EU RISK MANAGEMENT PLAN

for

ISTURISA®

(osilodrostat)

RMP version to be assessed as part of this application:	Version number 3.0
Data lock point for this RMP:	08 January 2023
Date of final sign off:	21 February 2024
Rationale for submitting an updated RMP:	Removal of 1 category 3 post-authorisation safety study (registry) from the pharmacovigilance plan following a request from the Pharmacovigilance Risk Assessment Committee.
Summary of significant changes in this RMP:	Removal of 1 category 3 post-authorisation safety study (registry) from the pharmacovigilance plan. Addition of information regarding study CLCI699C2302 (LINC4). Revision of Follow-up questionnaire for pregnancy (addition of new periods for follow-up)
Other RMP versions under evaluation:	Not applicable
Details of the currently approved RMP:	RMP Version 1.1, dated 15 November 2019

The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV.
The electronic signature is available on file.

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LIST OF ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
AE	Adverse event
AUC	Area under the curve
bid	Twice daily
CCDS	Company Core Data Sheet
CD	Cushing's disease
CI	Confidence interval
Cmax	Maximum concentration
CNS	Central nervous system
CS	Cushing's syndrome
CV	Cardiovascular
CYP	Cytochrome (P450)
ECG	Electrocardiogram
EEA	European Economic Area
EU	European Union
HPA	Hypothalamic-pituitary-adrenal
IC50	Half maximal inhibitory concentration
IR	Incidence rate
iv	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mUFC	Mean urinary free cortisol
NOAEL	No-observable-adverse-effect-level
PK	Pharmacokinetics
PL	Patient leaflet
PPND	Pre- and post-natal developmental
PT	Preferred term
PTY	Patient treatment-years
QTc	Corrected QT interval
QTcF	QT interval with Fridericia's correction
RMP	Risk Management Plan
RRD	Recordati Rare Diseases
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
TQT	Thorough QT/QTc
UDP-GT	Uridine 5'-diphospho--glucuronosyltransferase
US	United States of America

PART I: PRODUCT OVERVIEW

An overview of the product is provided in Table 1.

Table 1: Product overview

Active substance (International Non-proprietary Name or common name)	Osilodrostat.
Pharmacotherapeutic group (Anatomical Therapeutic Chemical Code)	Anticorticosteroids (H02CA0).
Marketing Authorisation Holder	Recordati Rare Diseases (RRD).
Medicinal products to which this Risk Management Plan (RMP) refers	One.
Invented name in the European Economic Area (EEA)	Isturisa®.
Marketing authorisation procedure	Centralised.
Brief description of the product	Chemical class: Anticorticosteroids.
	Summary of mode of action: Isturisa is a potent, orally bioavailable inhibitor of 11β-hydroxylase (cytochrome P450 [CYP] 11B1), the enzyme that catalyses the last step in the synthesis of cortisol.
Hyperlink to the Product Information	
Indication in the EEA	Current: Treatment of endogenous Cushing's syndrome (CS) in adults.
	Proposed: Not applicable.
Dosage in the EEA	Current: The recommended starting dose of Isturisa is 2mg twice daily (bid); for patients of Asian ancestry, a reduced starting dose of 1mg bid is recommended. The dose can be gradually titrated (initially by increments of 1 or 2mg bid) based on individual response and tolerability, with the goal of achieving normal cortisol levels. The maximum recommended dose of Isturisa is 30mg bid.
	Proposed: Not applicable.
Pharmaceutical form and strengths	Current: Isturisa is available as film-coated tablets in the following 3 strengths: 1mg (pale yellow tablets), 5mg (yellow tablets) and 10mg (pale orange-brown tablets).
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the European Union (EU)?	Yes.

Bid=twice daily; CS=Cushing's syndrome; CYP=cytochrome P450; EEA=European Economic Area; EU=European Union; RMP=Risk Management Plan; RRD=Recordati Rare Diseases; SmPC=Summary of Product Characteristics.

PART II: SAFETY SPECIFICATION

Part II: Module SI – Epidemiology of the Indication and Target Population

Endogenous CS is a rare endocrine disorder characterized by chronic exposure to excess cortisol. It is divided between adrenocorticotropic hormone (ACTH)-dependent (about 80%) and ACTH-independent (about 20%) causes (Table 2). Among ACTH-dependent forms, pituitary corticotroph adenoma (Cushing's disease [CD]) is the most common, outnumbering extra-pituitary (ectopic) tumours that secrete ACTH by a ratio of about 7:1. Up to 20% of ectopic ACTH tumours remain occult for many years. Rarely, neuroendocrine tumours, medullary thyroid carcinoma, and phaeochromocytoma produce corticotropin-releasing hormone, leading to excess pituitary ACTH secretion. Cortisol excess from primary unilateral adrenal adenomas or carcinomas suppresses ACTH; these tumours account for about 20% of endogenous CS cases. Rarely, CS is caused by primary bilateral macronodular adrenal hyperplasia or primary pigmented nodular adrenocortical disease and its non-pigmented variant, isolated micronodular adrenocortical disease [Lacroix *et al.*, 2015].

SI.1: Endogenous Cushing's syndrome in adults

SI.1.1: Incidence and prevalence

Endogenous CS has an estimated incidence of 0.2 to 5.0 per million people per year and a prevalence of 39 to 79 per million in various populations; median age of onset/diagnosis was 41.4 years with a female-to-male ratio of 3:1 [Lacroix *et al.*, 2015]. A lower overall prevalence of 7 per million for "overt" adrenal CS has been estimated for Japan [Ross, 1994], Table 2.

Table 2: Incidence and prevalence of CS (by cause)

	Proportion (%)	Age (peak)	Incidence (per million-year)	Prevalence (per million)	Female : Male ratio	Data for Japan
CS (any cause)	100	Median age of onset/diagnosis: 41.4 years	0.2 to 5.0	39 to 79	3:1	Age peak: 55 to 60 years
ACTH-dependent	70 to 80%	-	-	-	-	33 to 42%
Pituitary adenoma (CD)	60 to 70%	3rd to 4th decades	0.6 to 2.6	39	3 to 5:1	18.5 to 36%
Ectopic ACTH	5 to 10%	5th to 6th decades	-	-	0.6 to 1:1	~4%
ACTH-independent	20 to 30%	-	-	-	6:1	-
Adrenal adenoma	10 to 22%	4th to 5th decades	0.6 to 0.2	-	4 to 8:1	47%
Adrenal carcinoma	5 to 7%	1st, 5th to 6th decades	-	-	1.5 to 3:1	~2%
Others (e.g., pre- and post-natal developmental [PPND], adrenocorticotropi	~ 2%	5th to 6th decades	-	-	1 to 4:1	Very rare

c-independent macronodular adrenal hyperplasia)						

ACTH=adrenocorticotropic; CD=Cushing's disease; CS=Cushing's syndrome; PPND=pre- and post-natal developmental.
Source: Falhammar *et al.*, 2017 ; Lacroix *et al.*, 2015 ; Newell-Price *et al.*, 2006 ; Nieman *et al.*, 2008 ; Takayanagi *et al.*, 2000 ; Valassi *et al.*, 2011.

SI.1.2: Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease

CS is at least 3 times more prevalent in women than in men, and although it can occur at any age, it is more frequent during the 4th to 6th decades of life [Boscaro *et al.*, 2001; Newell-Price *et al.*, 2006; Pivonello *et al.*, 2008], see Table 2.

CD is 3 to 5 times more frequent in women than men [Lacroix *et al.*, 2015] with mean age at diagnosis of 36 years [De Martin *et al.*, 2006] and a peak age at diagnosis in the 3rd to 4th decades [Lacroix *et al.*, 2015]. It is very rare in childhood and adolescence with a predominance of males in the prepubertal patients [Savage *et al.*, 2007].

Data on race/ethnic origin of the CS are scarce. The few available publications showed that the age of Japanese patients with CS is higher (mean age 55.3 to 59.8 years) than that of CS patients in Europe (median age: 44 years). Also, in Japan male patients comprised 14.8 to 19.3% of CS patients, compared to 21% of CS patients in Europe [Doi *et al.*, 2008; Ueki *et al.*, 2014; Valassi *et al.*, 2017]. In studies from the United States (US), a higher percentage of pituitary macroadenomas (constituting 10% of intracranial tumours) has been reported in African Americans [Monson, 2000].

No published epidemiologic data have been identified for risk factors for CS.

SI.1.3: The main existing treatment options

The first-line treatment of nearly all forms of CS is surgical resection of the underlying tumour. Surgery may be deemed to be an unacceptable risk for some patients with adrenal or extra-adrenal CS and it may not be an option for others due to the lack of a definite surgical target on imaging [Pivonello *et al.*, 2015]. Exceptions include CS due to metastatic adrenal carcinoma, ectopic ACTH syndrome with an unknown source of ACTH secretion, and ectopic ACTH syndrome associated with a metastatic malignant tumour. Post-surgical remission rates of 60 to 90% have been reported in CD and up to 80% in ectopic ACTH syndrome [Kelly, 2007; Newell-Price *et al.*, 2006; Wagner-Bartak *et al.*, 2017]. Long-term follow-up of CD patients in remission shows a significant incidence of recurrence of up to 40% at 10 years [Newell-Price *et al.*, 2006; Nieman *et al.*, 2015].

Radiotherapy is a possible alternative for CD patients for whom surgery is not indicated or has not been successful, however, remission rates range between 53 to 83% and the treatment is associated with significant side effects [Biller *et al.*, 2008; Kelly, 2007]. In patients with CD, the mean recurrence rate after conventional radiotherapy is 15.9% at a mean time to recurrence of 48.6 months, whereas the mean recurrence rate after stereotactic surgery is 12.3% at a mean time to recurrence of 27.6 months [Pivonello *et al.*, 2015]. For patients with CD not cured by

removal of the ACTH-secreting tumour, bilateral adrenalectomy is considered after failed treatment attempts with other medical treatment and is the remaining non-medical treatment option considered as last resort, especially in patients with severe symptomatology that requires immediate relief/action. The consequences of bilateral adrenalectomy include primary adrenal insufficiency, possible hypercortisolism due to excess ACTH stimulation of residual adrenal tissue, and the development of an aggressive corticotroph tumour, Nelson syndrome [Azad *et al*., 2015; Katznelson, 2015]. Adrenal insufficiency can be a life-threatening condition and requires life-long replacement hormonal therapy (i.e., both glucocorticoids and mineralocorticoids) and monitoring.

Medications are often used to control hypercortisolism in patients with CD who have failed trans-sphenoidal pituitary surgery and have received radiation therapy [Tritos and Biller, 2018]. Medication treatment is progressively more often used as second line treatment before radiotherapy, due to long-term consequences of the radiotherapy/radiosurgery. In these patients, since it may take several years for the beneficial effects of radiotherapy to become apparent, there is opportunity for use of medical therapy in this interim phase. In addition, medical therapy can be considered to stabilize the condition of acutely ill patients with CD, who are not fit to undergo definitive surgery immediately. Medical therapy can also be recommended in patients whose surgery has been deferred for various reasons or those whose tumour location is uncertain. Patients with unresectable or metastatic tumours may also benefit from medical therapy to control hypercortisolism. The care of patients with CS generally requires a multimodality approach involving experienced physicians from several disciplines (surgery, neurosurgery, endocrinology, radiation oncology, and medical oncology) [Tritos and Biller, 2018].

The development of novel compounds and the successful use of drugs for different clinical conditions in CD over the last 10 years, as well as the achievement of regulatory approval for specific drugs for the treatment of groups of patients with CD, have significantly increased the role of medical therapy in the management of CD [Pivonello *et al*., 2015]. Medications for CD can be categorized depending on their site of action:

- Steroidogenesis inhibitors, which inhibit 1 or several enzymes involved in cortisol biosynthesis and can be used in patients with endogenous CS, regardless of its aetiology.
- Pituitary-directed drugs, which inhibit ACTH secretion from corticotroph tumours and cortisol production.
- Glucocorticoid receptor antagonists, which inhibit cortisol peripheral action.

To date, there is no single, clearly established standard of care medical therapy for CS across various regions and substantial room for improvement remains.

SI.1.4: Natural history of the indicated condition in the population, including mortality and morbidity

Patients with CS are at increased risk of mortality and morbidity. The increased risk of mortality in CS patients was reported to be 2 to 4 times higher than in the general population from 2 European studies including 343 CS patients of adrenal or pituitary origin and 386 CS patients of all aetiologies, respectively [Dekkers *et al*., 2013; Yaneva *et al*., 2013].

Untreated CD has a poor prognosis as the 5-year survival is estimated to be about 50%. Results from EU studies showed that CD patients (with varying treatments) have approximately 3 to 5 times higher risk of mortality compared to the general population [Clayton *et al*., 2011; Etxabe and Vazquez, 1994; Lindholm *et al*., 2001; Van Haalen *et al*., 2015].

SI.1.5: Important co-morbidities

Important co-morbidities found in the target population have been presented in Table 3.

Table 3: Important co-morbidities found in the target population (CD)

Comorbidity	Incidence and prevalence	Mortality
Hypertension	No published data on the incidence of hypertension have been identified. Hypertension occurs in 25 to 93% of patients with CS. Presence of hypertension has been reported in 25 to 54% of patients in remission from CS [Pivonello et al., 2016]. In CD patients, hypertension occurs in 55 to 85% [Sharma et al., 2015], but resolves after remission in 44 to 75% [Barahona et al., 2009; Fallo et al., 1996; Mancini et al., 2004].	In patients with CD, cardiovascular (CV) complications determine a mortality rate 4 times higher than in an age- and gender-matched population [Etxabe and Vazquez, 1994].
Hypokalaemia	Hypokalaemia is attributed to the large amount of cortisol (which characterizes the ectopic ACTH secretion) and the excessive secretion of 11-hydroxycortisone [Arteaga et al., 1999]. No published data on the incidence of hypokalaemia have been identified. Hypokalaemia affects more than half of patients with ectopic Cushing's syndrome, but it can occur in any patient with severe Cushing's syndrome. No difference was noted in the development of hypokalaemia in male and female patients with Cushing's syndrome. Indeed, a significant correlation was found between daily urinary cortisol excretion and severity of hypokalaemia [Pivonello *et al*., 2016].	Hypokalaemia, together with atherosclerosis and thromboembolism, contribute to the increase in cardiovascular risk (ventricular arrhythmias) and hence risk of mortality [Pivonello *et al*., 2016].
Other cardiovascular complications (coronary artery disease, congestive heart failure, cardiac infarction)	CS is associated with an increased risk for myocardial infarction [Hazard Ratio: 2.1] and cardiac failure [Hazard Ratio: 6.0]. The incidence of venous thromboembolism: 2.5 to 14.6 per 1000 persons/year [Stuijver et al., 2011; Van Zaane et al., 2009]. Thromboembolic events have been reported in 6 to 20% of patients with CS, particularly in the early postoperative period [Pivonello *et al*., 2016].	No published data.
Glucose intolerance and frank diabetes	No published data on the incidence have been identified. Impairment of glucose metabolism has been described in 27 to 87% of patients with CS; in particular, impaired glucose tolerance has been observed in 7 to 64% of patients with CS and diabetes in 11 to 47% of CS patients [Pivonello *et al*., 2016]. Approximately, 13 to 50% of the patients with CS experience overt diabetes	Clayton et al. (2016) indicated diabetes as a risk factor for death (hazard ratio of 2.82; 95% confidence interval [CI]: 1.29 to 6.17).

	mellitus whereas impaired glucose tolerance is present in 12.5 to 64% of patients [Scaroni et al., 2017; Sharma *et al*., 2015].	
Pathologic rib and vertebral fracture and other complications of osteoporosis	No published data on the incidence have been identified. Impairment of bone status has been described in 64 to 100% of patients with CS, in particular: • Osteopenia occurs in 40 to 78% of patients. • Osteoporosis occurs in 22 to 57% of patients. • Skeletal fractures occur in 11 to 76% of patients [Arnaldi et al., 2003; Pivonello et al., 2016 ; Trementino et al., 2014]. Male patients have a higher prevalence of osteoporosis and vertebral fractures than female patients with CS (47% versus 32% and 52% versus 18%, respectively) [Pivonello *et al*., 2016].	No published data.
Psychological alterations, ranging from irritability and emotional liability to severe depression, suicidal behaviour and manic episodes	No published data on the incidence have been identified. The prevalence is 50 to 80% of patients with CS that meet the Diagnostic and Statistical Manual of Mental Disorders IV criteria for major depression [Dorn et al., 1995; Sharma *et al*., 2015; Sonino and Fava, 2001]. Impaired cognitive function is observed in 86% of patients [Sharma *et al*., 2015]. Anxiety is reported in 66% and bipolar disorder in 30% of CS patients [Pivonello *et al*., 2016]. Psychotic disorders are less common and reported at frequency of 7.6% in CS patients [Bratek et al., 2015].	No published data.
Nephrolithiasis	No published data on the incidence have been identified. The prevalence is 50% of active patients with CD (compared to 6.5% in age- and gender-matched controls/without CD) [Faggiano et al., 2003; Sharma *et al*., 2015].	No published data.
Obesity	No published data on the incidence have been identified. An excess of weight is seen in 57 to 100% of patients with CS; in particular 33 to 48% of patients are overweight and obesity is observed in 25 to 100% of patients [Pivonello *et al*., 2016]. In patients with CS, central obesity is reported at 30 to 40% [Sharma *et al*., 2015; Pivonello *et al*., 2016].	No published data.
Hyperlipidaemia	No published data on the incidence have been identified. The prevalence is 38 to 71% [Colao et al., 1999; Mancini et al., 2004].	No published data.

