Study C2301 exclusively for the endpoint "mean urinary free cortisol". However, because of the lack of a bridge comparator and the lack of rationale for the comparability of the two study populations, the indirect comparison is associated with a very high risk of bias and is therefore not suitable for deriving the extent of the additional benefit.

Results of Studies C2301 and C2302:

Mortality

No deaths occurred in the 8-week comparison of osilodrostat vs placebo in the randomised withdrawal (RW) period of Study C2301. In the subsequent open-label treatment phase with osilodrostat, 2 subjects had died by Week 48.

No deaths occurred in the randomised phase of Study C2302 through Week 12.

Morbidity

Mean urinary free cortisol (mUFC response)

Normalisation of pathologically elevated cortisol (mean urinary free cortisol, mUFC) to below the upper limit of normal (ULN) is a clinically significant parameter in the indication of Cushing's syndrome as a therapy goal.

In Study C2301, the endpoint of complete response (defined as mUFC ≤ ULN with no therapy discontinuation in the RW period) showed a statistically significant change at the end of the RW period (Week 34) in favour of osilodrostat compared with placebo (91.7% vs 47.1%; RR = 1.9, 95% CI [1.35; 2.82]; $p < 0.001$). At Week 48, 66.4% of patients had a complete response (open-label treatment phase with osilodrostat).

In the randomised phase of Study C2302, the endpoint of complete response (defined as mUFC ≤ ULN with no therapy discontinuation by Week 12) showed a statistically significant change in favour of osilodrostat compared with placebo (77.1% vs 8.0%; RR = 9.64, 95% CI [2.53; 36.73]; $p < 0.0001$).

The results of both studies suggest that cortisol levels reach the normal range and that pathologically altered cortisol levels are stabilised by treatment with osilodrostat.

Health status (EQ-5D-VAS)

In the two studies, the global estimation of health status was surveyed using the EQ-5D VAS (*Euro Quality Visual Analogue Scale*). This scale can take a score from 0 to 100; higher scores mean a better health status.
Because of the lack of traceability of the evaluations and because of inconsistencies between the study report and Module 4 and the written statement of the pharmaceutical company, the results on the EQ-5D VAS for the 8-week comparison of osilodrostat vs placebo in the RW period of Study C2301 cannot be used. At Week 48 of the open-label treatment phase with osilodrostat, mean EQ-5D VAS scores were approx. 73 points. The health status of the patients thus improved by approx. 10 points compared with the start of study. However, in the absence of a comparator arm, no assessment of the effect is possible.

In the two study arms of Study C2302, the mean scores at the start of study were approx. 70 and 77 points and at Week 12 approx. 71 and 76 points (osilodrostat and control arm, respectively). Results were not statistically significantly different between treatment groups.

Severity of a depression (BDI-II)

In both studies, the severity of depression was assessed using the BDI-II *(Beck Depression Inventory-II)* questionnaire*.* The self-assessment questionnaire in adults and adolescents 13 years and older consists of 21 questions that survey the severity of each symptom during the past two weeks and can take scores from 0 to 63. Higher values indicate more severe depression.
Because of the lack of traceability of the evaluations and because of inconsistencies between the study report and Module 4 and the written statement of the pharmaceutical company, the results on the BDI-II for the 8-week comparison of osilodrostat vs placebo in the RW period of Study C2301 also cannot be used. The results of the open-label treatment phase with osilodrostat show that mean BDI-II scores at Week 48 decreased by approx. 6 points

compared with the start of study. However, in the absence of a comparator arm, no assessment of the effect is possible.

In Study C2302, BDI-II scores averaged approx. 12 and 8 points at the start of study and approx. 10 and 5 points at Week 12 (osilodrostat and control arm, respectively). The adjusted mean difference was 3.64, 95% CI [0.92; 6.37], thereby indicating a statistically significant difference between treatment groups in the severity of depression to the detriment of osilodrostat. The clinical relevance of these differences cannot be judged.

Suicidal thoughts, suicidal behaviour (C-SSRS)

The standardised clinical interview C-SSRS (*Columbia-Suicide Severity Rating Scale*) can be used to assess whether patients exhibit suicidal thoughts, suicidal behaviour, or self-harming behaviour without suicidal intent.
This endpoint was not surveyed in Study C2301.

