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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Isturisa (osilodrostat)
Treatment of Cushing's syndrome
EU/3/14/1345
Sponsor: Novartis Europharm Limited

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Active substance	Osilodrostat
International Non-Proprietary Name	Osilodrostat
Orphan condition	Treatment of Cushing's syndrome
Pharmaceutical form	Film-coated tablet
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	H02CA02
Sponsor's details:	Novartis Europharm Limited Vista Building Elm Park Merrion Road Dublin 4 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Novartis Europharm Limited
COMP opinion date	4 September 2014
EC decision date	5 October 2014
EC registration number	EU/3/14/1345
Post-designation procedural history	
Transfer of sponsorship	Transfer from Novartis Europharm Limited (UK) to Novartis Europharm Limited (Ireland) – EC decision of 8 May 2018
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	K. Dunder, B. Van der Schueren
Applicant	Novartis Europharm Limited
Application submission date	9 November 2018
Procedure start date	29 November 2019
Procedure number	EMA/H/C/0004821
Invented name	Isturisa
Therapeutic indication	Treatment of endogenous Cushing's syndrome in adults. Further information on Isturisa can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Isturisa
CHMP opinion date	14 November 2019
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	A. Magrelli, D. Matusevicius
Sponsor's report submission date	10 December 2018
COMP opinion date (adoption via written procedure)	18 November 2019

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2014 designation was based on the following grounds:

The sponsor Novartis Europharm Limited submitted on 21 May 2014 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing 4-[(5R)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl]-3-fluorobenzonitrile phosphate for treatment of Cushing's syndrome (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

The International Nonproprietary Name (INN) "osilodrostat" was recommended during evaluation and the name of the active substance was changed accordingly.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing osilodrostat was considered justified based on preliminary clinical data in patients with Cushing's disease;
- the condition is life-threatening and chronically debilitating due to the consequences of hypercortisolism, including cardiovascular disease, diabetes, clotting disorders, muscular weakness and osteoporosis, and psychiatric conditions;
- the condition was estimated to be affecting less than 1 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing osilodrostat may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating significant effects on 24 hour free urinary cortisol levels in patients with Cushing's disease. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing osilodrostat, as an orphan medicinal product for the orphan indication: treatment of Cushing's syndrome.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Cushing's syndrome is still a recognised condition in the current scientific literature and no changes to the classification of this condition were noted since the initial orphan designation.

Cushing's syndrome is a disease characterised by an excess of the hormone cortisol in the blood. It is usually caused by a tumour of the pituitary gland (a gland located at the base of the brain) that produces large amounts of adrenocorticotropic hormone (ACTH), which in turn stimulates the production of excess cortisol from the adrenal glands, which are situated above the kidney. Some patients with the syndrome have other kinds of tumours that produce ACTH, or tumours that produce excess cortisol directly.

Clinical manifestations of chronic hypercortisolism include metabolic syndrome, insulin resistance, visceral obesity, glucose intolerance, hypertension, dyslipidaemia, and hypercoagulable state. Other clinical signs and symptoms of CS include: supraclavicular and dorsal fat pads; proximal muscle weakness; osteoporosis with increased risk of fractures; skin changes (wide purple striae, hirsutism, acne); impaired immune function with increased risk of infection; neuropsychiatric disorders (depression, mood changes, and cognitive impairment), hypogonadism, and menstrual disorders in women.

The approved therapeutic indication "Treatment of endogenous Cushing's syndrome in adults" falls within the scope of the designated orphan condition "Treatment of Cushing's syndrome".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

Details of the clinical data submitted by the sponsor and of the benefit/ risk assessment can be found in the European public assessment report (EPAR) for Isturisa.

Chronically debilitating and/or life-threatening nature

There have been no changes in the chronically debilitating or life-threatening nature of the condition since the initial orphan designation on 15-Oct-2014. The sponsor acknowledged that Ketoconazole HRA was approved on 19-Nov-2014 for the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years but that this substance has been used in the EU/EEA for this indication since the 1980's.