ACTH=adrenocorticotropic hormone; CD=Cushing's disease; CI=confidence interval; CS=Cushing's syndrome.

Part II: Module SII – Non-clinical Part of the Safety Specification

The toxicity of Isturisa was evaluated in the following studies:

- A single dose toxicity (50, 100, 125 and 150mg/kg), 2-week (10, 50, 100 and 200mg/kg/day) and 13-week study (10, 30, 100 and 200mg/kg/day) in mice.
- A 2-week (30, 100, 300mg/kg/day reduced to 200mg/kg/day), 4-week (1, 5, 50mg/kg/day), 13-week (0.5, 5 and 50mg/kg/day), 26-week (0.2, 2 and 20mg/kg/day), 3-day continuous intravenous (iv) infusion (1, 3 and 10mg/kg/day) and 2-week continuous iv infusion study (1, 5, and 50mg/kg/day) in rats.
- A single descending dose (30, 15, and 7.5mg/kg), 2-week (0.5, 3, and 10mg/kg/day), 4-week (0.5, 1.5, and 10mg/kg/day), 13-week (0.1, 1, and 10mg/kg/day), 39-week (0.1, 1, and 10mg/kg/day), up to 4-day continuous iv infusion at 40mg/kg/day and 2-week continuous infusion study (0.5, 5, and 50mg/kg/day) in dogs.

No preclinical model of CS was used and all the results from the non-clinical studies were generated in normocortisolaemic animals. Isturisa was administered orally via gavage in all the above-mentioned studies unless otherwise mentioned.

Key preclinical safety findings for Isturisa are summarised in Table 4.

Table 4: Key Safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity	
Adrenal gland toxicity Morphological alterations of atrophy and/or vacuolation were observed in the adrenal cortex in dogs (zona glomerulosa), and hypertrophy and vacuolation at much higher exposure in rats (zona fasciculata) in repeat-dose toxicity studies. These findings were partially recovered in dogs and completely recovered in rats, given that the zona glomerulosa is the area of the adrenal cortex where aldosterone is produced [Maitra and Abbas, 2005] and the observed changes in the zona glomerulosa were considered an adaptive response to the inhibition of aldosterone synthesis by Isturisa. In the rat, effects on the zona fasciculata were considered as a result of the inhibition of 11 β-hydroxylase (which is responsible for corticosterone biosynthesis in rats) leading to an adaptive induction of the corticosterone synthesis pathway. No evidence of adrenal dysfunction was noted during the dosing or recovery phase in animals due to observed adrenal changes in toxicity studies. Mild decreased potassium levels were seen at high doses in 2-week rat and dog continuous iv studies but not observed in oral repeat-dose toxicity studies.	Adrenal changes noted in animal studies are considered adaptive changes (pharmacology) due to inhibition of corticosterone/cortisol and aldosterone synthesis by Isturisa. Hypocortisolism is classified as an important identified risk for Isturisa. Additionally, long-term safety (including hypocortisolism, CV safety and QT prolongation, hormones of the hypothalamic-pituitary-adrenal (HPA)-axis including ACTH increase, and clinical consequences of increased sexual hormones) is considered missing information for Isturisa.
Reproductive/developmental toxicity Effects on female reproductive organs (follicular degeneration in ovaries, atrophy, uterine weight decrease and vaginal mucification) were seen in both rats (doses ≥ 5mg/kg) and/or mice (doses ≥ 30mg/kg), and effects on male reproductive organs were limited to a decrease in prostate weights in rats at 20mg/kg in the 26-week study. In dogs, no effects on female or male reproductive organs were found. The observed alterations in rats and mice were consistent with effects seen after aromatase inhibition [Nunez et al., 1996; Junker Walker and Nogues, 1994]. Isturisa inhibited human recombinant aromatase (half maximal inhibitory concentration [IC50]: 1.7μM). Assuming similar aromatase activity between rodents and humans, the inhibition of aromatase has been observed in rodents at approximately 9.6 times the estimated human plasma maximum concentration (Cmax) at the highest clinically used dose of 30mg bid. In reproductive toxicity studies (embryofoetal development in rats and rabbits, fertility and early developmental study and PPND in rats), embryo/foetal toxicity was observed at doses that produced maternal toxicity in the rat and the rabbit. In addition to the aromatase inhibition, a role of corticosterone inhibition in causing reproductive toxicity cannot be ruled out. Dystocia and delays in the start of parturition were observed in a PPND study in rats at 20mg/kg. Safety margins at the no observed adverse effect level (NOAEL) doses of 0.5/5 and 3/3mg/kg for maternal/foetal toxicity were 0.55/9.3 and 0.62/0.62 in rat and rabbit embryofoetal development	Although the non-clinical effects were noted at maternally toxic doses in non-hypercortisolaemic animals, women of childbearing potential will be advised of the potential risk to the foetus and effective contraception will be recommended in female patients during Isturisa treatment and for a week post-treatment. Reproductive toxicity/embryofoetal development is classified as an important potential risk for Isturisa.

Key Safety findings (from non-clinical studies)	Relevance to human usage
studies, respectively, and at a NOAEL dose of 5mg/kg for females were 9.6 in the rat PPND study, compared to exposure (area under the curve [AUC]) at the 30mg bid human dose. The mean days to development of preputial separation in males (47.2 days versus 42.6 days in controls) and vaginal opening in females (33.2 versus 31.1 days in controls) were long at 50mg/kg 4-week juvenile rat study (administered between 28 and 55 post-natal days). However, mating/fertility in males or reproductive performance in females were not impacted. A slight decrease in testosterone levels in males and no changes in oestradiol levels were noted in the study. Therefore, Isturisa should be considered potentially embryotoxic/teratogenic to humans.	
Hepatotoxicity Hepatocellular hypertrophy and vacuolation were observed in repeat dose toxicity studies up to 26-weeks in rat (with partial recovery) and 13-weeks in mice, but not in dogs. Hepatocellular hypertrophy is consistent with the adaptive physiological response noted with the inducers of microsomal enzymes. Gene expression profiling of the liver from rats treated with Isturisa for 4 weeks revealed a strong induction of genes involved in all 3 phases of xenobiotic metabolism, including prominent increases in transcripts encoding CYP2B1/CYP2B2 and uridine 5'-diphospho-glucuronosyltransferase (UDP-GT) transcripts. In addition, in mice, a slight elevation of alanine transaminase was noted at high doses in a 13-week study and in female dogs, a transient increase in aspartate transaminase/alanine transaminase was noted in a 13-week study but were not noted in the 39-week study.	No significant liver enzyme abnormalities have been observed in clinical trials. Elevations of liver enzymes are mainly transient, often return to the baseline at the next visit. No patients discontinued the study drug due to abnormal liver chemistry parameters.
Genotoxicity *In vitro*, Isturisa was found to be negative in the Ames test and the micronucleus test. In human peripheral lymphocytes, Isturisa induced chromosomal aberrations at concentrations ≥ 2000µg/ml (>8.8 mM). However, *in vivo* sublethal doses of 200mg/kg in the micronucleus test and 150mg/kg in the comet assay did not show any genotoxicity potential. *In vitro* tests for chromosomal aberration found out to be less reliable compared to *in vivo* micronucleus tests [Kirkland et al., 2005; Matthews et al., 2006]. In addition, evidence for the lack of a deoxyribonucleic acid damaging potential *in vivo* from the negative comet assay, it is concluded that Isturisa has no relevant genotoxic risk in humans.	*In vivo* genotoxicity studies in rats did not show any deoxyribonucleic acid damage, therefore, Isturisa is not a genotoxic risk to humans.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Carcinogenicity Hepatocellular adenomas in male rats and mice at doses ≥ 10mg/kg and hepatocellular adenomas/carcinomas in female rats at 30 mg/kg were noted in both rats and mice in 104-week carcinogenicity studies. Isturisa was not a mutagenic or genotoxic agent based on the conducted genotoxicity studies and therefore, hepatic neoplasms noted in rat and/or mouse carcinogenicity studies with Isturisa were likely due to non-genotoxic mechanisms. Moreover, repeat-dose toxicity studies conducted in rats and mouse but not in dogs with Isturisa have consistently shown hepatocellular hypertrophy in the liver. Gene expression data from rat livers treated with Isturisa for 4-weeks demonstrated the induction of several xenobiotic enzymes including CYP2B1/CYP2B2 and UDP-GT transcripts which are known targets of the constitutive androstane receptor-mediated gene expression pathway. The constitutive androstane receptor activation is well known for activating rodent specific non-genotoxic hepatocarcinogenesis [Elcombe et al., 2013]. Above stated data from xenobiotics suggest that rodent-specific P450 induction, with subsequent proliferative liver changes, can lead to liver tumours in rodent carcinogenicity studies, and such findings are considered not likely relevant for risk of liver cancer in humans [Friedrich and Olejniczak, 2011; Holsapple et al., 2006; La Vecchia and Negri, 2014].	Isturisa-related hepatocellular neoplasms occurred via mechanisms that are rodent-specific and unlikely to occur in humans due to qualitative differences in the mechanism of action.
Thyroid toxicity Thyroid weight increases and/or follicular cell hyperplasia/hypertrophy were noted in repeat dose studies in rat and follicular cell adenomas were noted in male rats in a 104-week carcinogenicity study. Follicular cell hyperplasia was also noted in male mice in a 104-week carcinogenicity study. The likely mechanism of action consists of increased thyroid hormone clearance due to hepatic enzyme induction (UDP-GT) by Isturisa resulting in compensatory increase in thyroid stimulating hormone and proliferation/tumours of thyroid follicles. Due to species-specific differences in thyroid hormone metabolism, these events are unlikely to occur in humans with Isturisa [Alison et al., 1994; Capen et al., 1997].	Isturisa-related thyroid toxicity/neoplasms occurred via mechanisms that are rodent-specific and unlikely to occur in humans due to qualitative differences in the mechanism of action.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Safety pharmacology	
Cardiovascular system Effects on the cardiovascular system, including potential effects on the QT interval, proarrhythmic indices and corrected QT interval (QTc) prolongation were observed in the *in vitro* study in isolated rabbit heart or *in vivo* studies in dogs and monkeys with Isturisa. Proarrhythmic indices were observed at 10µM in an isolated rabbit heart assay (15-fold the estimated human plasma free-drug Cmax at the highest clinically used dose of 30mg bid). Additionally, QTc prolongation was noted at 50mg/kg after 2 weeks of iv dosing in dogs (15-fold the plasma-free drug Cmax exposure at the highest clinical dose), at 30mg/kg oral (gavage) after a single dose in monkeys and at 10mg/kg/day orally in monkeys for 2-weeks (23- and 11-fold, respectively, the plasma free drug Cmax exposure at 30mg bid clinical dose).	Based on the exposure-response relationship observed in clinical thorough QT/QTc (TQT) Study CLCI699C2105 and the Cmax predicted from the population pharmacokinetics (PK) analysis, the mean QT interval with Fridericia's correction (QTcF) for 30mg dose (the maximum recommended dose in clinical practice) is estimated to be 5.3ms. Therefore, electrocardiograms (ECGs) should be monitored when treating patients with cardiovascular issues. No unconfounded case of arrhythmia or confirmed QTcF interval prolongation to >500ms have been recorded in any subject in the available clinical trial data. QT prolongation is classified as an important identified risk for Isturisa. Also, long-term safety (including hypocortisolism, CV safety and QT prolongation, hormones of the HPA-axis including ACTH increase, and clinical consequences of increased sexual hormones) is considered missing information for Isturisa.
Nervous system Isturisa-related central nervous system (CNS) findings were noted mainly in mice and dogs; these included: aggressive behaviour, hypersensitivity to touch and increased locomotor activity. The estimated safety margins based on the plasma free-drug Cmax at the NOAEL in 13-week rat and mouse and 39-week dog repeat-dose toxicity studies exceeded by approximately 2- to 15-fold the estimated human plasma free-drug Cmax at the highest clinically used dose of 30mg bid. The mechanism for CNS findings in animals is currently unknown. Evidence suggests that the brain can synthesise aldosterone and has receptors for mineralocorticoids [Gomez-Sanchez et al., 2005]. An alternative mechanism would be the stimulation of central histamine-1 receptors. Isturisa inhibited histamine-1 receptor *in vitro* (IC50 10µM) 15 times the estimated human brain free-drug concentration (0.65µM) seen at 30mg bid which could play a role of agonist or antagonist activity.	Relevant adverse events (AEs) reflecting psychomotor changes from the Nervous system disorders and Psychiatric disorders MedDRA System Organ Class (SOC) reported in clinical trials with Isturisa were heavily confounded. Therefore, the observation of adverse CNS findings at high doses in animal studies do not appear to have translated into clinically-relevant CNS effects in humans at clinically relevant doses.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Steroid hormones Isturisa inhibited the corticosteroid stimulated activity of recombinant human aldosterone synthase dose-dependently with an IC50 of 0.7 ± 0.03nM (mean ± standard error of the mean, n=3). Isturisa, via oral administration, did not show any signs of aldosterone inhibition activity other than changes in the adrenal glands. However, in the 2-week iv continuous infusion studies at high doses, electrolyte changes were noted in rat and dog. Sex hormones (testosterone and oestradiol) were not measured in adult animal studies but were measured in a 4-week juvenile rat study (administered between 28 and 55 post-natal days). A slight decrease in testosterone levels in males and no change in the oestradiol levels in females were noted at 50mg/kg with no impact on the reproductive performance in either of the sexes.	Compared to baseline, a decrease in mean plasma aldosterone levels was observed over time in all patients accompanied by an increase in the mean plasma levels of the aldosterone precursor 11-deoxycortisosterone in both male and female patients in Study CLCI699C2301. Compared to baseline, a decrease in mean dehydroepiandrosterone sulphate, and an increase in both testosterone and oestradiol levels were noted in both female and male subjects in Study CLCI699C2301. The changes in testosterone resulted in androgenic effects in some of the female patients (acne and hirsutism), while the change in oestrogen had no clinical impact in male patients. These hormonal changes were reversible on discontinuation of Isturisa. Long-term safety (including hypocortisolism, CV safety and QT prolongation, hormones of the HPA-axis including ACTH increase, and clinical consequences of increased sexual hormones) is considered missing information for Isturisa.