In Study C2302, only patients in the osilodrostat arm had suicidal thoughts or behaviour.

Interim summary of morbidity

For the morbidity endpoint, there are statistically significant results for normalisation of mean urinary free cortisol (mUFC, complete response) in favour of osilodrostat in Studies C2301 and C2302. In addition, the results of Study C2302 show a statistically significant difference in the BDI-II (an instrument for self-assessment of the severity of depression) to the detriment of osilodrostat compared with placebo. However, the clinical relevance of these differences cannot be judged.

For the endpoints health status (EQ-5D-VAS) and severity of depression (BDI-II), no comprehensible evaluations were available for the comparative data in Study C2301. The results of the non-comparative data show improvements up to Week 48 compared with the start of study. However, because of the lack of a comparator arm, no assessment of the effect is possible. With respect to health status (EQ-5D VAS), Study C2302 showed no statistically significant differences between treatment groups. The endpoint suicidal thoughts, suicidal behaviour (C-SSRS) was recorded only in Study C2302. In this study, only patients in the osilodrostat arm had suicidal thoughts or suicidal behaviour.

Quality of life

CushingQoL

The Cushing's Disease Health-Related Quality of Life (CushingQoL) questionnaire was used in both studies to assess quality of life in patients with Cushing's syndrome. Consisting of 12 items, the following topics are surveyed: daily activities, healing and pain, mood and self-confidence, social concerns, physical appearance, memory, and concerns about the future. The results are depicted on a total score and two sub-scores (sub-scales "Physical problems" and "Psychosocial issues"), each on a scale from 0 to 100. Higher values mean a better quality of life.

Because of the lack of traceability of the evaluations and because of inconsistencies between the study report and Module 4 and the written statement of the pharmaceutical company, the results on the CushingQoL for the 8-week comparison of osilodrostat vs placebo in the RW period of Study C2301 also cannot be used. The results of the open-label treatment phase with osilodrostat show an improvement in quality if life: the mean CushingQoL scores at the start of study averaged approx. 42 points and at Week 48 approx. 58 points. Similar results

were found for the sub-scales “Physical problems” and “Psychosocial issues”. However, in the absence of a comparator arm, no assessment of the effect is possible.

In Study C2302, the values of the CushingQoL total score at the start of study averaged approx. 49 or 57 points. After the 12-week treatment period, there was an improvement in quality of life in both study arms (56 points in the osilodrostat and 66 points in the control arm). However, the results are not statistically significantly different between the treatment groups. Similar changes are seen in the “Physical problems” and “Psychosocial issues” sub-scales.

Side effects

In Studies C2301 and C2302, adverse events (AE) were surveyed in a standardised manner in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) using the system organ class (SOC) and preferred terms (PT). The evaluations of study C2301 are based on all patients who received at least one dose of osilodrostat for whom a post-baseline safety/tolerability assessment is available. In the analysis of uncontrolled data from Study C2301, AE that occurred during the RW period under treatment with placebo were not included. Study C2302 included all randomised patients who received at least one dose of study medication (osilodrostat or placebo).

In both studies, AE were surveyed up to 30 days after administration of the last dose; however, no specific data on the observation period are available. The median treatment duration was approx. 130 weeks (entire study) and 8 weeks (RW period) in Study C2301 and 12 weeks in both treatment groups in Study C2302.

In both the randomised phase (RW period) and the open-label treatment phase of Study C2301, the following common AE (AE of any severity with an incidence ≥ 10%) according to MedDRA-SOC occurred: gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, and investigations; however, there were no statistically significant results between treatment groups in the RW period. Furthermore, in the open-label treatment phase with osilodrostat, endocrine disorders (SOC) were still very common.

