Summary of the risk management plan

Active substance	Osilodrostat
Product(s) concerned (brand name(s)):	Isturisa
MAH/Applicant name	Recordati AG

Data lock point for this module	21-Feb-2018
Version number of RMP when this module was last updated	1.1 (revised 04-Oct-2019)

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of “Isturisa” is a concise document and does not claim to be exhaustive.
As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of “Isturisa” in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. “Recordati AG” is fully responsible for the accuracy and correctness of the content of the published summary RMP of “Isturisa”.

This summary of risk management plan is prepared in alignment with the current Isturisa European risk management version 1.1 (revised 04-Oct-2019).

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Important identified risks	Hypocortisolism QT prolongation
Important potential risks	Reproductive toxicity/Embryofetal 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-Cushing Disease Cushing Syndrome patients including long-term effects

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None.				
Category 3 - Required additional pharmacovigilance activities				
Study CLCI699C2X01B **Study title:** An open-label, multi-center, 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	To evaluate the long-term safety data with osilodrostat treatment (i.e., AEs and SAEs); To evaluate the clinical benefit as assessed by the Investigator; To evaluate the long-term safety of osilodrostat treatment, as assessed by physical examination, laboratory data, vital signs, ECG and pituitary MRI.	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)	Final report submission	Q4 2024
Registry **Study title:** Multi-country, observational study to collect clinical information	The aim is to further document the long-term safety of osilodrostat administered in routine clinical practice in patients	Long-term safety (including hypocortisolism, CV safety and QT-prolongation,	Final protocol	Within 4 months after market approval

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
on patients with endogenous Cushing's syndrome treated with osilodrostat and to document the long-term safety. **Status:** planned	with CS treated with osilodrostat. The primary objective is to collect and assess safety data with a particular focus on hypocortisolism, CV safety, QT prolongation and hormones of the HPA-axis including ACTH increase, and clinical consequences of increased sexual hormones. The long term safety of non-CD CS patients will also be assessed	hormones of the HPA-axis including ACTH increase, and clinical consequences of increased sexual hormones) Use in non-Cushing Disease Cushing Syndrome patients including long-term effects	Final report submission	Q4 2027

VI.1.3 Summary of Post authorisation efficacy development plan

There are no post-authorization efficacy studies planned or ongoing for osilodrostat.

VI.1.4 Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimization activities
Important identified risks	
Hypocortisolism	**Routine risk communication** SmPC section 4.4, section 4.8, and section 4.9. Package leaflet Section 2 (What you need to know before you take Isturisa). **Routine risk minimization activities recommending specific clinical measures to address the risk**: Cortisol levels should be monitored at regular intervals since hypocortisolism can occur during dose titration until the optimal dose regimen is achieved, or during treatment under conditions of relative cortisol deficiency due to increased glucocorticoid demand (e.g. in the event of stress, surgery, or infection). Patients should be informed of the symptoms associated with hypocortisolism (e.g. weakness, fatigue, anorexia, nausea, vomiting, and weight-loss). 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. In the event of suspected overdosage, cortisol levels should be assessed, Isturisa should be interrupted, 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 for a few days. **Other routine risk minimization measures beyond the Product Information**: None.
QT prolongation	**Routine risk communication** SmPC section 4.4, section 4.8, and section 4.9, Package leaflet Section 2. **Routine risk minimization activities recommending specific clinical**

Safety concern	Routine risk minimization activities
	measures to address the risk: Monitoring for an effect on the QTc interval is advisable. An ECG should be performed prior to the start of Isturisa treatment, within one week after treatment initiation, and as clinically indicated thereafter. If the QTc interval is >480 ms prior to or during treatment, cardiology consultation is recommended. Hypokalaemia or hypomagnesaemia must be corrected prior to Isturisa administration and levels should be monitored periodically during therapy. In patients with risk factors for QT prolongation (such as congenital Long QT Syndrome, congestive heart failure, bradyarrhythmias, uncorrected electrolyte abnormalities and concomitant medications known to prolong the QT interval), caution is advised and more frequent ECG monitoring is recommended. **Other routine risk minimization measures beyond the Product Information**: None.
Important potential risks	
Reproductive toxicity/Embryofetal development	**Routine risk communication** SmPC section 4.6 and section 5.3, Package leaflet Section 2. **Routine risk minimization activities recommending specific clinical measures to address the risk**: Pregnant women should be advised of the potential risk to a foetus. A pregnancy test is recommended prior to the initiation of treatment. Sexually active females of reproductive potential should use effective contraception (methods that result in less than 1% pregnancy rates) when using Isturisa during treatment and for at least one week after stopping treatment with Isturisa. **Other routine risk minimization measures beyond the Product Information**: None.
Missing information	
Breast-feeding women	**Routine risk communication** SmPC section 4.6, Package leaflet Section 2. **Routine risk minimization activities recommending specific clinical measures to address the risk**: None. **Other routine risk minimization measures beyond the Product Information**: 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 communication** None. **Routine risk minimization activities recommending specific clinical measures to address the risk**: None. **Other routine risk minimization measures beyond the Product Information**: None.
Use in non-Cushing Disease Cushing Syndrome patients including long-term effects	**Routine risk communication** None **Routine risk minimization activities recommending specific clinical measures to address the risk**:

Safety concern	Routine risk minimization activities
	None. **Other routine risk minimization measures beyond the Product Information**: None.

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Endogenous Cushing's syndrome (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. Among ACTH-dependent forms, pituitary corticotroph adenoma (Cushing's disease) is the most common, outnumbering extrapituitary (ectopic) tumors that secrete ACTH by about seven-to-one; up to 20% of ectopic ACTH tumors remain occult for many years. Rarely, neuroendocrine tumors, medullary thyroid carcinoma, and phaeochromocytoma produce corticotropin-releasing hormone (CRH), leading to excess pituitary ACTH secretion. Cortisol excess from primary unilateral adrenal adenomas or carcinomas suppresses ACTH; these tumors account for about 20% of endogenous Cushing's syndrome cases. Rarely, Cushing's syndrome is caused by primary bilateral macronodular adrenal hyperplasia (BMAH) or primary pigmented nodular adrenocortical disease (PPNAD) and its non-pigmented variant, isolated micronodular adrenocortical disease.

VI.2.2 Summary of treatment benefits

Isturisa was shown to be effective at lowering the levels of cortisol in one main study involving 137 patients with Cushing's syndrome. All patients were initially treated with Isturisa for 26 weeks. The dose was adjusted for each patient until their levels of cortisol were under control and within the normal range.

After this initial phase, patients whose cortisol levels were under control (71 patients) were given either Isturisa or placebo (a dummy treatment), and the study looked at the number of patients whose cortisol levels remained under control. After 8 weeks of treatment, 86% (31 out of 36) of patients treated with Isturisa had their cortisol levels under control, compared with 29% (10 out of 34) of patients given placebo.

VI.2.3 Unknowns relating to treatment benefits

The pivotal study enrolled patients with a median age of 40.0 years which is representative of the target patient population that is expected to be considered for treatment with osilodrostat. Little information is available for elderly patients. However, there is no evidence indicating a different treatment effect and safety profile in the elderly patients

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Hypocortisolism	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 osilodrostat.	Patients should be informed prior to administration of osilodrostat 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,

Risk	What is known	Preventability
		nausea, vomiting, hypotension, hyperkalemia, hyponatremia or hypoglycemia) should to 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 osilodrostat and temporary exogenous steroid (glucocorticoid) replacement therapy may be necessary. Information and management guidelines are included in the proposed product labelling.
QT prolongation	A thorough QT study (Study CLCI699C2105) demonstrated a positive exposure-related QTcF prolongation (a measure of the electrical activity of the heart) for osilodrostat. QTcF increased by 25.38 ms (90% CI: 23.53, 27.22) on osilodrostat 150 mg, but not on osilodrostat 10 mg (1.73 ms at 3 hours post-dose). The estimated mean QTcF for the maximum clinical dose of 30 mg was +5.3 ms. 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. Despite intense ECG monitoring, no cases of unconfounded treatment-related arrhythmia or events of QTcF > 500 ms were documented in Study CLCI699C2301.	ECG should be performed prior to the start of osilodrostat therapy and monitoring for an effect on the QT interval is advisable. Hypothyroidism, hypokalemia and/or hypomagnesemia should be corrected prior to osilodrostat administration and monitored periodically during therapy. Caution is required when co-administering osilodrostat with anti-arrhythmic medicines and other drugs that may prolong the QT interval. Information and management guidelines are included in the proposed product labelling.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Reproductive toxicity/embryofoetal development	Toxicity was noted in female reproductive organs (ovary, uterus and vagina) in female rats. Embryofetal toxicity was seen in rats and rabbits and teratogenic effects were seen in rats at maternally toxic doses, potentially due to aromatase inhibition. Osilodrostat, 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 program, hence this risk in humans is not known.

Risk	What is known (Including reason why it is considered a potential risk)
	Given the potential severity of teratogenicity with the impact on the risk-benefit balance, and the need for risk minimization activities involving product information advising on specific clinical actions to be taken to minimize the risk (avoidance of pregnancy, need for effective contraception), this risk is classified as an important potential risk. Females of child-bearing potential should be advised on the use of effective contraception methods. Pregnant women should be advised of the potential risk to a fetus if osilodrostat is used during pregnancy or if the patient becomes pregnant while taking this drug.