ACTH=adrenocorticotropic hormone; AUC=area under the curve; bid=twice daily; Cmax=maximum concentration; CNS=central nervous system; CV=cardiovascular; CYP=cytochrome P450; ECG=electrocardiogram; HPA=hypothalamic-pituitary-adrenal; IC50=half maximal inhibitory concentration; iv=intravenous; NOAEL=no observed adverse effect level; PK=pharmacokinetics; PPND=pre- and post-natal developmental; QTc=corrected QT interval; QTcF=Fridericia's corrected QT interval; TQT= thorough QT/QTc; UDP-GT=uridine 5'-diphospho-glucuronosyltransferase.

Part II: Module SIII – Clinical Trial Exposure

Isturisa is indicated for the treatment of endogenous CS in adults. At the data lock point of this RMP, a total of 575 subjects have been exposed to Isturisa in the endogenous CS clinical development programme (13 trials: 10 completed, 2 ongoing and 1 planned). Seven of 13 trials in the endogenous CS clinical development programme involved the use of Isturisa in healthy volunteers (Studies CLCI699C1101 [n=20], CLCI699C2101 [n=5], CLCI699C2102 [n=19], CLCI699C2103 [n=33], CLCI699C2104 [n=15], CLCI699C2105 [n=86] and CLCI699C2108 [n=24]).

The remaining 6 trials included the following:

- Study CLCI699C1201: subjects with CS due to causes other than CD (completed with 9 subjects).
- Study CLCI699C2201 – Part 2 (LINC2): subjects with CD (completed with 27 subjects).
- Study CLCI699C2203: paediatric patients with CD (ongoing; 4 subjects).
- Study CLCI699C2301 (LINC3): subjects with CD (completed with 137 subjects).
- Study CLCI699C2302 (LINC4): subjects with CD (completed; 73 subjects).
- Study CLCI699C2X01B: subjects with endogenous CS (ongoing; all 127 subjects were transitioned from the LINC2, LINC3 and LINC4 trials).

This RMP focuses on safety information from the following trials:

- **Study CLCI699C2201 – Part 2 (LINC2):** A Phase 2, initially proof of concept study assessing the safety/tolerability and efficacy of 10-weeks treatment with Isturisa followed by a 12-week treatment period in patients with CD; currently the study is in an extension phase to assess the long-term safety and efficacy of Isturisa in patients with CD.
- **Study CLCI699C2301 (LINC3):** A Phase 3, multi-centre, double-blind, randomised withdrawal study of Isturisa following a 24-week, single-arm, open-label dose titration and treatment period to evaluate the safety and efficacy of Isturisa for the treatment of patients with CD.
- **Study CLCI699C2302 (LINC4)**: A Phase 3, multi-centre, randomised, double-blind, 48-week study with an initial 12-week placebo-controlled period to evaluate the safety and efficacy of Isturisa in patients with CD.

Exposure data from Studies CLCI699C2201 (LINC2), CLCI699C2301 (LINC3), and CLCI699C23002 (LINC4) by treatment duration are presented in Table 5, Table 6 and Table 7, respectively.

Table 5: Duration of exposure – Study CLCI699C2201 – Part 2
(Safety analysis set, data cut-off date: 14 November 2017)

Duration	All patients (N=19) n (%)
Less than 3 months	2 (10.5)
At least:	
3 months	17 (89.5)
6 months	16 (84.2)
9 months	15 (78.9)
12 months	15 (78.9)
18 months	13 (68.4)
24 months	13 (68.4)
30 months	11 (57.9)
36 months	11 (57.9)
48 months	11 (57.9)

Source: Annex 7 (Brief statistical description and Supportive outputs – Table 1.4-1.4)

Table 6: Duration of exposure – Study CLCI699C2301
(Safety analysis set, data cut-off date: 21 February 2018)

Duration	All patients (N=137) n (%)
Less than 2 weeks	2 (1.5)
At least:	
4 weeks	135 (98.5)
8 weeks	132 (96.4)
12 weeks	131 (95.6)
16 weeks	126 (92.0)
20 weeks	124 (90.5)
24 weeks	121 (88.3)
28 weeks	118 (86.1)
32 weeks	115 (83.9)
36 weeks	114 (83.2)
40 weeks	113 (82.5)
44 weeks	109 (79.6)
48 weeks	105 (76.6)
52 weeks	95 (69.3)
104 weeks	49 (35.8)
156 weeks	6 (4.4)

Source: Annex 7 (Brief statistical description and Supportive outputs – Table 1.4-1.3)

Table 7: Duration of exposure during – Study CLCI699C2302
(Primary Analysis, safety analysis set, data cut-off date: 25 February 2020)

Duration	All patients (N=73) n (%)
Less than 2 weeks	1 (1.4)
At least:	
4 weeks	1 (1.4)
6 weeks	1 (1.4)
10 weeks	0
12 weeks	0
20 weeks	1 (1.4)
24 weeks	1 (1.4)
28 weeks	1 (1.4)
34 weeks	1 (1.4)
36 weeks	2 (2.7)
38 weeks	3 (4.1)
44 weeks	2 (2.7)
48 weeks	5 (6.8)
50 weeks	2 (2.7)
52 weeks	1 (1.4)
56 weeks	4 (5.5)
58 weeks	1 (1.4)
60 weeks	1 (1.4)
62 weeks	2 (2.7)
64 weeks	1 (1.4)
66 weeks	3 (4.1)
68 weeks	3 (4.1)
70 weeks	1 (1.4)
72 weeks	1 (1.4)
74 weeks	3 (4.1)
76 weeks	2 (2.7)
78 weeks	2 (2.7)
82 weeks	3 (4.1)
84 weeks	5 (6.8)
86 weeks	1 (1.4)
88 weeks	2 (2.7)
94 weeks	4 (5.5)
96 weeks	9 (12.3)
104 weeks	2 (2.7)
112 weeks	1 (1.4)

Source: Section 14.3 (Table 14.3-1.3) of Primary Analysis Report for Study CLCI699C2302.

Exposure data from Studies CLCI699C2201 (LINC2), CLCI699C2301 (LINC3) and CLCI699C2302 (LINC4) by age and gender, and race are presented in Table 8 and Table 9, respectively.

Table 8: Exposure to Isturisa by age group and gender – Studies CLCI699C2301 (data cut-off date: 21 February 2018), CLCI699C2201 - Part 2 (data cut-off date: 14 November 2017) and CLCI699C2302 (data cut-off date: 25 February 2020) (Safety analysis set)

Category		Study CLCI699C2301 (N=137)		Study CLCI699C2201 – Part 2 (N=19)		Study CLCI699C2302 (N=73)		Total (N=229)	
Age	**Sex**	**Patients n (%)**	**Patient-time (years)**	**Patients n (%)**	**Patient-time (years)**	**Patients n (%)**	**Patient-time (years)**	**Patients n (%)**	**Patient-time (years)**
All ages	**Total**	**137 (100)**	**210.9**	**19 (100)**	**57.5**	**73 (100)**	**95**	**229 (100)**	**363.4**
	Male	31 (22.6)	48.5	5 (26.3)	16.1	12 (16.4)	15.4	48 (21.0)	80
	Female	106 (77.4)	162.5	14 (73.7)	41.4	61 (83.6)	79.6	181 (79.0)	283.5
18 to <65 years	**Total**	**130 (94.9)**	**201.8**	**19 (100)**	**57.5**	**71 (97.3)**	**91.3**	**220 (96.1)**	**350.6**
	Male	31 (22.6)	48.5	5 (26.3)	16.1	11 (13.5)	13.5	47 (20.5)	78.1
	Female	99 (72.3)	153.3	14 (73.7)	41.4	60 (77.8)	77.8	173 (75.5)	272.5
≥65 years	**Total**	**7 (5.1)**	**9.1**	**0**	**0**	**2 (2.7)**	**3.7**	**9 (3.9)**	**12.8**
	Male	0	0	0	0	1 (1.8)	1.8	1 (0.4)	1.9
	Female	7 (5.1)	9.1	0	0	1 (1.8)	1.8	8 (3.5)	10.9

Patient-time is the sum of each patient's treatment exposure to Isturisa in years. Patient -time is based on the number of patients in each category.
Source: Annex 7 (Table 1.4-1.1) and the Primary Analysis Report for Study CLCI699C2302.

Table 9: Exposure to Isturisa by race – Studies CLCI699C2301 (data cut-off date: 21 February 2018), CLCI699C2201 - Part 2 (data cut-off date: 14 November 2017) and CLCI699C2302 (data cut-off date: 25 February 2020) (Safety analysis set)

Race	Study CLCI699C2301 (N=137)		Study CLCI699C2201 – Part 2 (N=19)		Study CLCI699C2302 (N=73)		Total (N=229)	
	Patients n (%)	Patient-time (years)	Patients n (%)	Patient-time (years)	Patients n (%)	Patient-time (years)	Patients n (%)	Patient-time (years)
All races	**137 (100)**	**210.9**	**19 (100)**	**57.5**	**73 (100)**	**95**	**229 (100)**	**363.4**
Caucasian	89 (65.0)	141.0	15 (78.9)	51.4	49 (67.1)	65.8	153 (66.8)	258.2
Black or African American	4 (2.9)	6.0	1 (5.3)	0.4	2 (2.7)	1	7 (3.1)	7.4
Asian	39 (28.5)	58.3	3 (15.8)	5.7	17 (23.3)	20.4	59 (25.8)	84.4
Other	5 (3.6)	5.6	0	0	2 (2.7)	3.5	7 (3.1)	9.1
Unknown	Not applicable	Not applicable	Not applicable	Not applicable	3 (4.1)	4.4	3 (4.4)	4.4

Patient-time is the sum of each patient's treatment exposure to Isturisa in years. Patient -time is based on the number of patients in each category.
Source: Annex 7 (Table 1.4-1.2) and the Primary Analysis Report for Study CLCI699C2302.

Part II: Module SIV – Populations not Studied in Clinical Trials

SIV.1: Exclusion criteria in pivotal clinical studies within the development programme

Important exclusion criteria in the pivotal clinical studies across the development programme are included in Table 10.

Table 10: Important exclusion criteria in pivotal study in the development programme

Criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale for not including as missing information
Children and adolescents (<18 years of age)	The safety and efficacy of Isturisa in children and adolescents aged <18 years have not been established. No data are available and Isturisa is not indicated for use in paediatric patients.	No. Isturisa is not indicated for use in paediatric patients. In addition, CS/CD is extremely rare in the paediatric population.
Pregnant women and breast-feeding women	There are no adequate data from the use of Isturisa during pregnancy. Embryofoetal toxicities were observed in the rat embryofoetal development study at maternally toxic doses of 50mg/kg/day; thus, Isturisa should be considered potentially teratogenic to humans.	Yes.
Patients (diagnosed with CD) with moderate to severe renal impairment	Patients with estimated glomerular filtration rate <60mL/min were excluded because reduced urine free cortisol excretion has been reported in patients with moderate or severe renal impairment and therefore any assessment of disease activity and response to treatment is difficult and/or not accurate.	No. A Phase 1 study (Study CLCI699C2104) was conducted to evaluate the PK and safety of a single dose of 30mg of Isturisa in subjects with varying degrees of impaired renal function (severely impaired: n=6, end-stage renal disease: n=3). The study results indicated that varying degrees of renal impairment did not influence the PK of Isturisa to any significant extent.
Patients (diagnosed with CD) with moderate to severe hepatic impairment	Patients with severe hepatic impairment may be intrinsically more sensitive to liver enzyme and bilirubin elevations.	No. A Phase 1, open-label, multicentre, single dose, parallel group study (Study CLCI699C2103) was conducted to evaluate the PK and safety of a single Isturisa 30mg dose in subjects with varying degrees of hepatic function according to the Child-Pugh classification (mild, moderate, severe). The PK data analysis indicated that administration of Isturisa in the cohort with mild hepatic impairment resulted in similar exposures as compared to the cohort with normal hepatic function, while the cohorts with moderate and severe had approximately 1.4-fold and 2.6-fold higher AUC exposure, respectively, than the cohort with normal hepatic function.

Criteria	Reason for exclusion	Is it considered to be included as missing information? Rationale for not including as missing information
Patients with cardiovascular impairment	Isturisa has been associated with prolongation of the QT interval on the ECG.	No. The safety concern of QT prolongation is classified as an important identified risk for Isturisa.

AUC=area under the curve; CD=Cushing's disease; ECG=electrocardiogram; PK=pharmacokinetics.

SIV.2: Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3: Limitations in respect to populations typically underrepresented in clinical trial development programmes

Limitations in special populations are summarised in Table 11.

Table 11: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Pregnant or lactating women were excluded from the clinical development programme. Embryofoetal toxicities were observed in the rat embryofoetal development study at maternally toxic doses of 50mg/kg/day; thus, Isturisa should be considered potentially teratogenic to humans. It is also advised that breast-feeding should be discontinued during treatment with Isturisa and for at least 1 week after treatment.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Patients with moderate or severe renal or hepatic impairment were excluded from CS trials, but the impact was investigated in dedicated organ impairment studies. Patients with clinically significant impairment in cardiovascular function were excluded from CS trials. Further exposure data for use in patients with other relevant comorbidities in Studies CLCI699C2201 (LINC2), CLCI699C2301 (LINC3) and CLCI699C2302 (LINC4) are provided in Table 12. Overall, use in patients with other relevant comorbidities does not constitute a safety concern.
Population with relevant different ethnic origin	Patient populations from different ethnic origins were included in the clinical development programme (for further details on exposure, see Table 9).
Subpopulations carrying relevant genetic polymorphisms	Patients with Carney Complex, McCune-Albright syndrome, multiple endocrine neoplasia, or aryl hydrocarbon receptor interacting protein mutation were excluded from CS trials because patients with relevant genetic polymorphisms present with a multitude of different clinical and morphological symptoms which cannot be expected to be sufficiently treated by the

Type of special population	Exposure
	investigational drug. For example, patients with Carney complex present with multiple organ affections such as multiple neoplasia and myxomas especially in the heart. Myxoma of the heart can potentially cause serious life-threatening complications (stroke, valvular obstruction, and heart failure).

CS=Cushing's syndrome; PK=pharmacokinetics.

Exposure data available for use in patients with other relevant comorbidities are provided in Table 12.