Number of people affected or at risk

The estimate is based on the highest reported prevalence of Cushing's disease (CD) in population-based studies in Europe (0.55 per 10,000, Daly et al 2006) and the published observation that CD comprises 80% of all cases of Cushing's syndrome (Newell-Price et al 2006). A recent publication

(Lacroix et al 2015) places the estimated incidence of endogenous Cushing's syndrome at 0.2–5.0 per million people per year, and the prevalence at 39–79 per million in various populations; median age of onset/diagnosis was 41.4 years with a female-to-male ratio of 3:1. The sponsor therefore maintains that the estimated prevalence of Cushing's syndrome in the EU is around 0.69 in 10,000 persons and has not changed since this initial orphan designation. Since the definition of the condition is the same, and the consulted literature does not indicate changes in incidence, this estimate can be accepted.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The main objectives for the treatment of hypercortisolism include: 1) normalization of cortisol secretion; 2) reversal of the clinical picture; 3) prevention or recovery of the concomitant comorbidities and clinical complications; and 4) long-term disease control without disease recurrence (Pivonello et al 2015). The achievement of these objectives frequently requires a multimodal treatment approach.

The sponsor provided a table of all authorised products for treatment of Cushing's syndrome (Table 1).

Table 1. Approved medical therapy in EU for Cushing's syndrome

Active Substance	Indication	EU countries where product is registered
Trilostane	For the control of the manifestation of adrenal cortical hyperfunction in such conditions as hypercortisolism and primary aldosteronism.	UK
Metyrapone	As a diagnostic test for ACTH insufficiency and in the differential diagnosis of ACTH-dependent Cushing's syndrome. For the management of patients with endogenous Cushing's syndrome.	Many EU countries
Mitotane	Mitotane (Lysodren®) is a steroidogenesis inhibitor and an adrenolytic agent used for the symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenocortical carcinoma. The effect of mitotane (Lysodren®) on non-functional adrenal cortical carcinoma is not established.	EU
Aminoglutethimide	Cushing's syndrome due to: - Adrenocortical tumours (adenoma or carcinoma) - Adrenocortical hyperplasia - ACTH production at sites other than the pituitary (ectopic ACTH syndrome) In Cushing's patients, Orimeten can be used as premedication prior to surgery, as treatment for relapses following subtotal adrenalectomy or as treatment for inoperable cases.	NL
Pasireotide	Treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed.	EU (orphan)
Ketoconazole	Ketoconazole HRA is indicated for the treatment of endogenous Cushing's syndrome in adults and adolescents above the age of 12 years.	EU (orphan)

The article describing treatment of Cushing's syndrome cited by the sponsor was superseded by more recent but similar publications (e.g. Nieman LK. Recent Updates on the Diagnosis and Management of Cushing's Syndrome. Endocrinol Metab (Seoul). 2018;33(2):139–146).

Significant benefit

Protocol assistance for the justification of significant benefit has been sought, and the recommendations have been followed. The sponsor claims significant benefit of improved efficacy based on an indirect comparison to existing treatment options and the results from Phase 3 studies showing control of free urinary cortisol, lack of treatment escape phenomenon and improved patient quality of life as measured by several standard questionnaires.

The efficacy and safety of osilodrostat were evaluated in a prospective phase III study (study C2301) that used a randomised withdrawal design. The study consisted of a 26-week open-label period of single-arm osilodrostat treatment, followed by an 8-week randomised withdrawal period in which patients were randomised in 1:1 ratio to either osilodrostat or placebo and a subsequent osilodrostat open-label period.

The eligibility criteria included a mean urinary free cortisol (mUFC, derived from three 24-hour urine collections) value greater than 1.5 times the upper limit of normal (ULN) at screening, and a confirmation of the pituitary source of excess adrenocorticotrophic hormone (ACTH). A total of 137 adult patients were enrolled. The mean age was 41.2 years, and the majority of patients were female (77%). Prior therapy included pituitary surgery in 88% of patients and prior medical therapy in 75% of patients. The median baseline mUFC was 476.4 nmol/24 h (ULN: 138 nmol/24 h). Comorbidities at baseline included hypertension (67.9% of patients), obesity (29.9%), diabetes mellitus (21.9%) and osteoporosis (27.7%).