Missing information

Risk	What is known
Breast-feeding women	Pregnant and lactating women were excluded from all clinical studies. There are no data on the effects of osilodrostat on the breastfed child or the effects on milk production. It is not known if osilodrostat is transferred through breast 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 osilodrostat in Cushing's syndrome patients across studies ranged from 80 days to 226 weeks, and in the pivotal study median exposure was 74.7 weeks (0.9 to 165.3 weeks). The safety of patients with long-term use is therefore considered missing information.
Use in non-Cushing Disease Cushing Syndrome patients including long-term effects	The clinical development program included 9 patients with non CD CS, and therefore information in this patient population is considered limited.

VI.2.5 Summary of risk minimisation measures by safety concern

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet 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 minimize its risks.

Together, these measures constitute routine risk minimization measures. This medicine has no additional risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, 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.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan:

Study	Summary of objectives	Safety concerns addressed	Milestones
Roll-over study (Study CLCI699C2X01B) **Study title:** An open-label, multi-center, 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 osilodrostat treatment (i.e., AEs and SAEs). **Secondary objectives:** • To evaluate the clinical benefit as assessed by the Investigator; • To evaluate the long-term safety of osilodrostat treatment, as assessed by physical examination, laboratory data, vital signs, ECG and pituitary MRI.	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)	Final report submission (Q4 2024).
Registry **Study title:** Multi-country, observational study to collect clinical information on patients with endogenous Cushing's syndrome treated with osilodrostat and to document the long-term safety. **Status:** planned	The aim is to further document the long-term safety of osilodrostat administered in routine clinical practice in patients with CS treated with osilodrostat. The primary objective is to collect and assess safety data with a particular focus on hypocortisolism, CV safety, QT prolongation and hormones of the HPA-axis including ACTH increase, and clinical consequences of increased sexual hormones. The long term safety of non-CD CS patients will also be assessed.	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-Cushing Disease Cushing Syndrome patients including long-term effects	Final protocol: Within 4 months after market approval Start of data collection: Within 6 months after PRAC endorsement of the study Final report submission (Q4 2027)

Studies which are a condition of the marketing authorisation

None of the above studies are conditions of the marketing authorisation.

VI.2.7 Summary of changes to the Risk Management Plan over time

Rationale for submitting an updated RMP: The Risk Management Plan (RMP) v1.1 (revised 04-Oct-2019) is updated in alignment with the response to the Day 180 Assessment Report and includes a minor

revision concerning the SmPC section referenced as routine risk minimization measure for the missing information “breast-feeding women”.

Summary of significant changes in this RMP: Compared to osilodrostat EU RMP Version 1.0 (dated 03-Oct-2018), this version has been updated, in response to the CHMP List of Outstanding Issues (EMA/CHMP/412580/2019) for procedure number EMEA/H/C/4821, to remove two missing information topics “Children and adolescents (patients less than 18 years)” and “Pregnant women”; and to add two missing information topics “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)” and “Use in non-Cushing Disease Cushing Syndrome patients including long-term effects”. In addition, a proposal for two PASS studies (a registry and a roll-over study, ‘CLCI699C2X01B’) was added to the pharmacovigilance plan (with both being categorized as Category 3). Further, the proposal for a patient alert card was removed.

Part	Major changes compared to RMP v1.0
Part I	None.
Part II	**Module SI** None. **Module SII** None. **Module SIII** None. **Module SIV** None. **Module SV** None. **Module SVI** None. **Module SVII** **Removal of the following missing information topics:** • Children and adolescents (patients less than 18 years); • Pregnant women. **Addition of the following missing information topics:** • 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-Cushing Disease Cushing Syndrome patients including long-term effects. **Module SVIII** Updated to reflect the current summary of safety concerns.
Part III	Addition of 2 category 3 PASS studies: Study LCI699C2X01B and Registry study.
Part IV	None.
Part V	Removal of the patient alert card, planned to be used for the identified risk “Hypocortisolism”, from the list of additional risk minimization measures. Addition of a targeted follow-up checklist (pregnancy) for the potential risk “Reproductive toxicity/embryofetal development”.
Part VI	Updated and aligned with the other RMP sections.
Part VII	Annex 2: the details for the two category 3 PASS study were added. Annex 3: updated and aligned with the other RMP sections Annex 4: addition of the targeted follow-up checklist for “Pregnancy” Annex 6: removal of the patient alert card previously added as an additional risk minimization measure for the important identified risk of hypocortisolism. Annex 8: Updated with the latest changes made in the version 1.1.