Table 12: Exposure to Isturisa in patients with other relevant comorbidities (Safety analysis set)

	Study CLCI699C2301 (LINC3)		Study CLCI699C2201 (LINC2)		Study CLCI699C2302 (LINC4)		Total	
	N=137		N=19		N=73		N=229	
Type of impairment	**Patients n (%)**	**Patient-time (years)**	**Patients n (%)**	**Patient-time (years)**	**Patients n (%)**	**Patient-time (years)**	**Patients n (%)**	**Patient-time (years)**
Patients with any impairment	39 (28.5)	56.5	9 (47.4)	32.5	73 (100)	95.0	121 (52.8)	184.0
Patients with hepatic impairment	23 (16.8)	35.5	2 (10.5)	1.1	16 (21.9)	26.1	41 (19.9)	62.7
Patients with renal impairment	10 (7.3)	16.9	3 (15.8)	10.4	19 (26.0)	20.6	32 (14.0)	47.9
Patients with cardiovascular impairment	20 (14.6)	26.2	6 (31.6)	26.6	12 (16.4)	16.8	38 (16.6)	69.6

Patient-time is the sum of each patient's treatment exposure to Isturisa in years. Patient-time is based on the number of patients in each category.

Source: Annex 7 (Table 1.4-1.5) and the Primary Analysis Report for Study CLCI699C2302.

Part II: Module SV – Post-authorisation Experience

SV.1: Post-authorisation exposure

SV.1.1: Method used to calculate exposure

Each pack of 1, 5 or 10mg Isturisa contains a total of 60 tablets. The average daily dose is estimated at 10mg, based on the maintenance dose in clinical trials which varied between 2mg and 7mg bid.

Exposure estimates expressed as patient treatment-years (PTY) using sales volume and the average daily dose are calculated using the following formula:

- Estimated exposure in PTY = Quantity of Isturisa sold (mg) ÷ average daily dose (10mg) ÷ 365 days

The cumulative patient exposure to Isturisa in PTY has been estimated below by taking the above information into account.

SV.1.2: Exposure

Cumulatively, a total of 38,191 packs (1mg: 29,663 packs; 5mg: 5,035 packs; 10mg: 3,493 packs) of Isturisa have been sold, which corresponds to an estimated total of 5,386,080mg (active substance). Based on an average daily dose of 10mg, the estimated cumulative exposure is 1,475.64 PTY.

A stratification of exposure based on gender, age and indication is not available.

Part II: Module SVI – Additional European Union Requirements for the Safety Specification

SVI.1: Potential for misuse for illegal purposes

No potential for misuse of Isturisa for illegal purposes (e.g. as a recreational drug) is expected.

Part II: Module SVII – Identified and Potential Risks

SVII.1: Identification of safety concerns in the initial Risk Management Plan submission

SVII.1.1: Risks not considered important for inclusion in the list of safety concerns in the Risk Management Plan

Reason for not including an identified or potential risk in the list of safety concerns in the RMP

Risks that were not considered important for inclusion in the list of safety concerns for Isturisa with the reasons for non-inclusion are provided in Table 13.

Table 13: Risks not considered important for inclusion in the list of safety concerns

Adverse reaction	Reason for non-inclusion as an RMP safety concern
Effects on blood pressure and body weight	This risk is due to precursor accumulation in the adrenal cortex with minimal clinical impact on patients (in relation to the severity of the indication treated) and which therefore does not impact the risk-benefit profile. In Study CLCI699C2301, at the end of the Core Period (Week 48), in the overall study population a decrease in weight (4.6%), body mass index (4.6%), waist circumference (4.2%), systolic blood pressure (6.8%) and diastolic blood pressure (6.6%) from baseline was reported in the overall study population. Adverse events of oedema did not correlate with significant body weight change. No clinically meaningful changes in weight or blood pressure were seen in Study CLCI699C2201.
Effects on electrolytes homeostasis	This risk is due to precursor accumulation in the adrenal cortex with minimal clinical impact on patients (in relation to the severity of the indication treated) and which therefore does not impact the risk-benefit profile. In Study CLCI699C2301, hypokalaemia or blood potassium decreased (Grade 3) occurred as a single episode in 6 patients and 1 patient had a single episode of Grade 4 hypokalaemia. Most patients with hypokalaemia AEs required additional therapy and had ongoing hypokalaemia prior to Isturisa initiation. As abnormal laboratory results, 8 patients had Grade 3 hypokalaemia via lab data and 3 patients had hyperkalaemia. Isturisa exposure was found to have statistically significant impact on the change of potassium level from baseline; the fitted models suggest a decreasing trend in change of potassium from baseline as Isturisa exposure levels increase (Study CLCI699C2301). No Grade 3/4 hypernatremia or hyponatremia have been observed (Study CLCI699C2301). In Study CLCI699C2201, decreased blood potassium (also “hypokalaemia”) were observed in 4/19 patients; all were Grade 1 or 2 in severity. All events except in 1 patient were suspected to be related to study drug. In 1 patient, dose interruption was required; no action was taken with study drug in the other 4 patients.

Adverse reaction	Reason for non-inclusion as an RMP safety concern
Effect on sex hormones	This risk is due to precursor accumulation in the adrenal cortex that require no further characterisation and is followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are sufficient. Compared to baseline, a decrease in mean dehydroepiandrosterone sulphate, and an increase in both testosterone and oestradiol levels were noted in both female and male patients in Study CLCI699C2301. The changes in testosterone resulted in androgenic effects in some female patients (all AEs of acne/hirsutism were of Grade 1/2), while the change in oestrogen had no clinical impact in male patients. These hormonal changes were reversible on discontinuation of Isturisa. In Study CLCI699C2201, acne was observed in 3/19 patients (Grade 2 in 2 patients and Grade 1 in 1 patient). In 2 patients, the acne was concurrent with hirsutism.
Corticotroph tumour volume increased	Tumour volume increase has been seen in some patients treated with other medical treatments and may be part of the natural history of the disease. Follow-up of patients with CD in routine clinical practice already includes periodical imaging (magnetic resonance imaging or computed tomography, contrast-enhanced imaging) and plasma ACTH assessment. In Study CLCI699C2301, during the 48-week period, the median pituitary tumour size (assessed as both volume and max diameter) remained stable in patients with measurable tumour at baseline. Therefore, there was no evidence of tumour enlargement overall, and any fluctuations in size were not associated with a parallel increase in ACTH or any temporal relationship.
Hepatotoxicity	Despite the slight elevation of liver enzymes noted in animal studies, these findings have not translated into clinically relevant observations in humans. Aminotransferase elevations were infrequent, typically mild and reversed spontaneously or following dose adjustment. There were no clinically-significant elevations without clear confounders and no patients discontinued Isturisa due to increased liver parameters. No clinically-relevant relationship was observed between Isturisa concentration and change from baseline in aminotransferases in the exposure-response analysis.
Effects on CNS	This is a risk with minimal clinical impact on patients (in relation to the severity of the indication treated). The behavioural changes seen in animal studies has not translated to into clinically relevant observations in humans. Isturisa crosses the blood-brain-barrier, however, the estimated human brain free-drug concentration is 0.65µM at the maximum clinical dose of 30mg bid, which is <1/15 of the IC50 for relevant CNS receptors. The CNS-related findings were generally present at the higher doses in mice, rats and dogs. In Study CLCI699C2201 and Study CLCI699C2301, the reported neurologic and psychiatric AEs, were nonspecific or were confounded by the effects of the underlying disease, which is known to have associated psychiatric symptoms up to 80% [Pivonello et al., 2016]. The events did not suggest the kind of CNS toxicity observed in mouse and dog repeat-dose toxicology studies.

ACTH=adrenocorticotropic hormone; AE=adverse event; CD=Cushing's disease; CNS=central nervous system; RMP=Risk Management Plan.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the Risk Management Plan

The rationale for considering the important identified and potential risks and missing information to impact the risk-benefit balance of Isturisa is presented in Table 14, Table 15 and Table 16, respectively.

Table 14: Important Identified Risks

Risk	Risk-benefit impact (Reasons for classification as important identified risk)
Hypocortisolism	Inhibition of cortisol synthesis by any effective treatment has the potential of causing hypocortisolism-related AEs such as adrenal insufficiency and glucocorticoid withdrawal syndrome. Symptomatic hypocortisolism, including serious adverse events (SAEs), has been reported in clinical trials with Isturisa. These events were managed by dose reduction or temporary interruption of Isturisa, and/or by administration of glucocorticoid replacement therapy in some patients. Given the potential severity of hypocortisolism with the impact on the benefit-risk balance, and the need for risk minimisation activities involving wording in the product information to advise on specific clinical actions to be taken to minimise the risk (cortisol monitoring and dose adjustments, management of hypocortisolism), this risk is classified as an important identified risk for Isturisa.
QT prolongation	Cardiac safety of Isturisa was evaluated *in vitro* and *in vivo*. The IC50 for the Human Ether-à-go-go-Related Gene assay was 54µM. Isolated rabbit hearts: *in vitro* proarrhythmic indices indicative of a torsadogenic potential seen at 10µM. In TQT Study CLCI699C2105, there was a positive correlation between Isturisa concentration and QTcF. There was evidence of QT prolongation at the Isturisa 150mg dose level (5-fold higher than maximal clinical dose) where a mean maximum QTcF of 25.38ms (90% CI: 23.53, 27.22) was observed. The concentration-QTcF effect model from Study CLCI699C2105 in the population-PK analysis was applied to the predicted Cmax values for Isturisa at 30mg. Based on the predicted exposure levels, the predicted maximum mean QTcF on Isturisa 30mg is 5.3ms. The results remained below the QTcF effect of regulatory concern (i.e., an upper boundary of the 90% CI <10ms). No patient experienced a QTcF values >500ms, or increases from baseline of >60ms. The maximum effect was observed at 1 hour post-dose (time taken to reach the Cmax). No dose-related effects were observed for the cardiac intervals (QRS, PR, or HR), or on blood pressure of Isturisa/LCI699 10 mg or 150mg. In Study CLCI699C2301, there was no QTcF prolongation >480ms confirmed by central reading. No confirmed case of QTcF prolongation (>500ms) has been seen in the Cushing's programme to date. Given the potential severity of QT prolongation with the impact on the risk-benefit balance (particularly in the event of potassium disturbance), and the need for risk minimisation activities involving specific clinical actions to be taken to minimise the risk (ECG monitoring, avoidance of concomitant QT-prolonging medication), this risk is classified as an important identified risk for Isturisa.

AE=adverse event; CI=confidence interval; Cmax=maximum concentration; ECG=electrocardiogram; IC50=half maximal inhibitory concentration; PK=pharmacokinetics; QTc=corrected QT interval; QTcF=Fridericia's corrected QT interval; SAE=serious adverse event; TQT=thorough QT/corrected QT interval.

Table 15: Important Potential Risks

Risk	Risk-benefit impact (Reasons for classification as important potential risk)
Reproductive toxicity/Embryofoetal development	Toxicity was noted in female reproductive organs (ovary, uterus and vagina) in female rats. Embryofoetal toxicity was seen in rats and rabbits and teratogenic effects were seen in rats at maternally toxic doses, potentially due to aromatase inhibition. Isturisa, at high doses was not tolerated in pregnant rats and resulted in mortality at the end of gestation/at parturition effects on clinical condition indicative of dystocia and delays in the start of parturition. Pregnant women or women of childbearing potential not using effective methods of contraception were excluded from the clinical trial programme, hence this risk in humans is not known. Given the potential severity of teratogenicity with the impact on the benefit-risk balance, and the need for risk minimisation activities involving wording in the SmPC to advise on specific clinical actions to be taken to minimise the risk (avoidance of pregnancy, need for effective contraception), this safety concern is classified as an important potential risk for Isturisa.

SmPC=Summary of Product Characteristics.

Table 16: Missing Information

Missing information	Risk-benefit impact (Reasons for classification as missing information)
Breast-feeding women	Breast-feeding women were excluded from the clinical development programme. Therefore, there are no data on the effects of Isturisa on milk production or the breastfed child, and use in breast-feeding is considered missing information for Isturisa. It is not known if Isturisa is transferred into human milk.
Long-term safety (including hypocortisolism, CV safety and QT-prolongation, hormones of the HPA-axis including ACTH increase, and clinical consequences of increased sexual hormones)	At the time of submission, the median exposure to Isturisa in CS patients across studies ranged from 80 days to 226 weeks, and in the pivotal study median exposure was 74.7 weeks (range: 0.9 to 165.3 weeks). The safety of patients with long-term use is therefore considered missing information.
Use in non-CD CS patients including long-term effects	The clinical development programme included 9 patients with non-CD CS, and therefore information in this patient population is considered limited.

ACTH=adrenocorticotropic hormone; CD=Cushing's disease; CS=Cushing's syndrome; CV=cardiovascular; HPA=hypothalamic-pituitary-adrenal.

SVII.2: New safety concerns and reclassification with a submission of an updated Risk Management Plan

Not applicable; there were no changes to the safety concerns of Isturisa.

SVII.3: Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Hypocortisolism and QT prolongation are considered important identified risks for Isturisa. Information pertaining to these safety concerns are presented in Table 17, Table 18, Table 19 and Table 20, respectively.

Table 17: Clinical trial data pertaining to hypocortisolism

	Study CLCI699C2301 (N=137) n (%) 95% CI	Study CLCI699C2201 – Part 2 (N=19) n (%) 95% CI	Study CLCI699C2302 (N=73) n (%) 95% CI	Total (N=229) n (%) 95% CI
Number of patients with at least 1 event	70 (51.1) (42.4, 59.7)	8 (42.1) (20.3, 66.5)	20 (27.4)	98 (42.8) (41.9, 58.1)
Exposure-adjusted overall incidence, n (exposure-adjusted incidence rate [IR] per 100 PTY)	70 (57.6)	8 (20.1)	20 (24.2)	98 (39.9)
Grade 3 AEs	14 (10.2)	1 (5.3)	2 (2.7)	17 (7.4)
Grade 4 AEs	0	0	0	0
SAEs	13 (9.5)	1 (5.3)	2 (2.7)	16 (7.0)
Fatal AEs	0	0	0	0

AE=adverse event; CI=confidence interval; IR=incidence rate; PTY=patient treatment-years; SAE=serious adverse event.
The IR represents the number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in PTY is counted up to the first qualifying event (or end of time at risk for patients without event).
For Study LCI699C2301, any events experienced by patients randomised to placebo while on placebo are not included in this analysis.
Source: Annex 7 (Table 2.3-1.1a).

Table 18: Important identified risk: Hypocortisolism

Important identified risk: Hypocortisolism	
Medical Dictionary for Regulatory Activities (MedDRA) terms	Company MedDRA Query of Hypocortisolism (adrenal insufficiency/corticosteroid withdrawal syndrome) which includes the Preferred Terms (PTs) of Addison's disease, Adrenal insufficiency, Adrenal suppression, Adrenocortical insufficiency acute, Cortisol decreased, Cortisol deficiency, Cortisol free urine decreased, Glucocorticoid deficiency, Glucocorticoids decreased, Primary adrenal insufficiency, Secondary adrenocortical insufficiency, and Steroid withdrawal syndrome.