In Study C2302, the following AE of any severity occurred more frequently in the osilodrostat arm: Cardiac disorders (PT tachycardia: 7 events (14.6%) in the osilodrostat arm vs no event in the control arm), endocrine disorders (especially PT adrenal insufficiency: 7 (14.6%) vs 0 events), gastrointestinal disorders (especially PT diarrhoea: 10 (20.8%) vs 0 events), general disorders and administration site conditions (especially PT asthenia: 11 (22.9%) vs 0 events), musculoskeletal and connective tissue disorders (especially PT arthralgia: 17 (35.4%) vs 2 events (8.0%) and PT myalgia: 11 (22.9%) vs 1 event (4.0%)). These results were statistically significantly different between treatment groups to the detriment of osilodrostat.

Severe AE and serious adverse events (SAE)

Severe AE occurred in 5.6% of patients in the osilodrostat arm and in 8.8% of patients in the control arm during the RW period of Study C2301. The most frequent severe AE were endocrine disorders (SOC), investigations (SOC), and vascular disorders (SOC) and occurred in approx. 12–13% of patients by the end of Study C2301.

There were no statistically significant differences in the overall rate of serious adverse events (SAE) between treatment groups during the RW period of Study C2301 (5.6% in the osilodrostat arm vs 2.9% in the control arm). By the end of Study C2301, approx. 40% of patients experienced an SAE; the most common SAE was adrenal insufficiency (PT) (5.8% of patients).

In Study C2302, severe AE occurred in approx. 20% of patients in both treatment arms. Common severe AE were musculoskeletal and connective tissue disorders (SOC, 3 events (6.3%) in the osilodrostat arm vs no event in the control arm) and vascular disorders (PT

hypertension: 4 (8.3%) vs 4 (16.0%) events). No statistically significant differences were seen between treatment groups.

During the 12-week treatment phase of Study C2302, SAE occurred in approx. 4% of the patients.

Therapy discontinuation because of AE

Adverse events leading to discontinuation of treatment occurred infrequently during the RW period of Study C2301; by the end of Study C2301, 18.2% of patients had discontinued treatment because of AE.

In Study C2302, AE leading to discontinuation of treatment also occurred infrequently.

AE of special interest

The following AE of special interest occurred by the end of the open-label treatment phase in Study C2301: AE associated with hypocortisolism (approx. 54% of patients), AE associated with accumulation of adrenal hormone precursors (approx. 58%), AE associated with enlargement of pituitary tumour (approx. 16%), AE associated with QT prolongation/AE with arrhythmogenic potential (approx. 4%). The AE of special interest surveyed occurred very rarely during the RW period.

In Study C2302, statistically significantly more AE related to hypocortisolism occurred under treatment with osilodrostat (7 (14.6%) vs 0 events). In addition, in the study, AE associated with adrenal hormone precursor accumulation occurred more frequently in the osilodrostat arm (43.8% vs. 36.0%); however, this did not show statistically significant differences between treatment groups.

Interim summary of side effects

In Study C2301, there were no statistically significant differences between treatment groups with respect to side effects during the 8-week RW period and until the end of the open-label treatment phase with osilodrostat. Specifically, AE of special interest occurred very rarely during the RW period. By the end of the study, AE related to hypocortisolism or adrenal hormone precursor accumulation occurred in more than 50% of patients. By the end of Study C2301, 18.2% of patients had discontinued treatment because of AE.

In Study C2302, significantly more AE of any severity occurred in the osilodrostat arm (with respect to SOCs cardiac disorders, endocrine disorders, gastrointestinal disorders, general disorders and administration site conditions, and musculoskeletal and connective tissue disorders). There were no statistically significant differences between the treatment groups with regard to severe and serious AE and AE leading to discontinuation of treatment. Specifically, for the AE of special interest in Study C2302, there were significantly more AE associated with hypocortisolism under osilodrostat treatment (7 (14.6%) vs 0 events in the control arm).

Overall assessment/conclusion

The pivotal, multi-centre Study C2301 (in a randomised withdrawal design) and the multi-centre Study C2302 (investigating the efficacy and safety of osilodrostat compared with placebo over 8 and 12 weeks in patients with confirmed Cushing's disease) were available for the benefit assessment. In addition, data from the open-label treatment phase of Study C2301 are available through Week 48.

For the endpoint category mortality, no statement on additional benefit can be derived based on the study data presented.