Table 2. Key results: Phase III study in Cushing's disease patients (C2301)

	Osilodrostat n=36	**Placebo n=34**	
Primary endpoint: Proportion of responders at the end of the randomised withdrawal period (week 34) n (%) (95% CI)	31 (86.1) (70.5, 95.3)	10 (29.4) (15.1, 47.5)	
Response rate difference (odds ratio): osilodrostat vs. placebo	13.7 (3.7, 53.4) 2-sided p value <0.001		
Secondary endpoints			**All patients N=137**
Key secondary endpoint: Proportion with mUFC ≤ULN at week 24 and no dose increase after week 12 (95% CI)			72 (52.6%) (43.9, 61.1)
Complete mUFC response rate (mUFC ≤ULN) at week 12			98 (71.5%) (63.2, 78.9)
Complete mUFC response rate (mUFC ≤ULN) at week 24			93 (67.9) (59.4, 75.6%)
Complete mUFC response rate (mUFC ≤ULN) at week 48			91 (66.4%) (57.9, 74.3)
Median mUFC value and percentage change at week 48			63.3 nmol/24 h (-87.9%)
mUFC: mean urinary free cortisol; ULN: upper limit of normal; CI: confidence interval; response: mUFC ≤ULN			

Importantly, no requirement for continuous dose increases to overcome an ACTH-driven "escape" phenomenon was observed. After the initial (protocol-mandated) dose escalation phase in the pivotal Phase III study, the average dose levels remained consistently in the 5 mg bid range while mean mUFC levels remained in the normal range.

Consistent improvements were observed in cardiovascular and metabolic parameters, and 85.6% of patients showed an improvement in at least one physical feature of Cushing's disease (facial rubor, dorsal and supraclavicular fat pads, central/abdominal obesity, ecchymosis/bruising, proximal muscle wasting/atrophy, striae, and/or female hirsutism) at week 48.

Improvements from baseline above the established minimal important difference (MID) were consistently observed for Cushing's QoL (total score, Physical Problems subscale and Psychosocial issues subscale), EQ 5D Utility index and BDI II (depression) scores. The mean Cushing QoL total score improved from 42.2 at baseline to 51.0 (+8.4; +29.1% change from baseline) at week 12 and to 58.3 (+14.1; +52.4% change from baseline) at week 48.

As proposed in the protocol assistance letter, the sponsor performed an indirect comparison of own data to published clinical data on the relevant comparators.

With regards to pasireotide the sponsor compared two clinical trials with both products: osilodrostat (study C2301) and pasireotide (Study G2304). The inclusion criteria differed between studies, with more severe patients (higher mUFC values) included in C2301 study. This study also was longer in duration (80.3 vs 67.6 weeks). Based on this comparison, the response rate (ORR 83.5% vs. 53.3%) and the durability of response (100% vs. 44% ORR at 12 months) seem to be better for osilodrostat. All other aspects, including QOL, physical changes and safety seem comparable between the two studies (Table 3).