Important identified risk: Hypocortisolism	
Potential mechanisms	Isturisa is a potent, orally bioavailable inhibitor of 11β-hydroxylase (CYP11B1), the enzyme that catalyses the last step in the synthesis of cortisol. Decrease of cortisol may lead to development of hypocortisolism-related AEs including adrenal insufficiency or cortisol withdrawal syndrome.
Evidence source and strength of evidence	Post-marketing experience, clinical trial experience and literature. Cumulatively, a total of 98 subjects experiencing hypocortisolism were reported from clinical trials experience and 149 case reports describing 164 events pertaining to hypocortisolism were identified from post-marketing experience. Events of decreased cortisol and decreased response to ACTH stimulation testing were noted in patients with hypertension and healthy volunteer studies. Events of hypocortisolism, including serious and symptomatic, have been reported in clinical trials with Isturisa.
Characterisation of the risk	Based on clinical trial experience, Adrenal insufficiency is listed as a very common adverse drug reaction in the Company Core Data Sheet (CCDS) for Isturisa. **Clinical trial experience** Adverse events pertaining to hypocortisolism were reported in 98 patients (70 patients in Study CLCI699C2301, 8 patients in Study CLCI699C2201 and 20 patients in Study CLCI699C2302). Of the 98 patients with AEs, 17 patients had Grade 3 events and no Grade 4 events were reported. Additionally, SAEs were reported in 16 patients. No deaths were reported due to AEs pertaining to hypocortisolism. The occurrence of hypocortisolism-related events (70/137, 51.1%) in Study CLCI699C2301 was highest during initial dose titration, or periods of intercurrent illness. These events reflected both adrenal insufficiency and glucocorticoid withdrawal syndrome (following rapid lowering of cortisol levels). There was no correlation with any specific dose level, reflecting the high inter-subject variability of effective dose required to reduce cortisol levels to the normal range. All events resolved following dose reduction or temporary interruption of Isturisa, and by administration of glucocorticoid replacement therapy when indicated. In Study CLCI699C2301, a total of 13 patients experienced a SAE of hypocortisolism: 9 SAEs of adrenal insufficiency were reported in 8 patients, 5 of the SAEs were of Grade 3. In 1 patient, the Grade 1 SAE was preceded by a Grade 1 SAE of Isturisa overdose. One patient with 2 episodes of Grade 3 adrenal insufficiency SAEs experienced a right adrenal venous thrombosis (Grade 2) 44 days before the first SAE of adrenal insufficiency; the second episode occurred in concomitance with AE of influenza with fever. An additional 3 episodes in 3 other patients occurred in concomitance or shortly after (within 1 week of) an AE of infection (influenza, gastroenteritis, respiratory tract infection). Two additional patients had 3 SAEs of glucocorticoid deficiency. All episodes of adrenal insufficiency SAE were managed with temporary reduction or interruption of the study drug, and with or without administration of glucocorticoids in some patients; in two patients the event led to study discontinuation. All adrenal insufficiency SAEs resolved. Hypocortisolism events were observed in patients with CS treated with other surgical and/or medical treatments. In Study CLCI699C2302, Hypocortisolism-related AEs were expected based on the mechanism of action of Isturisa and mostly occurred during the open-label period. The AEs occurred in 20 (27.4%) patients, which included 8 of 25 patients who transitioned from placebo to Isturisa. Hypocortisolism-related AEs were

<table>
<tr><th colspan="2">Important identified risk: Hypocortisolism</th></tr>
<tr><td></td><td>neither associated with any specific Isturisa dose (events occurred on 1 mg to 10 mg bid), nor with mean urinary free cortisol (mUFC) levels. All of the AEs were suspected to be related to study drug. Hypocortisolism-related AEs were reported mainly as Grade 1/2, and managed by dose reduction/interruption and concomitant medication (13; 17.8%), including steroid supplementation. The AEs in 27.4% patients were either resolved or resolving (condition was improved); AEs in 6.8% patients were ongoing at the time of the data lock point. The hypocortisolism-related AEs were adrenal insufficiency (27.4%), acute adrenal insufficiency, and steroid withdrawal syndrome (1.4% each). Most of the patients with hypocortisolism-related AEs had 1 episode. One patient had more than 2 episodes of the hypocortisolism-related AEs. All the events were of Grade 3 or lower. Grade 3 AEs were infrequent, serious and coded to adrenal insufficiency (2.7%). Except for the AEs in 5 patients, AEs in all other patients resolved. The AE of steroid withdrawal syndrome in Patient C2302-2001-004 was Grade 2 in severity and suspected to be related to study drug. The patient's mUFC was less than the upper limit of the normal at the time of the AE, and the patient was receiving a dose of 10mg/day. Hypocortisolism-related AEs required adjustment or interruption of Isturisa treatment in nearly all patients, and 13 patients (17.8%) required glucocorticoid replacement.

Cumulative post-marketing data
Cumulatively, a total of 149 case reports describing 164 events (116 serious, 48 non-serious) pertaining to hypocortisolism have been identified from post-marketing experience. The AEs reported were as follows:
<table>
<tr><th>Event (PT)</th><th>Frequency</th></tr>
<tr><td>Adrenal insufficiency</td><td>78</td></tr>
<tr><td>Cortisol decreased</td><td>54</td></tr>
<tr><td>Adrenocortical insufficiency acute</td><td>14</td></tr>
<tr><td>Steroid withdrawal syndrome</td><td>7</td></tr>
<tr><td>Cortisol free urine decreased</td><td>6</td></tr>
<tr><td>Glucocorticoid deficiency</td><td>4</td></tr>
<tr><td>Glucocorticoids decreased</td><td>1</td></tr>
</table>
The events outcomes were as follows: unknown (n=64), resolved (n=58), resolving (n=18), not resolved (n=18), fatal (n=3), resolved with sequelae (n=2) and not applicable (n=1).

Impact on individual patient/quality of life
The impact on the individual patient is significant but preventable by monitoring clinical signs and symptoms and serum cortisol or urinary free cortisol levels, and dose modification as indicated in the CCDS.

Reversibility
Readily reversible by administration of corticosteroids.</td></tr>
<tr><td>Risk factors and risk groups</td><td>All patients treated for endogenous CS. The occurrence of hypocortisolism in Study CLCI699C2301 was highest during initial dose titration, after dose up-titration (when the last mUFC levels were in the low part of the normal range) or periods of intercurrent illness. There was no correlation with any specific dose level.</td></tr>
<tr><td>Preventability</td><td>Patients should be informed prior to administration of Isturisa to ensure that they seek medical attention should signs and symptoms of hypocortisolism occur. Cortisol levels and signs and symptoms related to hypocortisolism (e.g., weakness, fatigue, anorexia, nausea, vomiting, hypotension, hyperkalaemia, hyponatremia or</td></tr>
</table>

Important identified risk: Hypocortisolism	
	hypoglycaemia) should be monitored, particularly during dose titration and periods of relevant physical or psychological stress. In case of hypocortisolism, dose reduction or interruption of treatment with Isturisa and temporary exogenous steroid (glucocorticoid) replacement therapy may be necessary. Information and management guidelines are included in the product labelling.
Impact on the benefit-risk balance of the product	The risk of hypocortisolism is a direct consequence of the efficacy of Isturisa in reducing cortisol levels and is balanced by appropriate and timely medical management. In Study CLCI699C2301, there was a low rate of study discontinuation (5.7%) due to events of hypocortisolism, and therefore the actual benefit-risk balance for this risk is considered to be moderately impacted. The expected benefit-risk balance of Isturisa is moderately impacted by this risk considering the nature of the treated indication, the familiarity of the prescribers (endocrinologists) with hypocortisolism in terms of how to diagnose and manage, the requirement in the label for regular cortisol monitoring to enable early detection and corrective action, the information for patients to alert them to signs or symptoms and to inform the prescriber immediately.
Public health impact	The public health impact on overall public health is minimal as the patient population is small. The public health impact is significant within this population but reduced by monitoring of clinical signs and symptoms and cortisol levels as well as dose modification.

ACTH=adrenocorticotropic hormone; AE=adverse event; bid=twice daily; CCDS=Company Core Data Sheet; CS=Cushing's syndrome; MedDRA=Medical Dictionary for Regulatory Activities; mUFC=mean urinary free cortisol; PMS=post-marketing surveillance; PT=Preferred Term; SAE=serious adverse event.

Table 19: Clinical trials data of QT prolongation

	Study CLCI699C2301 (N=137) n (%) 95% CI	**Study CLCI699C2201 – Part II (N=19) n (%) 95% CI**	**Study CLCI699C2302 (N=73) n (%) 95% CI**	**Total (N=229) n (%) 95% CI**
Number of patients with at least 1 event	5 (3.6) (1.2, 8.3)	2 (10.5) (1.3, 33.1)	3 (4.1)	10 (4.4) (1.8, 9.0)
Exposure-adjusted overall incidence, n (exposure-adjusted IR per 100 PTY)	5 (2.4)	2 (3.6)	3 (3.1)	10 (2.8)
Grade 3 AEs	2 (1.5)	0	0	2 (0.9)
Grade 4 AEs	0	0	0	0
SAEs	1 (0.7)	1 (5.3)	0	2 (0.9)
Fatal AEs	0	0	0	0

AE=adverse event; CI=confidence interval; IR=incidence rate; PTY=patient treatment-years; SAE=serious adverse event.

The IR represents the number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in PTY is counted up to the first qualifying event (or end of time at risk for patients without event).

For Study CLCI699C2301, any events experienced by patients randomised to placebo while on placebo are not included in this analysis.

Source: Annex 7 (Table 2.3-1.1b).

Table 20: Important identified risk: QT prolongation

Important identified risk: QT prolongation	
MedDRA terms	Standardised MedDRA Query of Torsade de pointes/QT prolongation.
Potential mechanisms	The mechanism by which Isturisa may cause QT-prolongation is not yet understood.
Evidence sources and strength of evidence	A thorough QT study (Study CLCI699C2105) demonstrated a positive exposure-related Friderica's corrected QT interval (QTcF) prolongation (a measure of the electrical activity of the heart) for Isturisa. The QTcF increased by 25.38ms (90% confidence interval: 23.53, 27.22) on Isturisa 150mg, but not on Isturisa 10mg (1.73ms at 3 hours post-dose). The estimated mean QTcF for the maximum clinical dose of 30mg was +5.3ms. In both *in vivo* and *in vitro* studies, osilodrostat showed concentration/dose-dependent QT prolongation and a potential to cause cardiac rhythm abnormalities, including torsades de pointes.
Characterisation of the risk	**Clinical trial experience** The AEs of QT prolongation/potential arrhythmia were reported in 10 patients (5 patients in Study CLCI699C2301, 2 patients in Study CLCI699C2201 and 3 patients in Study CLCI699C2302). Of the 10 patients with AEs, 2 patients had Grade 3 events and no Grade 4 events were reported. Serious events were observed in 2 patients (1 patient in Study CLCI699C2301 experienced syncope without any reported arrhythmia and 1 patient in Study CLCI699C2201 had QTcF prolongation by >480ms [central reading]). No deaths were reported due to AEs of arrhythmogenic potential. Pecori Giraldi *et al.* (2011) measured QT interval in 19 men and 35 women with CD; QTc prolongation (upper normal limit for QTc was considered 440ms in men and 460ms in women) was found in 5 men (prevalence 26%) and no women. They listed hypokalaemia and low testosterone as potential risk factors. In Study CLCI699C2302, 3/73 patients (4.1%) had arrhythmogenic potential and QT prolongation AEs, 2 in the Isturisa arm and 1 in placebo arm. The AEs were: electrocardiogram QT prolonged (2/73; 2.7%) and syncope (1/73; 1.4%). All AEs were Grade 1/2, and had resolved by data lock point. Both the QT prolongation AEs were suspected to be related to study drug. One of the ECG prolongation events was an SAE. The QT prolongation AE in the second patient was Grade 2 in severity and resolved in 27 days with no intervention. The Grade 1 syncope event in the third patient required dose interruption and concomitant medication. At the time of the event of syncope, the patient was receiving a dose of 2mg/day. **Cumulative post-marketing data** Cumulatively, a total of 23 case reports describing 23 AEs pertaining to QT prolongation have been identified from post-marketing experience. The AEs reported were as follows: **Event (PT)** / **Frequency** Electrocardiogram QT prolonged: 10 Loss of consciousness: 6 Cardiac arrest: 3 Syncope: 3 Electrocardiogram QT interval abnormal: 1 Out of the 23 events, 22 were serious events and 1 was non-serious event. The event outcomes were as follows: resolved (n=9), unknown (n=6), not resolved (n=4), fatal (n=3), and resolving (n=1). None of the 3 fatal cases were associated with the event

Important identified risk: QT prolongation	
	of 'QT prolongation', and had alternative explanations for the fatal event of cardiac arrest (n=2) and loss of consciousness (n=1). **Impact on individual patient/quality of life** Corrected QT prolongation may have a significant impact on the individual patient, as it can be life threatening, if not treated. **Reversibility** Temporary interruption and dose reduction of treatment is likely to reverse any QT interval prolongation observations.
Risk factors and risk groups	Patients with the following conditions are at risk of developing prolongation of the QT interval: pre-existing long QT-interval, hypothyroidism, hypokalaemia, hypomagnesaemia, use of drugs causing low serum potassium (non-potassium sparing diuretics), concomitant intake of QT-prolonging drugs, e.g., ketoconazole, macrolides, antiarrhythmics (Class Ia & III), antihistamines and tricyclic antidepressants. The QT interval changes were dose-dependent in TQT Study CLCI699C2105 and non-clinical studies; patients with higher dose (including overdose) are more at risk.
Preventability	An ECG should be performed prior to the start of Isturisa therapy and monitoring for an effect on the QT interval is advisable. Hypothyroidism, hypokalaemia and/or hypomagnesaemia should be corrected prior to Isturisa administration and monitored periodically during therapy. Caution is required when co-administering Isturisa with anti-arrhythmic medicines and other drugs that may prolong the QT interval. Information and management guidelines are included in the product labelling.
Impact on the benefit-risk balance of the product	In Study CLCI699C2301, no events of QTcF > 500ms were documented. One of the five subjects with an AE of QT interval prolongation discontinued study medication due to the event although the corrected prolongation was below the threshold of concern (QTcF interval was 478ms), therefore the actual benefit-risk balance for this risk is considered to be low. The expected risk-benefit balance of Isturisa is minimally impacted by this risk considering the nature of the treated indication, very low frequency of QTcF prolongation seen in clinical trials, the recommendation for baseline and regular ECG and electrolyte monitoring and avoidance of concomitant treatment with QTc-prolonging drugs.
Public health impact	The public health impact on overall public health is minimal as the patient population is small. The public health impact is minimal within this population but reduced by the monitoring of ECG and electrolytes and avoidance of concomitant treatment with QTc-prolonging drugs.

AE=adverse event; CCDS=Company Core Data Sheet; CD=Cushing's disease; CI=confidence interval; ECG=electrocardiogram; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; QTc=corrected QT interval; QTcF=Fridericia's corrected QT interval; TQT= thorough QT/QTc.

Reproductive toxicity/embryofoetal development is considered an important potential risk for Isturisa. Information pertaining to this safety concern is presented in Table 21 and Table 22.

Table 21: Clinical trial data pertaining to reproductive toxicity/embryofoetal development

	Study CLCI699C2301 N=137 n (%) 95% CI	Study CLCI699C2201 – Part 2 (N=19) n (%) 95% CI	Study CLCI699C2302 (N=73) n (%) 95% CI	Total (N=229) n (%) 95% CI
Number of patients with at least 1 event	1 (0.7) (0.0, 4.0)	0 (0.0) (0.0, 17.6)	0 (0.0)	1 (0.4) (0.0, 3.5)
Exposure-adjusted overall incidence, n (exposure-adjusted IR per 100 PTY)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)
Grade 3 AEs	0	0	0	0
Grade 4 AEs	0	0	0	0
SAEs	0	0	0	0
Fatal AEs	0	0	0	0

AE=adverse event; CI=confidence interval; IR=incidence rate; PTY=patient treatment-years; SAE=serious adverse event.

The IR represents the number of patients with an event divided by the corresponding sum of the exposure duration for all patients, where duration of exposure in PTY is counted up to the first qualifying event (or end of time at risk for patients without event).