For the morbidity endpoint, there are statistically significant results for normalisation of mean urinary free cortisol (mUFC, complete response) in favour of osilodrostat in Studies C2301 and C2302. In addition, the results of the 12-week placebo-controlled phase of Study C2302 show a statistically significant difference in the BDI-II (an instrument for self-assessment of the severity of depression) to the detriment of osilodrostat compared with placebo. However, the clinical relevance of these differences cannot be judged. For the endpoints health status (EQ-5D-VAS) and severity of depression (BDI-II), no comprehensible evaluations were available for the comparative data in Study C2301. The results of the non-comparative data show improvements up to Week 48 compared with the start of study. However, because of the lack of a comparator arm, no assessment of the effect is possible. With respect to health status (EQ-5D VAS), Study C2302 showed no statistically significant differences between treatment groups. The endpoint suicidal thoughts or suicidal behaviour (C-SSRS) was recorded only in Study C2302. In this study, only patients in the osilodrostat arm had suicidal thoughts or suicidal behaviour.

Regarding disease-specific quality of life (CushingQoL), no comprehensible evaluations were available for the comparative data in Study C2301. The results of the open-label treatment phase with osilodrostat showed a improvement of quality of life at Week 48 compared with the start of study. However, no assessment of the effect is possible because of the lack of a comparator arm. In Study C2302, after the 12-week treatment period, there is an improvement in quality of life in both study arms. However, the results are not significantly different.

In the side effects endpoint category, there were no statistically significant differences between treatment groups during the 8-week RW period and until the end of the open-label treatment phase with osilodrostat in Study C2301. In study C2302, significantly more AE of any severity occurred in the osilodrostat arm. There were no statistically significant differences between the treatment groups with regard to severe and serious AE and AE leading to discontinuation of treatment. Specifically, for the AE of special interest in Study C2302, there were significantly more AE associated with hypocortisolism.

In the overall view of the results of Studies C2301 and C2302, there was a statistically significant effect for osilodrostat in normalizing mean urinary free cortisol as a clinically significant parameter. The results of both studies suggest that cortisol levels reach the normal range and that pathologically altered cortisol levels are stabilised by treatment with osilodrostat. No clinically relevant differences can be derived in the other endpoints on morbidity and quality of life. There were no statistically significant differences between the treatment groups with regard to severe and serious AE and AE leading to discontinuation of treatment. In detail, statistically significant disadvantages are shown for individual specific side effects in Study C2302. Against this background, the G-BA classified the extent of the additional benefit for osilodrostat as non-quantifiable based on the criteria in Section 5, paragraph 7 AM-NutzenV, taking into account the severity of the disease, the written statements, and the oral hearing.

Significance of the evidence

The present assessment is based on the both Studies C2301 and C2302. However, the overall significance of the two studies is subject to uncertainty.

The risk of bias in the two studies is estimated to be low at the study level.

Because of the randomised withdrawal design of Study C2301, only patients who responded to osilodrostat therapy at 26 weeks and achieved a response in mUFC were included in the 8-week randomised phase of the study. This represented only approx. 50% of the patients

originally included and treated in the study. The results of this phase thus provide information only for a selected population. Furthermore, because all patients were already receiving osilodrostat prior to randomisation, the results of the RW period are not suitable for deriving statements about treatment effects in patients starting osilodrostat therapy.
Patients with *de novo* Cushing's syndrome who were eligible for surgery, patients with Cushing's syndrome as a result of ectopic ACTH secretion, and patients with ACTH-independent (adrenal) Cushing's syndrome were also excluded from both studies. The overall significance of Studies C2301 and C2302 with regard to the present therapeutic indication must therefore also be regarded as critical.

There is a further limitation with regard to the significance of the studies. This is because the comparative phases of the studies are very short (8 and 12 weeks in the present therapeutic indication of endogenous Cushing's syndrome). The effects in the open-label treatment phase of Study C2301 up to Week 48 cannot be assessed because of the lack of a comparator arm.

Overall, the available data basis is subject uncertainties, which leads to a downgrading of the significance of the evidence for the overall assessment. The significance of the evidence for the additional benefit identified is therefore classified as a "hint".