Table 3. Comparison to pasireotide

Parameter	**Osilodrostat (clinical study report C2301 and additional clinical trials)**	**Pasireotide (clinical study report G2304)**	**Comments**
Modified GRADE evidence level (Swiglo et al 2008)	High	Moderate to High	Marginally higher for osilodrostat
Treatment	Film-coated tablets, 1/5/10 mg (diameter 6.1 to 9.1mm), twice daily p.o. with or without food Starting dose 2 mg bid, max dose 30 mg bid Up to 60 dose levels possible	Suspension for i.m. injection, once every 28 days Starting dose 10 or 30 mg Max dose 40 mg Four dose levels available	Osilodrostat: small tablets, gradual dose titration but bid frequency; Pasireotide: i.m. injection, once monthly
Study design	Prospective, double-blind, randomized withdrawal	Prospective, double-blind, dose-controlled	Comparable
Sample size	137 adult patients with Cushing's disease	150 adult patients with Cushing's disease	Comparable
Treatment duration	Mean exposure 80.3 weeks	Mean exposure 67.6 weeks	Comparable
Demographics	Mean age 41.2 years 77.4% female 87.6% previous surgery	Mean age 38.5 years 78.7% female 82.0% previous surgery	Comparable
Disease severity at baseline	Mean mUFC 1006 nmol/24h (7.28xULN) (triplicate assessments, central lab, GC-MS/MS) Mean LNSC: 12.5 nM	Mean mUFC 470 nmol/24h (triplicate assessments, central lab, GC-MS/MS) LNSC: 10.4 nM	Due to different inclusion criteria, the osilodrostat study C2301 included more severe patients
mUFC response	mUFC ≤ ULN at m6 (primary analysis): 67.9% (95% CI 59.4, 75.6) response rate Overall response rate: 82.5% (95% CI 75.1,88.4)	mUFC ≤ULN at m7 (primary analysis): 41.3% (95% CI 33.4, 49.7) response rate Overall response rate 53.3% (95% CI 40.7,58.0)	Higher response rates for osilodrostat
Other efficacy endpoints	Mean change at month 6: Serum cortisol: -43.3% LNSC: -42.0%	Mean change at month 7: Serum cortisol m7: -6.5% LNSC m7: +19.8%	Larger improvements for osilodrostat

Clinical signs	Mean change at month 6: SBP –6.3 mmHg DBP –4.0 mmHg BMI –0.9 kg/m2 Cholesterol -0.6 mM HbA1c: -0.3 units (%) At most recent timepoint: • HbA1c improved in 24/32 (75%) patients with baseline HbA1c>=6.5% to <6.5% including 5 (15.6%) with normalization to <5.7%.	Mean change at month 7: SBP -5.6 mmHg DBP -3.8 mmHg BMI -1.3 kg/m2 Cholesterol -0.5 mM HbA1c: +1.1 units (%) At most recent timepoint: • HbA1c improved in 1/21 (4.8%) patients with baseline HbA1c>=6.5% to <6.5%	Comparable impact on clinical signs, with the known exception of pasireotide- associated hyperglycemia
Physical signs	% improved at month 6: Any improvement: 82.1% Facial rubor 42.9% Hirsutism 26.8% Striae 23.6% Bruising 29.2% Supraclavicular fat pad 46.2% Dorsal fat pad 47.2% Central obesity 31.1% Atrophy 28.3%	% improved at month 7: Facial rubor 43.5% Hirsutism 26.1% Striae 23.4% Bruising 19.4% Supraclavicular fat pad 34.3% Dorsal fat pad 34.6% Muscle strength 6.6%	Comparable impact on all physical signs predefined in the protocol, slightly favouring osilodrostat
Bone mineral density	Mean increase at week 48: L1-L4 3.0%, total hip 0.4%	Not studied	
Patient Reported Outcomes	CD HRQoL (m6): +9.6	CD HRQoL (m7): +6.8	Both treatments indicate significant improvements in Cushing HRQoL
Discontinuation reasons at data cut-off	Any reason: 25.5% Adverse events: 14.6% Lack of efficacy: 0%	Any reason: 50.0% Adverse events: 12.0% Lack of efficacy: 18.7%	AE discontinuations were comparable, but significantly, not a single patient on osilodrostat discontinued due to lack of efficacy
Drug interaction potential	Low (weak CYP3A4 inhibitor, no interaction with hormonal contraceptives)	Very low (Signifor SmPC)	
Cardiac safety	ΔΔQTcF effect at highest recommended dose (30mg) estimated at +5.3 ms	ΔΔQTcF +17.5 ms at a supratherapeutic dose; bradycardia	
Tolerability	High	High	
Maintenance of effect	88.3% responding at last available timepoint	44.0% overall response rate at month 12 (controlled +partially controlled)	Significantly better maintenance of efficacy for osilodrostat