For Study CLCI699C2301, events reported during placebo treatment were excluded.
Source: Annex 7 (Table 2.3-1.1c).

Table 22: Important potential risk: Reproductive toxicity/embryofoetal development

Important potential risk: Reproductive toxicity/embryofoetal development	
MedDRA terms	Standardised MedDRA Queries (broad) of Congenital, familial and genetic disorders, Foetal disorders, Neonatal disorders and Termination of pregnancy and risk of abortion.
Potential mechanisms	A role of aromatase inhibition in the manifestation of reproductive toxic effects seen in animals cannot be excluded, since Cmax–values for Isturisa in plasma reached or exceeded IC50-values for aromatase inhibition at doses that produced reproductive toxic effects. The observed alterations in rats and mice are consistent with effects seen after aromatase inhibition [Nunez et al., 1996; Junker Walker and Nogues, 1994].
Evidence source and strength of evidence	Embryofoetal toxicities were observed in the rat and rabbit embryofoetal development studies. Increased embryonic and foetal deaths, decreased foetal weights, external malformations, and visceral and skeletal variations occurred in rats and increased resorptions and decreased foetal viability were observed in rabbits. In the pre-and post-natal developmental study, dystocia and delayed parturition were observed in rats. The NOAEL for the embryofoetal toxicities for rats and rabbits were considered to be 5 and 3mg/kg/day, respectively, with systemic exposure level (based on AUC) 9 and 0.6 times higher than that expected in humans at the highest recommended dose of 30mg bid. Thus, Isturisa should be considered potentially teratogenic to humans.

Important potential risk: Reproductive toxicity/embryofoetal development	
Characterisation of the risk	**Clinical trial experience** No Grade 3/4 events, SAEs or deaths due to reproductive toxicity/embryofoetal development have been reported during clinical trial experience. No foetal abnormalities following intrauterine exposure to Isturisa in humans have been reported. A case report in Study CLCI699C2301 referred to 'umbilical discharge' which did not reflect reproductive toxicity. One case report described the non-serious event of Abortion spontaneous, which was assessed by both the Investigator and RRD as unrelated to Isturisa ("no reasonable possibility"). Pregnant women or women of childbearing potential not using effective methods of contraception were excluded from the clinical development programme. One healthy volunteer participating in Study CLCI699C2108, a drug-drug interaction study investigating the impact of Isturisa on combined hormonal contraception, had a positive pregnancy test following 11 days of Isturisa at exposure. However, the pregnancy was not confirmed by ultrasound scan (reported as possible spontaneous abortion). A second case concerned a patient who became pregnant following 7 months of Isturisa exposure in Study CLCI699C2301: pregnancy was detected at 6 weeks gestation, elective abortion was performed due to social reasons and no abnormalities were reported in the foetus. No AEs related to reproductive toxicity/embryofoetal development have been reported in Study CLCI699C2302. **Cumulative post-marketing data** Cumulatively, 4 cases pertaining to reproductive toxicity/embryofoetal development have been identified from post-marketing sources. Reported PTs were Abortion spontaneous (n=2), Portal venous system anomaly and Failure to thrive (n=1 each). Two of these 4 events were serious [Failure to thrive and Abortion spontaneous] and 2 events were non-serious. Event outcomes were: resolved (n=1; Abortion spontaneous) and unknown for the 3 remaining events. **Impact on individual patient/quality of life** The impact on the individual patient is significant if females of childbearing potential not using an effective form of contraception are on treatment, also nursing infants may potentially develop serious ADRs. **Reversibility** The reversibility is unknown at this stage.
Risk factors and risk groups	Female patients of child-bearing potential exposed to Isturisa. There is no risk from transfer of the drug via semen; the Isturisa safety margin for causing embryofoetal toxicity and teratogenicity through seminal fluid transfer is >100-fold.
Preventability	Section "Special warnings and precautions for use" of the SmPC mentions that Isturisa may cause foetal harm. Females of child-bearing potential should be advised on the use of highly effective contraception methods (i.e., a method with <1% failure rate). Pregnant women should be advised of the potential risk to a foetus if Isturisa is used during pregnancy or if the patient becomes pregnant while taking Isturisa.
Impact on the benefit-risk balance of the product	In Study CLCI699C2301, no events of reproductive or embryofoetal toxicity were observed, therefore the actual benefit-risk balance for this risk is considered to be low. The expected benefit-risk balance of Isturisa is minimally impacted by this risk considering the toxicities seen in animal studies occurred at a high safety margin and the requirement for female patients to use effective methods of contraception.

Important potential risk: Reproductive toxicity/embryofoetal development	
Public health impact	The public health impact on overall public health is minimal as the patient population is small. The public health impact within this population is unknown.

AE=adverse event; ADR=adverse drug reaction; AUC=area under the curve; bid=twice daily; Cmax=maximum concentration; IC50=half maximal inhibitory concentration; MedDRA=Medical Dictionary for Regulatory Activities; NOAEL=no observed adverse effect level; SAE=serious adverse event; SmPC=Summary of Product Characteristics.

SVII.3.2. Presentation of the missing information

Missing information that is considered a safety concern for Isturisa is described in Table 23, Table 24 and Table 25.

Table 23: Missing information: Breastfeeding women

Evidence source	Breastfeeding women were excluded from the clinical development programme. Therefore, there are no clinical data on the effects of Isturisa on milk production or the breastfed child.
Population in need of further characterisation	It is unknown if Isturisa is transferred into human milk. Due to the potential for ADRs in the breastfed child, breast-feeding is not recommended during treatment and for 1 week after stopping treatment with Isturisa.

ADR=adverse drug reaction.

Table 24: Missing information: Long-term safety (including hypocortisolism, CV safety and QT prolongation, hormones of the HPA-axis including ACTH increase, and clinical consequences of increased sexual hormones)

Evidence source	At the time of submission, the median exposure to Isturisa in CS patients across studies ranged from 80 days to 226 weeks, and in the pivotal study (Study CLCI699C2301 [n=137]), median exposure was 74.7 weeks (range: 0.9 to 165.3 weeks). The safety of patients with long-term use was therefore considered missing information. With the completion of the extension period (open-label Isturisa treatment starting at Week 48), median exposure had increased to 129.6 weeks (range: 0.9 to 245.1), including 52 patients that were exposed to Isturisa for more than 3 years (>156 weeks). In Phase 2 Study CLCI699C2201 (n=19), which included 2 optional long-term extension periods, the median duration of exposure to Isturisa was 281.7 weeks (approximately 64 months; up to 350.6 weeks). Isturisa was generally well tolerated in this study, in which the most frequently reported AEs were fatigue and nausea. In the core phase of the Phase 3 Study CLCI699C2302, the median exposure was estimated at 70.0 weeks (range up to 112.7 weeks). The primary analysis of this study showed that Isturisa was well tolerated, and its safety profile was in line with other clinical studies with Isturisa. The most frequently reported AEs were arthralgia, decreased appetite, fatigue, nausea and headache.
Population in need of further characterisation	Study CLCI699C2X01B is currently ongoing to collect clinical information on patients with endogenous CS treated with Isturisa and to document the long-term safety data with Isturisa treatment (including events pertaining to hypocortisolism, CV safety and QT-prolongation, hormones of the HPA axis including ACTH increase, and clinical consequences of increased sexual hormones) which may help further characterise this missing information topic.

ACTH=adrenocorticotropic hormone; AE=adverse event; CS=Cushing's syndrome; CV=cardiovascular; HPA=hypothalamic-pituitary-adrenal.

Table 25: Missing information: Use in non-CD CS patients including long-term effects

Evidence source	The clinical development programme included 9 patients with non-CD CS, and therefore information in this patient population is considered limited. However, cases identified from RRD GSDB showed a safety profile consistent with the current CCDS and did not reveal any new safety findings.
Population in need of further characterisation	Study CLCI699C2X01B is currently ongoing to collect clinical information on patients with endogenous CS treated with Isturisa and to document the long-term safety data with Isturisa treatment, which may help further characterise this missing information topic.

CCDS=Company Core Data Sheet; CD=Cushing's disease; CS=Cushing's syndrome; GSDB=Global Safety Database; RRD=Recordati Rare Diseases.

Part II: Module SVIII – Summary of the Safety Concerns

A summary of the safety concerns for Isturisa is presented in Table 26.

Table 26: Summary of safety concerns

Important identified risks	• Hypocortisolism • QT prolongation
Important potential risks	• Reproductive toxicity/Embryofoetal development
Missing information	• Breast-feeding women • Long-term safety (including hypocortisolism, CV safety and QT-prolongation, hormones of the HPA-axis including ACTH increase, and clinical consequences of increased sexual hormones) • Use in non-CD CS patients including long-term effects

ACTH=adrenocorticotropic hormone; CD=Cushing's disease; CS=Cushing's syndrome; CV=cardiovascular; HPA=hypothalamic-pituitary-adrenal.

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

Part III.1: Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:

Specific adverse reaction follow-up questionnaires for Hypocortisolism, QT prolongation and Reproductive toxicity/Embryofoetal development

The following specific adverse reaction follow-up checklists are to be used to collect further data to help further characterise and/or closely monitor each of the respective risks for Isturisa:

- Checklist for "Hypocortisolism disorders".
- Checklist for "QT interval prolongation or Torsades de Pointes".
- Checklist for "Pregnancy".

The full checklists are provided in Annex 4 of the RMP.

Other forms of routine pharmacovigilance activities

There are no other forms of routine pharmacovigilance activities for Isturisa.

Part III.2: Additional Pharmacovigilance Activities

Details of the planned/ongoing study in the pharmacovigilance plan are presented below.

Study CLCI699C2X01B

Study short name and title:

Study CLCI699C2X01B; An open-label, multi-centre, roll-over study to assess long term safety in patients with endogenous Cushing's syndrome who have completed a prior Novartis-sponsored osilodrostat (LCI699) study and are judged by the Investigator to benefit from continued treatment with osilodrostat.

Rationale and study objectives:

The purpose of this ongoing post-authorisation safety study is the evaluation of long-term safety of Isturisa in patients who have already received Isturisa treatment in a previous global Novartis-sponsored trial and who, based on Investigators' judgement, will continue benefiting with its administration.

The primary objective of the study is as follows:

- To evaluate the long-term safety data with Isturisa treatment (i.e., AEs and SAEs).

The secondary objectives of the study are as follows:

- To evaluate the clinical benefit as assessed by the Investigator.

- To evaluate the long-term safety of Isturisa treatment, as assessed by physical examination, laboratory data, vital signs, ECG and pituitary Magnetic Resonance Imaging (MRI).

Study design:

This voluntary post-authorisation safety study is a multicentre, open label Phase 2b study in patients who have already received Isturisa in a previous global Novartis-sponsored study.

Study population:

The study population includes adult male or female patients diagnosed with any type of endogenous CS, who have fulfilled all their requirements in the parent study, and who are currently benefiting from treatment with Isturisa, as determined by the Investigator of the parent study. Approximately, 160 patients are expected to be enrolled into the study.

Milestones:

- First patient first visit: 05 October 2018.
- Last patient last visit: October 2023.
- Interim study reports: 6 monthly during the study until January 2022, and then annually (interim safety analyses will be included in each of the Periodic Safety Update Reports as requested by the Pharmacovigilance Risk Assessment Committee).
- Final study report: May 2024.

Part III.3: Summary Table of Additional Pharmacovigilance Activities

Ongoing additional pharmacovigilance activities are summarized in Table 27.

Table 27: Ongoing additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
Study CLCI699C2X01B **Study title:** An open-label, multi-centre, roll-over study to assess long-term safety in patients with endogenous Cushing's syndrome who have completed a prior Novartis-sponsored osilodrostat (LCI699) study and are judged by the Investigator to benefit from continued treatment with osilodrostat. **Status:** Ongoing.	**Primary objective:** To evaluate the long-term safety data with Isturisa treatment (i.e., AEs and SAEs). **Secondary objectives:** 1. To evaluate the clinical benefit as assessed by the Investigator. 2. To evaluate the long-term safety of Isturisa treatment, as assessed by physical examination,	Long-term safety (including hypocortisolism, CV safety and QT-prolongation, hormones of the HPA-axis including ACTH increase and the clinical consequences of increased sexual hormones).	First patient first visit:	05 October 2018.
			Last patient last visit:	October 2023.
			Interim study reports:	6 monthly during the study until January 2022, and then annually.
			Final study report:	May 2024.

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	laboratory data, vital signs, ECG and pituitary magnetic resonance imaging.			

ACTH=adrenocorticotropic hormone; AE=adverse event; CD=Cushing's disease; CS=Cushing's syndrome; CV=cardiovascular; ECG=electrocardiogram; HPA=hypothalamic-pituitary-adrenal; SAE=serious adverse event.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no imposed post-authorisation efficacy studies planned or ongoing for Isturisa.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Part V.1: Routine Risk Minimisation Measures

Routine risk minimization measures for Isturisa are summarised in Table 28.

Table 28: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
Hypocortisolism	Routine risk communication SmPC Sections 4.4, 4.8 and 4.9. Package leaflet (PL) Sections 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk Section 4.4 of the SmPC notes that cortisol levels should be monitored at regular intervals since hypocortisolism can occur at any time during treatment. Additional monitoring is recommended especially during conditions of increased cortisol demand, such as physical or psychological stress, or during changes in concomitant medications that may affect Isturisa's exposure. Patients should be alerted to the signs and symptoms associated with hypocortisolism (e.g., nausea, vomiting, fatigue, abdominal pain, loss of appetite and dizziness). Symptomatic patients should be monitored for hypotension, hyponatraemia, hyperkalaemia and/or hypoglycaemia. If hypocortisolism is suspected, cortisol levels should be measured and temporary dose reduction or interruption of Isturisa considered. If necessary, corticosteroid substitution should be initiated. Isturisa may be resumed after resolution of symptoms at a lower dose, provided that cortisol levels are above the lower limit of normal in the absence of glucocorticoid substitution. Section 2 of the PL also advises that patients contact their doctor immediately if they have 2 or more of the symptoms that may indicate adrenal insufficiency (low cortisol levels): weakness, light-headedness tiredness, lack of appetite, nausea and vomiting. Section 4.9 of the SmPC advises that in the event of suspected overdosage, Isturisa should be interrupted, cortisol levels should be assessed, and if necessary, corticosteroid supplementation should be initiated. Close surveillance may be necessary including monitoring of the QT interval, blood pressure, glucose, fluid and electrolyte balance until the patient's condition is stable. Other routine risk minimisation measures beyond the Product Information Legal status: Subject to restricted medical prescription.
QT prolongation	Routine risk communication SmPC Sections 4.4, 4.5 and 4.8. PL Sections 2 and 4.