2.1.3 Summary of the assessment

The present assessment refers to the benefit assessment of the new medicinal product Isturisa with the active ingredient osilodrostat. Isturisa was approved as an orphan drug and is used for the treatment of endogenous Cushing's syndrome in adults.

The pivotal Study C2301 in a randomised withdrawal design and Study C2302, both investigating the efficacy and safety of osilodrostat compared with placebo over 8 and 12 weeks in patients with confirmed Cushing's disease, were available for the benefit assessment. In addition, data from the open-label treatment phase of Study C2301 are available through Week 48.

For mortality and disease-specific quality of life, no advantage or disadvantage can be found from treatment with osilodrostat.

In the overall assessment of the morbidity endpoint, there are statistically significant results for normalisation of the mean urinary free cortisol as a clinically significant parameter in favour of osilodrostat in Studies C2301 and C2302. The results of both studies suggest that cortisol levels reach the normal range and that pathologically altered cortisol levels are stabilised by treatment with osilodrostat. The 12-week placebo-controlled phase of Study C2302 shows a statistically significant deterioration in the severity of depression from osilodrostat compared with placebo. However, the clinical relevance of these differences cannot be judged. Thus, for the other morbidity and quality-of-life endpoints, no statement on additional benefit can be derived based on the study data presented.

In the endpoint category side effects, Study C2301 showed no statistically significant differences between treatment groups. In Study C2302, significantly more AE of any severity and AE of special interest (AE related to hypocortisolism) occurred in the osilodrostat arm. There were no statistically significant differences between the treatment groups with regard to severe and serious AE and AE leading to discontinuation of treatment.

Overall, however, the present data basis is subject to uncertainties. In particular, with respect to the present therapeutic indication, the short duration of the comparative phases of the studies, and the randomised withdrawal design of Study C2301 the transferability of the patient population included is to be considered critical and leads to a downgrading of the significance of the evidence.

In the overall view, there is a hint for a non-quantifiable additional benefit for osilodrostat.

2.2 Number of patients or demarcation of patient groups eligible for treatment

This information on the number of patients refers to the target population in the statutory health insurance.

The derivation of the patient numbers in the dossier appears plausible overall; however, the patient numbers are subject to uncertainties because of the insufficient data basis and the reference made to expert opinions based on this. Overall, especially the upper limit of prevalence estimated by the pharmaceutical company based on 2 sources is considered to be overestimated. It is assumed that the number of the target population is in the lower range of the range of the patient numbers of approx. 1,130–1,550 reported by the pharmaceutical company.

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 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

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 December 2020).

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

Treatment duration:

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 varies from patient to patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Osilodrostat	continuously, 2 × daily	365	1	365

Usage and consumption:

Designation of the therapy	Dosage/application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Osilodrostat	2 mg – 30 mg	4 mg – 60 mg	4 × 1 mg – 6 × 10 mg	365	1,460 × 1 mg – 2,190 × 10 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated based on the pharmacy sales price level as well as less the statutory rebates according to Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined based on consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package 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					
Osilodrostat 1 mg	60 FCT	€ 1,912.65	€ 1.77	€ 108.78	€ 1,802.10
Osilodrostat 10 mg	60 FCT	€ 7,855.59	€ 1.77	€ 456.96	€ 7,396.86
Abbreviations: FCT: film-coated tablets					

Pharmaceutical selling price (LAUER-TAXE®) as last revised: 15 December 2020

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 assessed 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.

No additionally required SHI services are taken into account for the cost representation.

3. Bureaucratic costs

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 15 July 2020, the pharmaceutical company submitted a dossier for the benefit assessment of osilodrostat 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 October 2020 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 5 November 2020.

The oral hearing was held on 23 November 2020.

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 22 December 2020, and the proposed resolution was approved.

On 7 January 2021, plenum resolved by written procedure to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	26 October 2020	Information of the benefit assessment of the G-BA
Working group Section 35a	18 November 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	23 November 2020	Conduct of the oral hearing
Working group Section 35a	2 December 2020 16 December 2020	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 on Medicinal Products	22 December 2020	Concluding discussion of the draft resolution
Plenum	7 January 2021	Written resolution on the amendment of Annex XII of the AM-RL

Berlin, 7 January 2021

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

Prof. Hecken