The indirect comparison to ketoconazole is based on the largest retrospective patient series currently available in the literature (Castinetti et al 2014) and on top-level results reported from a study with the experimental compound levoketoconazole. The comparability of the populations was difficult to establish. However, independent of the inclusion criteria the sponsor concluded that Ketoconazole is associated with serious (and in some cases fatal) hepatotoxicity, lower initial control rates and a significant loss of efficacy during long-term treatment (up to 15% in Ketoconazole vs. 0% in osilodrostat), and an extensive number of clinically relevant drug-drug interactions. In particular, the lack of escape cases in the osilodrostat study speaks in favour of this product, which is also associated with more manageable safety profile. The results with levoketoconazole (SONICS study) showed comparable efficacy to that of enantiomeric mix of ketoconazole.

Table 4. Comparison to ketoconazole

Parameter	**Osilodrostat (clinical study report C2301 and additional clinical trials)**	**Ketoconazole (retrospective data review; Castinetti 2014)**	**Comments**
Modified GRADE evidence level (Swiglo et al 2008)	High	Low	Higher evidence quality for osilodrostat
Treatment	Film-coated tablets, 1/5/10 mg (diameter 6.1 to 9.1mm), twice daily p.o. with or without food Starting dose 2 mg bid, max dose 30 mg bid Up to 60 dose levels possible	Tablets 200 mg (diameter 10mm), 2-3 times daily p.o. Starting dose 400-600mg/day, max dose 1200mg/day Up to 6 dose levels possible	Osilodrostat: smaller tablets, less frequent administration, more gradual titration possible
Study design	Prospective, double-blind, randomized withdrawal	Retrospective data review, limited methodology information	Higher data quality for osilodrostat
Sample size	137 adult patients with Cushing's disease	Patient records of 200 Cushing's disease patients	Higher case number for ketoconazole
Mean treatment duration	Mean exposure 80.3 weeks	9.7 to 27.6 months	Longer reported observation period for ketoconazole (retrospective chart review period)
Demographics	Mean age 41.2 years 77.4% female 87.6% previous surgery	Mean age at diagnosis 41.9 years, 78% female 70.1% prior surgery	Comparable
Disease severity at baseline	Mean mUFC 1006 nmol/24h (7.28xULN) (triplicate assessments, central lab) Mean LNSC: 12.5 nM	Mean UFC 4.1x local ULN (duplicate assessments, local assays) LNSC not reported	UFC assay and collection details not available for ketoconazole
mUFC response	mUFC ≤ ULN at m6: 67.9% (95% CI 59.4, 75.6) Overall response rate: 82.5% (95% CI 75.1, 88.4) Mean final UFC: 1.7xULN	UFC ≤ ULN at most recent timepoint: 48.5% (95% CI 41.4, 55.7)* Overall response rate: 74% (95% CI 67.3, 79.9)* Mean final UFC: 1.8 to 2.5 times ULN (*CI calculated by Novartis)	Higher response rates for osilodrostat
Other endpoints	Mean change at month 6: Serum cortisol: -43.3% LNSC: -42.0%	Not reported	
Clinical signs	Mean change at month 6: SBP –6.3 mmHg DBP –4.0 mmHg BMI –0.9 kg/m2 Cholesterol -0.6 mM HbA1c: -0.3 units (%) At most recent timepoint: • SBP <140mmHg in 30/37 (81.1%) patients with baseline SBP ≥140mmHg; including 9 (24.3%) with normalization to <120 • DBP <90mmHg in 43/53 (81.1%) patients with baseline DBP≥90mmHg, including 14 (26.4%) with normalization to <80. • HbA1c <6.5% in 24/32	At most recent timepoint: Hypertension improved in 49/116 (42.2%) patients with HT at baseline, diabetes improved in 31/55 (56.4%) patients with diabetes at baseline	Beneficial effects reported for both treatments, more marked for osilodrostat