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk Section 2 of the PL recommends that patients tell their doctor before taking Isturisa if they have a heart disorder or a heart rhythm disorder, such as an irregular heartbeat, including a condition called prolonged QT syndrome (QT interval prolongation). Section 4.4 of the SmPC advises that an ECG should be performed prior to the start of Isturisa treatment (as also noted in PL Section 2), within 1 week after treatment initiation, and as clinically indicated thereafter. If the QTc is >480ms prior to or during treatment, cardiology consultation is recommended. Temporary dose reduction or interruption may be required. Any hypokalaemia, hypocalcaemia or hypomagnesaemia must be corrected prior to Isturisa administration and electrolyte levels should be monitored periodically during therapy. Isturisa should be used with caution in patients with risk factors for QT prolongation (such as congenital long QT syndrome, significant cardiovascular disease [including congestive heart failure, recent myocardial infarction, unstable angina, sustained ventricular tachycardia, advanced heart block and clinically significant bradyarrhythmia] and use of concomitant medications known to prolong the QT interval). If Isturisa is used in patients with these risk factors, more frequent ECG monitoring is recommended. Section 2 of the PL advises that patients tell their doctor if they are taking, have recently taken or might take any other medicines. It is particularly important that they mention medicines that may cause QT prolongation. Section 4.5 of the SmPC further advises that a washout period should be considered when switching from other products known to affect the QT interval such as pasireotide or ketoconazole. Other routine risk minimisation measures beyond the Product Information Legal status: Subject to restricted medical prescription.
Important potential risks	
Reproductive toxicity/Embryofoetal development	Routine risk communication SmPC Sections 4.4, 4.6 and 5.3. PL Section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk Sections 4.4. and 4.6 of the SmPC note that in women of childbearing potential, the pregnancy status should be checked before initiating treatment with Isturisa, and that these patients should be advised of the potential risk to the foetus. Section 4.6 of the SmPC states that Isturisa should not be used in women of childbearing potential not using contraception. Sections 4.4. and 4.6 of the SmPC, as well as Section 2 of the PL advise that women of childbearing potential should use effective contraception during treatment with Isturisa and for at least 1 week after stopping treatment with Isturisa. Section 4.6 of the SmPC further notes that if hormonal contraceptives other than the oral combination of ethinylestradiol and levonorgestrel are used, an additional barrier method of contraception is recommended. Other routine risk minimisation measures beyond the Product Information Legal status: Subject to restricted medical prescription.

Safety concern	Routine risk minimisation activities
Missing information	
Breast-feeding women	Routine risk communication SmPC Section 4.6. PL Section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk Section 4.6 of the SmPC states that breast-feeding should be discontinued during treatment with Isturisa and for at least 1 week after treatment. Section 2 of the PL also advises that Isturisa should not be used during breast-feeding unless your doctor has advised the patient to do so. It is noted that if the patient is breast-feeding, they should ask their doctor for advice before taking Isturisa. Other routine risk minimisation measures beyond the Product Information Legal status: Subject to restricted medical prescription.
Long-term safety (including hypocortisolism, CV safety and QT-prolongation, hormones of the HPA-axis including ACTH increase, and clinical consequences of increased sexual hormones)	Routine risk communication None. Routine risk minimisation activities recommending specific clinical measures to address the risk None. Other routine risk minimisation measures beyond the Product Information Legal status: Subject to restricted medical prescription.
Use in non-CD CS patients including long-term effects	Routine risk communication None. Routine risk minimisation activities recommending specific clinical measures to address the risk None. Other routine risk minimisation measures beyond the Product Information Legal status: Subject to restricted medical prescription.

ACTH=adrenocorticotropic hormone; CD=Cushing's diseases; CS=Cushing's syndrome; CV=cardiovascular; ECG=electrocardiogram; HPA=hypothalamic-pituitary-adrenal. PL=Package Leaflet; QTc=corrected QT interval; SmPC=Summary of Product Characteristics.

Part V.2: Additional Risk Minimisation Measures

The routine risk minimisation measures described in Section V.1 are considered sufficient to manage the safety concerns of Isturisa.

Part V.3: Summary of Risk Minimisation Measures

A summary of the risk minimisation measures for Isturisa are summarized in Table 29.

Table 29: Summary of Risk Minimisation Measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Hypocortisolism	Routine risk minimisation measures SmPC Sections 4.4, 4.8 and 4.9. PL Sections 2 and 4. Section 4.4 of the SmPC and Section 2 of the PL where advice on the monitoring of cortisol levels and the observation of signs and symptoms associated with hypocortisolism/adrenal insufficiency is given. Section 4.9 of the SmPC where advice is given in the context of suspected overdosage and low cortisol levels. Legal status: Subject to restricted medical prescription. Additional risk minimisation measures None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Targeted follow-up checklist. Additional pharmacovigilance activities None.
QT prolongation	Routine risk minimisation measures SmPC Sections 4.4, 4.5 and 4.8. PL Sections 2 and 4. Section 4.4 of the SmPC and Section 2 of the PL where advice on measures to be taken before and during treatment (e.g., review of medical history, an ECG, correction of hypokalaemia, hypocalcaemia, or hypomagnesaemia, monitoring of electrolyte levels) is given. Section 4.5 of the SmPC and Section 2 of the PL where recommendations on treatment with other medicines that may cause QT prolongation is included. Legal status: Subject to restricted medical prescription. Additional risk minimisation measures None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Targeted follow-up checklist. Additional pharmacovigilance activities None.
Important potential risks		
Reproductive toxicity/Embryofoetal development	Routine risk minimisation measures SmPC Sections 4.4, 4.6 and 5.3. PL Section 2. Sections 4.4. and 4.6 of the SmPC, and Section 2 of the PL where advice on the	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Targeted follow-up checklist.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	confirmation of pregnancy status before treatment with Isturisa and awareness of the potential risk to the foetus is given. Sections 4.4 and 4.6 of the SmPC, and Section 2 of the PL where advice on the use of contraception is given. Legal status: Subject to restricted medical prescription. Additional risk minimisation measures None.	Additional pharmacovigilance activities None.
Missing information		
Breast-feeding women	Routine risk minimisation measure SmPC Section 4.6. PL Section 2. Section 4.6 of the SmPC where it advised that breast-feeding should be discontinued during treatment with Isturisa and for at least 1 week after treatment. Section 2 of the PL where advice on seeking advice from the doctor when breast-feeding is given. Legal status: Subject to restricted medical prescription. Additional risk minimisation measures None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None. Additional pharmacovigilance activities None.
Long-term safety (including hypocortisolism, CV safety and QT-prolongation, hormones of the HPA-axis including ACTH increase, and clinical consequences of increased sexual hormones)	Routine risk minimisation measures Legal status: Subject to restricted medical prescription. Additional risk minimisation measures None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None. Additional pharmacovigilance activities Study CLCI699C2X01B.
Use in non-CD CS patients including long-term effects	Routine risk minimisation measures Legal status: Subject to restricted medical prescription. Additional risk minimisation measures None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None. Additional pharmacovigilance activities Study CLCI699C2X01B.

ACTH=adrenocorticotropic hormone; CD=Cushing's diseases; CS=Cushing's syndrome; CV=cardiovascular; ECG=electrocardiogram; HPA=hypothalamic-pituitary-adrenal; PL=Package Leaflet; SmPC=Summary of Product Characteristics.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR ISTURISA (OSILODROSTAT)

This is a summary of the risk management plan (RMP) for Isturisa. The RMP details important risks of Isturisa, how these risks can be minimised, and how more information will be obtained about Isturisa's risks and uncertainties (missing information).

Isturisa's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how Isturisa should be used.

This summary of the RMP for Isturisa should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Isturisa's RMP.

Part VI.1: The Medicine and What it is Used for

Isturisa is authorized for the treatment of endogenous Cushing's syndrome (CS) in adults. Isturisa contains osilodrostat as the active substance and it is given orally.

Further information about the evaluation of Isturisa's benefits can be found in Isturisa's European Public Assessment Report, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage: https://www.ema.europa.eu/en/documents/product-information/isturisa-epar-product-information_en.pdf.

Part VI.2: Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Isturisa, together with measures to minimise such risks and the proposed studies for learning more about Isturisa's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment so that immediate

action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Isturisa is not yet available, it is listed under 'missing information' below.

Part VI.2.1: List of Important Risks and Missing Information

Important risks of Isturisa are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Isturisa. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Hypocortisolism • QT prolongation
Important potential risks	• Reproductive toxicity/Embryofoetal development
Missing information	• Breast-feeding women • Long-term safety (including hypocortisolism, cardiovascular [CV] safety and QT-prolongation, hormones of the hypothalamic-pituitary-adrenal [HPA]-axis including adrenocorticotropic hormone [ACTH] increase, and clinical consequences of increased sexual hormones) • Use in non-Cushing's Disease (CD) CS patients including long-term effects

ACTH=adrenocorticotropic hormone; CD=Cushing's disease; CS=Cushing's syndrome; CV=cardiovascular; HPA=hypothalamic-pituitary-adrenal.

Part VI.2.2: Summary of Important Risks

Summaries of the important risks and missing information for Isturisa are provided in the following tables.

Important identified risk of hypocortisolism	
Evidence for linking the risk to the medicine	Post-marketing experience, clinical trial experience and literature. Cumulatively, a total of 98 subjects experienced hypocortisolism were reported from clinical trials experience and 149 case reports describing 164 events pertaining to hypocortisolism were identified from post-marketing experience. Events of decreased cortisol and decreased response to ACTH stimulation testing were noted in patients with hypertension and healthy volunteer studies. Events of hypocortisolism, including serious and symptomatic, have been reported in clinical trials with Isturisa.

Risk factors and risk groups	All patients treated for endogenous CS. The occurrence of hypocortisolism in Study CLCI699C2301 was highest during initial dose titration, after dose up-titration (when the last previous mean urinary free cortisol levels were in the low part of the normal range) or periods of intercurrent illness. There was no correlation with any specific dose level.
Risk minimisation measures	Routine risk minimisation measures SmPC Sections 4.4, 4.8, and 4.9. PL Sections 2 and 4. Section 4.4 of the SmPC and Section 2 of the PL where advice on the monitoring of cortisol levels and the observation of signs and symptoms associated with hypocortisolism/adrenal insufficiency is given. Section 4.9 of the SmPC where advice is given in the context of suspected overdosage and low cortisol levels. Legal status: Subject to restricted medical prescription. Additional risk minimisation measures None.

ACTH=adrenocorticotropic hormone; CS=Cushing's syndrome; PL=Patient Leaflet; SmPC=Summary of Product Characteristics.

Important identified risk of QT prolongation	
Evidence for linking the risk to the medicine	A thorough QT study (Study CLCI699C2105) demonstrated a positive exposure-related Friderica's corrected QT interval (QTcF) prolongation (a measure of the electrical activity of the heart) for Isturisa. The QTcF increased by 25.38ms (90% confidence interval: 23.53, 27.22) on Isturisa 150mg, but not on Isturisa 10mg (1.73ms at 3 hours post-dose). The estimated mean QTcF for the maximum clinical dose of 30mg was +5.3ms. In both *in vivo* and *in vitro* studies, osilodrostat showed concentration/dose-dependent QT prolongation and a potential to cause cardiac rhythm abnormalities, including torsades de pointes.
Risk factors and risk groups	Patients with the following conditions are at risk of developing prolongation of the QT interval: pre-existing long QT-interval, hypothyroidism, hypokalaemia, hypomagnesaemia, use of drugs causing low serum potassium (non-potassium sparing diuretics), concomitant intake of QT-prolonging drugs, e.g., ketoconazole, macrolides, antiarrhythmics (Class Ia & III), antihistamines and tricyclic antidepressants. The QT interval changes were dose-dependent in thorough QT/corrected QT interval Study CLCI699C2105 and non-clinical studies; patients with higher dose (including overdose) are more at risk.
Risk minimisation measures	Routine risk minimisation measures SmPC Sections 4.4, 4.5 and 4.8. PL Sections 2 and 4. Section 4.4 of the SmPC and Section 2 of the PL where advice on measures to be taken before and during treatment (e.g., review of medical history, an ECG, correction of hypokalaemia, hypocalcaemia or hypomagnesaemia, monitoring of electrolyte levels) is given. Section 4.5 of the SmPC and Section 2 of the PL where recommendations on treatment with other medicines that may cause QT prolongation is included.

	Legal status: Subject to restricted medical prescription. Additional risk minimisation measures None.

ECG=electrocardiogram; PL=Patient Leaflet; QTcF=Fridericia's corrected QT interval; SmPC=Summary of Product Characteristics.

Important potential risk of reproductive toxicity/embryofoetal development	
Evidence for linking the risk to the medicine	Embryofoetal toxicities were observed in the rat and rabbit embryofoetal development studies. Increased embryonic and foetal deaths, decreased foetal weights, external malformations, and visceral and skeletal variations occurred in rats and increased resorptions and decreased foetal viability were observed in rabbits. In the pre-and post-natal developmental study, dystocia and delayed parturition were observed in rats. The no observed adverse effect level for the embryofoetal toxicities for rats and rabbits were considered to be 5 and 3mg/kg/day, respectively, with systemic exposure level (based on the area under the curve) 9 and 0.6 times higher than that expected in humans at the highest recommended dose of 30mg bid. Thus, Isturisa should be considered potentially teratogenic to humans.
Risk factors and risk groups	Female patients of child-bearing potential exposed to Isturisa. There is no risk from transfer of the drug via semen: The Isturisa safety margin for causing embryofoetal toxicity and teratogenicity through seminal fluid transfer is >100-fold.
Risk minimisation measures	Routine risk minimisation measures SmPC Sections 4.4, 4.6 and 5.3. PL Section 2. Sections 4.4. and 4.6 of the SmPC where advice on the confirmation of pregnancy status before treatment with Isturisa and awareness of the potential risk to the foetus is given. Sections 4.4 and 4.6 of the SmPC, and Section 2 of the PL where advice on the use of contraception is given. Legal status: Subject to restricted medical prescription. Additional risk minimisation measures None.

PL=Patient Leaflet; SmPC=Summary of Product Characteristics.

Missing information of breast-feeding women	
Risk minimisation measures	Routine risk minimisation measures SmPC Section 4.6. Section 4.6 of the SmPC where it advised that breast-feeding should be discontinued during treatment with Isturisa and for at least 1 week after treatment. Section 2 of the PL where advice on seeking advice from the doctor when breast-feeding is given. Legal status: Subject to restricted medical prescription. Additional risk minimisation measures None.

PL=Patient Leaflet; SmPC=Summary of Product Characteristics.

Missing information of long-term safety (including hypocortisolism, CV safety and QT prolongation, hormones of the HPA-axis including ACTH increase, and clinical consequences of increased sexual hormones)	
Risk minimisation measures	Routine risk minimisation measures Legal status: Subject to restricted medical prescription. Additional risk minimisation measures None.
Additional pharmacovigilance activities	Study CLCI699C2X01B.

ACTH=adrenocorticotropic hormone; CV=cardiovascular; HPA=hypothalamic-pituitary-adrenal.

Missing information of use in non-CD CS patients including long-term effects	
Risk minimisation measures	Routine risk minimisation measures: Legal status: Subject to restricted medical prescription. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Study CLCI699C2X01B.

CD=Cushing's disease; CS=Cushing's syndrome.

Part VI. 2.3: Post-authorisation development plan

VI.2.3.1: Studies which are conditions of the marketing authorisation

There are no studies, which are conditions of the marketing authorisation or specific obligation of Isturisa.

VI.2.3.2: Other studies in post-authorisation development plan

Other studies in the post-authorisation development plan are included in the table below.

Study short name	**Purpose of the study**
Study CLCI699C2X01B	The purpose of this study is the evaluation of long-term safety of Isturisa in patients who have completed a prior Novartis-sponsored Isturisa (LCI699) study and are judged by the Investigator to benefit from continued treatment with Isturisa. The primary objective of the study is as follows: • To evaluate the long-term safety data with Isturisa treatment (i.e., adverse events and serious adverse events). The secondary objectives of the study are as follows:

Study short name	Purpose of the study
	• To evaluate the clinical benefit as assessed by the Investigator. • To evaluate the long-term safety of Isturisa treatment, as assessed by physical examination, laboratory data, vital signs, ECG and pituitary magnetic resonance imaging.

