SUMMARY OF RISK MANAGEMENT PLAN

for

ISTURISA®

(osilodrostat)

Active substance:	Osilodrostat
Product(s) concerned (brand name(s)):	Isturisa
MAH / Applicant name:	Recordati AG
Data lock point for this module:	08 January 2023
Version number of RMP when this module was last updated:	3.0

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 European Risk Management Plan (RMP) for Isturisa (version 3.0, dated 21 Feb. 2024).

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.

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.

2.1. Summary table 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.

2.2. Summary table of Safety Concerns

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	<u>Routine risk minimisation measures</u> 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. <u>Additional risk minimisation measures</u> None.

ACTH=adrenocorticotropic hormone; CS=Cushing's syndrome; PL=Package 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	<u>Routine risk minimisation measures</u> 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. <u>Additional risk minimisation measures</u> None.

ECG=electrocardiogram; PL=Package 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=Package 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=Package 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.

3. Table of ongoing 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 authorisation				
None.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None.				
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, laboratory data, vital signs, ECG and pituitary magnetic resonance imaging.	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.

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.

4. Summary of Post Authorisation efficacy development plan

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

5. Summary of changes to the Risk Management Plan over time

A list of all significant changes to the Risk Management Plan for Isturisa over time is provided below.

Version	Approval date Procedure	Change
1.0	03 October 2018	Not applicable; this is the first Risk Management Plan for Isturisa.
1.1	15 November 2019	**Safety concerns** • Important identified risks: no change. • Important potential risks: no change. • The following safety concerns were removed from missing information for Isturisa: o Children and adolescents (patients less than 18 years). o Use in pregnant women. • The following safety concerns were added to missing information for Isturisa: o Long-term safety (including hypocortisolism, cardiovascular safety and QT-prolongation, hormones of the hypothalamic-pituitary-adrenal axis including adrenocorticotropic hormone increase, and clinical consequences of increased sexual hormones). o Use in non-Cushing's disease Cushing's syndrome patients including long-term effects. **Pharmacovigilance plan** • Addition of 2 category 3 post-authorisation safety studies: Study LCI699C2X01B and a registry. • Addition of a targeted follow-up checklist for the important potential risk of Reproductive toxicity/embryofoetal development. **Risk minimisation measures** • Removal of the patient alert card previously added as an additional risk minimisation measure for the important identified risk of Hypocortisolism. • A minor revision concerning the Summary of Product Characteristics section referenced as the routine risk minimisation measure for the missing information, Breast-feeding women, was implemented.

Version	Approval date Procedure	Change
3.0	07 March 2024 Intermediate versions: - Version 2.0 submitted on 08 September 2023 to EMA - Version 2.1 submitted on 05 January 2024 following 1st round of CHMP/PRAC questions - Version 2.2 submitted on 21 February 2024 following 2nd round of CHMP/PRAC questions, corresponds to final approved version 3.0	Addition of information regarding Study CLCI699C2301 (LINC3) CLCI699C2302 (LINC4). **Pharmacovigilance Plan** • Removal of 1 category 3 post-authorisation safety study (registry). • Addition of a new non-interventional study. • Revision of Follow-up questionnaire for pregnancy (addition of new periods for follow-up) • Removal of non-interventional LCI699-RECAG-PASS-0572 study following PRAC request.