	(75%) patients with baseline HbA1c>=6.5%, including 5 (15.6%) with normalization to <5.7%.		
Physical signs	% improved at month 6: Any improvement: 82.1% Facial rubor 42.9% Hirsutism 26.8% Striae 23.6% Bruising 29.2% Supraclavicular fat pad 46.2% Dorsal fat pad 47.2% Central obesity 31.1% Atrophy 28.3%	At most recent timepoint: Any improvement: 44% (no details or individual signs reported)	Beneficial overall effect reported for both treatments, more marked for osilodrostat
Bone mineral density	Mean increase at week 48: L1-L4 3.0%, total hip 0.4%	Not studied	
Patient Reported Outcomes	CD HRQoL (m7): +9.3	Not reported	
Discontinuation reasons at data cut-off	Any reason: 25.5% Adverse events: 14.6% Lack of efficacy: 0%	Any reason: 73.8% Adverse events: 25.6% Lack of efficacy: 26.9%	Ketoconazole patients discontinued more often due to adverse events and due to lack of efficacy
Drug interaction potential	Low (weak CYP3A4 inhibitor, no interaction with hormonal contraceptive)	Very high (cf. Ketoconazole HRA EU SmPC sections 4.3 and 4.5)	Significant safety benefit for osilodrostat
Cardiac safety	ΔΔQTcF effect at highest recommended dose (30mg) estimated at +5.3 ms	No E14 study results available; literature reports indicate QTc prolongation of +7.4 to +9.3 ms at low doses (400mg; Tyl et al 2012)	Smaller impact for osilodrostat
Tolerability	High	Moderate	
Maintenance of effect	C2301: 88.3% responding at last available timepoint	49% controlled at last follow-up	Significantly better maintenance of efficacy for osilodrostat

The sponsor discussed also metyrapone, an orally administered drug which induces normalization of cortisol secretion at the end of the treatment period in an average of 50% of patients, with a consequent improvement in the clinical features (Daniels et al 2015), but it is affected by an escape from the response in up to 18.7% (mean 7.8%) of patients with initial response to treatment (Pivonello et al 2015). The sponsor claims lack of escape cases (defined as the first loss of control of UFC after at least one instance of UFC normalization, that is not due to treatment interruption or AE) in the study of osilodrostat. This comparison should be interpreted with caution based on small sample sizes in the studies with metyrapone. Based on the totality of evidence to date, however, this reduction of escapes would bring a clear benefit in terms of lasting efficacy. The response rate to metyrapone is reported to be around 71% (Pivonello et al 2015) comparable to the complete response rates of osilodrostat at Week 24 of 67.9% (ORR 82.5%).

Mitotane is an adrenolytic drug for the symptomatic treatment of unresectable, metastatic or relapsed adrenocortical carcinoma; it has a very slow onset of action and is associated with significant toxicities. The sponsor discussed it and concluded that osilodrostat has a significantly broader therapeutic scope and this would constitute a clinically relevant advantage.

Other products used off label in treatment of Cushing's syndrome were also discussed in terms of their significant limitations such as sedative effect in case of etomidate and the withdrawn regulatory status of mifepristone.

Taken together the sponsor discussed all authorised products and provided critical appraisal of their relative features and efficacies. Taken together, in accordance with the protocol assistance advice, the sponsor confirmed the assumption of improved efficacy by presenting data from the pivotal study with osilodrostat supported by Phase 2 data. Osilodrostat showed improved efficacy in terms of high rate of mUFC levels control in pre-treated patients as well as in treatment-naïve patients and improved durability of the treatment effect due to reduced escape rate when using this medicine over a long period of time. This was combined by manageable safety profile with reassuring tolerability and documented improvement of the patient quality of life.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 18 November 2019

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of Cushing's syndrome (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.7 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to the consequences of hypercortisolism, including cardiovascular disease, diabetes, clotting disorders, muscular weakness and osteoporosis, and psychiatric conditions;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Isturisa may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor provided data to demonstrate that the use of Isturisa leads to a high response rate in treatment–naïve and pretreated patients and that the responses are maintained, with no treatment escape cases reported in the pivotal clinical study. This constitutes a clinically relevant advantage over all existing authorised products as established in the pivotal trial and by indirect comparisons.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Isturisa, osilodrostat, EU/3/14/1345 for treatment of Cushing's syndrome is not removed from the Community Register of Orphan Medicinal Products.