ACTH=adrenocorticotropic hormone; CD=Cushing's disease; CS=Cushing's syndrome; CV=cardiovascular; ECG=electrocardiogram; HPA=hypothalamic-pituitary-adrenal.

PART VII: ANNEXES

Annex 1	EudraVigilance Interface
Annex 2	Tabulated Summary of Planned, Ongoing and Completed Pharmacovigilance Study Programme
Annex 3	Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan
Annex 4	Specific Adverse Drug Reaction Follow-up Forms
Annex 5	Protocols for Proposed and Ongoing Studies in Risk Management Plan Part IV
Annex 6	Details of Proposed Additional Risk Minimisation Activities (if applicable)
Annex 7	Other Supporting Data (Including Referenced Materials)
Annex 8	Summary of Changes to the Risk Management Plan Over Time

Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Hypocortisolism disorders

Name of the checklist (version/date): Hypocortisolism disorders

(Version 2.0/July 2018)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Dosing Regimen of Osilodrostat

Dose at onset of event: _____

Duration of treatment at the above dose (days/months): _____

How long had the patient been treated on any previous dose: _____

Event Description

For this adverse event, did the patient present with any of the following signs or symptoms?

Check all that apply:

☐ Muscle weakness	☐ Anorexia	☐ Vomiting
☐ Fatigue	☐ Nausea	☐ Hypotension
☐ Hyponatremia	☐ Hypoglycaemia	☐ Joint pain
☐ Weight loss	☐ Light-headedness upon standing	☐ Anxiety
☐ Diarrhoea	☐ Fever	☐ Hyperpigmentation
☐ Headache	☐ Changes in mood or personality	☐ None of the above

☐ Other (please specify) _____

Diagnostic tests

Were any of the following diagnostic tests performed for this adverse event? **Check all that apply:**

(Please specify tests, dates and results)

☐ Serum cortisol	☐ Urinary free cortisol (mUFC)	☐ Plasma ACTH
☐ Na+	☐ K+	☐ FPG

☐ None of the above

☐ Other diagnostic tests (please specify) _____

Relevant medical history (concurrent and pre-existing conditions)

(Please specify medical condition and date of onset)

☐ Pituitary surgical intervention; Onset date: _____

☐ Adrenalectomy; Onset date: _____

☐ Radiation of the pituitary gland; Onset date: _____

☐ Acute recent illness; Onset date: _____

☐ Previous episodes of hypoglycaemia; Onset date: _____

☐ Recent weight loss/malnutrition; Onset date: _____

☐ Type I diabetes ☐ Vitiligo

☐ Hashimoto's thyroiditis ☐ Celiac disease

☐ Other autoimmune disease ☐ Amyloidosis

☐ Metastasis from elsewhere ☐ Haemorrhage

☐ Mucocutaneous candidiasis and/or hypoparathyroidism (autoimmune polyendocrine syndrome type 1)

☐ Autoimmune thyroid and/or disease type 1 diabetes (autoimmune polyendocrine syndrome type 2)

☐ Infection (tuberculosis, histoplasmosis, coccidioidomycosis)

☐ None of the above

Please indicate the treatment (if any) provided to the patient for this event.

(Please specify treatment and outcome)

Drug	**Dose**	**Dates (Start-Stop)**
Beclo-/betamethasone		
Cortisone/Cortisone acetate		
Deflazacort		
Dexamethasone		
Fludrocortisone		
Fluprednisolone		
Hydrocortisone		
Meprednisone/Methylprednisolone		
Parametasone		
Prednisolone/Prednisone		
Triamcinolone		
Other (please specify)		

QT prolongation

Name of the checklist (version/date): QT interval prolongation or Torsades de Pointes (Version 2.0/June 2018)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Patient:

Age: _____ Gender: _____ Height (cm):_____ Weight (kg): _____

Event Description:

What was the duration of the raw and corrected QT interval that demonstrated the prolonged measurement?

QT _____msec QTc _____msec

What was the patient's baseline QT and QTc interval?

QT _____msec QTc _____msec

	Yes	No
Were the above measurements confirmed by manual over read?	☐	☐

Which correction formula was used?

Bazett's ☐

Fredericia's ☐

Other ☐ Please, specify

_____

If no correction formula was used, what was the patient's heart rate at the time the QT interval was measured? _____ beats per minute

	Yes	No
Was arrhythmia present at the time of the QT measurement?	☐	☐
Was there any evidence of U waves?	☐	☐
Was there evidence of notched or abnormal T waves?	☐	☐
Was a rhythm strip obtained of the arrhythmia? (either electronically/manually) and available for further analysis?	☐	☐

What were the patient symptoms of the arrhythmia?

Palpitations	☐	☐
Syncope	☐	☐
Light-headedness	☐	☐
Cardiac arrest	☐	☐

Diagnostic test (if yes, please attach all applicable**):**

Results of ECG showing the prolonged QT interval	☐	☐
Results of Pre-event ECG	☐	☐
Results of Post-event ECG	☐	☐
Results of echocardiogram and/or other cardiac studies	☐	☐
Was the patient seen by a cardiologist?	☐	☐
Is the Cardiologist consultant report available?	☐	☐

If yes, provide diagnostic and relevant results:

_____

_____

Were any of the following blood chemistry results abnormal? ☐ ☐

If yes, what were the levels at the time of the most recent ECG in question?

☐ Potassium: level_____ ☐ Magnesium: level_____ ☐ Calcium: level_____

Were arterial blood gases done? ☐ ☐

If so, what were the results? _____

Did the patient have an acid-base abnormality? ☐ ☐

If so, what was the pH? _____

Relevant medical history (concurrent and pre-existing conditions)

(Please specify medical condition and date of onset)

Does the patient have a history of any of the following risk factors?	**Yes**	**No**
Coronary ischemia, myocardial infarction	☐	☐
Cardiomyopathy	☐	☐
Valvular Heart disease	☐	☐
High degree AV block heart block	☐	☐
Syncope	☐	☐
Hypothyroidism	☐	☐
Hyperthyroidism	☐	☐
Bradycardia	☐	☐
Congenitally prolonged QT interval (e.g.: Romano-Ward syndrome)	☐	☐
Any family history of prolonged QT interval/Long-QT syndrome, or of sudden death?	☐	☐
Is the patient concurrently receiving any drugs that can prolong QT interval?	☐	☐

If yes, please indicate all that apply below:

Albuterol	☐	Flecainide	☐	Paroxetine	☐
Alfuzosin	☐	Fluconazole	☐	Pentamidine	☐
Amantadine	☐	Fluoxetine	☐	Perflutren lipid	☐
Amiodarone	☐	Foscarnet	☐	microspheres	☐
Amitriptyline	☐	Fosphenytoin	☐	Phentermine	☐
Amoxapine	☐	Galantamine	☐	Phenylephrine	☐
Amphetamine	☐	Gatifloxacin	☐	Phenylpropanolamine	☐
Arsenic trioxide	☐	Gemifloxacin	☐	Pimozide	☐
Atomoxetine	☐	Granisetron	☐	Procainamide	☐
Azithromycin	☐	Halofantrine	☐	Protriptyline	☐
Bepridil	☐	Haloperidol	☐	Pseudoephedrine	☐
Chloral hydrate	☐	Ibutilide	☐	Quetiapine	☐
Chloroquine	☐	Imipramine	☐	Quinidine	☐
Chlorpromazine	☐	Indapamide	☐	Ranolazine	☐
Ciprofloxacin	☐	Isoproterenol	☐	Risperidone	☐
Cisapride	☐	Isradipine	☐	Ritodrine	☐
Citalopram	☐	Itraconazole	☐	Roxithromycin	☐
Clarithromycin	☐	Ketoconazole	☐	Salmeterol	☐
Clomipramine	☐	Levalbuterol	☐	Sertraline	☐
Clozapine	☐	Levofloxacin	☐	Sibutramine	☐
Cocaine	☐	Levomethadyl	☐	Solifenacin	☐
Dopamine	☐	Moexipril/HCTZ	☐	Thioridazine	☐
Doxepin	☐	Moxifloxacin	☐	Tizanidine	☐
Droperidol	☐	Nicardipine	☐	Tolterodine	☐
Ephedrine	☐	Norepinephrine	☐	Trimethoprim-Sulfa	☐
Epinephrine	☐	Nortriptyline	☐	Trimipramine	☐
Erythromycin	☐	Octreotide	☐	Vardenafil	☐
Felbamate	☐	Ofloxacin	☐	Venlafaxine	☐
Fenfluramine	☐	Ondansetron	☐	Voriconazole	☐

☐ Other (*Please refer to* www.QTdrugs.org for more information):

_____

_____

Pregnancy

Name of the checklist (version/date): Pregnancy follow-up checklist

(Version 1.1/03 April 2023)

FOLLOW-UP 1 after birth ☐	**FOLLOW-UP 2 after 3 months ☐**	**FOLLOW-UP 3 after 12 months ☐**

☐ **Pregnancy in a female patient**		☐ **Pregnancy in a partner of male patient**	
1. Country:		**2. Patient Identification No:**	
Ia. PATERNAL INFORMATION			
3. AGE years	4. RACE ☐ Asian ☐ Black ☐ Caucasian ☐ Hispanic ☐ Oriental ☐ Other_____	5. HEIGHT cm	6. WEIGHT kg
Ib. MATERNAL INFORMATION			
7. AGE years	8. RACE ☐ Asian ☐ Black ☐ Caucasian ☐ Hispanic ☐ Oriental ☐ Other_____	9. HEIGHT cm	10. WEIGHT kg
11. Date of Last Menstrual Period dd mmm yyyy		12. Expected Date of Delivery dd mmm yyyy Please specify method of calculation (LMP, ultrasound, etc.)	

13. Was a contraception method used?
☐ Yes (please mention method) _____
☐ No

Do you think there was a failure in contraception? ☐ Yes ☐ No ☐ Unknown
Cause/reason for failure (non-compliance, mechanical, drug interaction…):
_____

14. Procreation between blood relatives?
☐ Yes ☐ No ☐ Unknown
(If yes, specify degree):
_____

II. RELEVANT MEDICAL HISTORY

15. MATERNAL PAST MEDICAL HISTORY (include information on familial disorders, known risk factors or conditions that may affect the outcome of the pregnancy)

☐ Hypertension ☐ Smoking ☐ History of infertility
☐ Diabetes (including gestational) ☐ Thyroid disorder ☐ Infertility treatment
☐ Eclampsia ☐ Infections during pregnancy ☐ Other (specify details)
☐ Alcohol ☐ Environment or occupational exposure that may pose a risk factor

16. PREVIOUS OBSTETRIC HISTORY – provide details on all previous pregnancies below, including abortion or stillbirth (use page 4 if needed)

	Gestation week	Outcome including any abnormalities
1		
2		
3		
4		

17. DRUG INFORMATION – please list all medications and dietary supplements taken prior to or during pregnancy

Drug names	Daily dose	Route	Treatment dates		Indication	(Specify week of pregnancy)	
			Start	Stop		Start	Stop

18. Were administered drugs discontinued due to pregnancy? ☐ Yes ☐ No ☐ Unknown
If yes, which drugs?
_____

III. PREGNANCY INFORMATION

19. **PRENATAL**

Have any specific tests, e.g. amniocentesis, ultrasound, maternal serum AFP, serology tests, etc. been performed during the pregnancy so far?
☐ Yes ☐ No ☐ Unknown

(if yes, please specify test date and results): _____

20. **PREGNANCY OUTCOME** (Select the relevant outcome and specify further details in the respective section)

☐ **Abortion**	☐ **Delivery (live infant)**	☐ **Stillbirth (22 weeks gestation or greater)**
☐ Elective ☐ Therapeutic ☐ Spontaneous Date of abortion: dd mmm yyyy Gestational week: _____ Specify reason for abortion: ☐ Unknown ☐ Other, specify details: _____	☐ Normal vaginal delivery ☐ Caesarean ☐ Forceps/Ventouse Delivery date dd mmm yyyy Gestational week: _____ Maternal birth complications: ☐ None ☐ Unknown ☐ Other, specify: _____	Date of stillbirth dd mmm yyyy Gestational week: _____ Additional comments: _____

21. **MATERNAL PREGNANCY ASSOCIATED EVENTS**

If the mother experienced an adverse event during pregnancy, please complete a data collection form and submit as requested

IV. ASSESSMENT OF PREGNANCY OUTCOME

22. SERIOUSNESS CRITERIA

☐ Non-serious

☐ Life-threatening (immediate risk of death)

☐ Other significant medical events (may jeopardise the patient or require intervention to prevent one of other criteria)

☐ Death of mother (date of death)
dd mmm yyyy

☐ Congenital anomaly/birth defect

☐ Involved or prolonged inpatient hospitalisation

☐ Resulted in persistent or significant disability/incapacity

☐ Death of neonate (date of death)
dd mmm yyyy

23. **ASSESSMENT OF CAUSALITY**: Please indicate the relationship between the **pregnancy outcome** and Recordati drug

☐ Not suspected ☐ Suspected

V. NEONATE INFORMATION (at the time of birth)

24. NEONATE

☐ Live (normal)
☐ Live with congenital abnormality
☐ Live with medical problems
☐ Full term
☐ Stillbirth at week
☐ Premature Number of weeks
☐ Post-mature Number of weeks

Sex	Length	Weight	Apgar Scores	Head circumference
☐ Male ☐ Female	cm	kg	1 min. 5 mins. 10 mins.	cm

For additional neonate information, please use page 4 (please provide copies of relevant documentation)

VI. INFANT INFORMATION (after birth)

25. INFANT DETAILS

Age months

26. BREASTFEEDING

Is the infant breast fed? ☐ Yes, continues ☐ Has been weaned dd mmm yyyy ☐ No ☐ Unknown

Is there any complementary feeding in addition to breast milk taken? ☐ Yes ☐ No ☐ Unknown
(if yes, please specify details of the feeding): _____
_____

27. CURRENT STATUS OF INFANT

☐ Thriving, no medical or developmental problem or congenital abnormality (Section 28 and 29 not applicable)

☐ Medical or developmental problems or congenital abnormalities
☐ Deceased (date or age at death, cause of death, please provide autopsy result)

28. DEVELOPMENTAL HISTORY

Has the infant shown any evidence of developmental delay? ☐ Yes ☐ No ☐ Unknown
(if yes, please specify the type of delay)
☐ Motor development (specify details if known): _____
_____
☐ Language development (specify details if known): _____
_____
☐ Social/emotional development (specify details if known): _____
_____
☐ Other (specify details): _____
_____

29. INFANT MEDICAL HISTORY

Has the infant experienced serious infection requiring hospitalisation? ☐ Yes ☐ No ☐ Unknown
(if yes, please specify the infection (site, organism), treatment and outcome)
_____

Is there evidence the infant is immunocompromised? ☐ Yes ☐ No ☐ Unknown
(if yes, please provide details)

_____

Has the infant had other relevant illness, surgeries, or hospitalisation? ☐ Yes ☐ No ☐ Unknown
(if yes, please specify illness (diagnosis), when it began, treatment and outcome)

_____

Have any congenital malformations been diagnosed since birth? ☐ Yes ☐ No ☐ Unknown
(if yes, please specify the details)

_____

FOR ADDITIONAL INFORMATION:

INFORMATION SOURCE

30. NAME, ADDRESS AND TELEPHONE NUMBER OF REPORTER	31. REPORTING DATE BY REPORTER
Signature _____	dd mmm yyyy

Annex 6: Details of Proposed Additional Risk Minimisation Activities (if applicable)

None.