Isturisa®
(osilodrostat)
1mg - 5mg - 10mg film-coated tablets

ISTURISA® IN CLINICAL PRACTICE:

A user guide to understanding initiation, titration and hypocortisolism

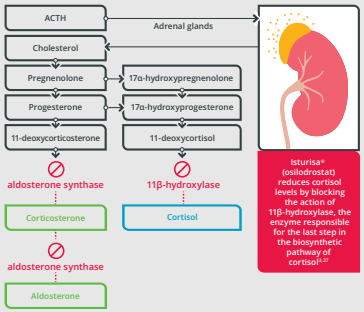
This educational material is based on the expert clinical experience of Professor Antoine Tabarin (Bordeaux, France), Doctor Ulrich Dischinger (Würzburg, Germany) and Professor Andrea Isidori (Rome, Italy).

This brochure is intended for healthcare professionals only.

Isturisa® is indicated for the treatment of adults with endogenous Cushing's syndrome.[1]

RECORDATI RARE DISEASES

How does Isturisa® treat Cushing's disease?



Adapted from Isturisa SmPC[1] and Bertagna X *et al.*, 2014[3]

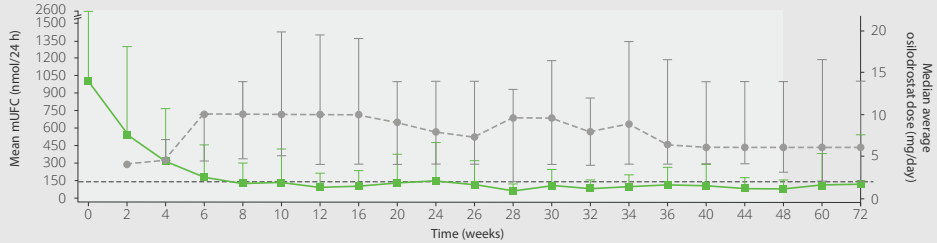
Isturisa® is an orally administered potent inhibitor of the enzyme that regulates the last step of cortisol production (11β-hydroxylase).

Isturisa® can rapidly achieve and maintain cortisol normalisation to alleviate the signs and symptoms of Cushing's disease[1,4] during long-term treatment, as shown in Phase III clinical trials.[5–8] Alongside cortisol control, signs and symptoms of hypercortisolism improve during Isturisa® treatment,[5–8] and Isturisa® treatment is generally well tolerated.[5]

Summary of LINC 3 and LINC 4 studies[5,6,8,9]

	LINC 3[9] Phase III[6,9]	LINC 4[5] Phase III[5,8]
	48 weeks + optional extension **8-week**, double-blind, **randomised withdrawal** period	**48 weeks** + optional extension **Initial 12-week**, placebo-controlled, double-blind, **randomised** period
	N=137 patients with **CD** mUFC >1.5 x ULN Median (range) exposure: 130 (1–245) weeks	**N=73** patients with **CD** mUFC >1.3 x ULN Median (range) exposure: 87 (2–127) weeks
	86.1% vs 29.1% (*P*<0.0001) maintained mUFC ≤ULN with osilodrostat vs **placebo** at week 34	**77.1% vs 8.0% (*P*<0.0001)** maintained mUFC ≤ULN with osilodrostat vs **placebo** at week 12
	Most common (≥30%) AEs: • Nausea (**45.3%**) • Headache (**36.5%**) • Fatigue (**32.8%**)	Most common (≥30%) AEs: • Decreased appetite (**46.6%**) • Arthralgia (**45.2%**) • Fatigue (**39.7%**) • Nausea (**37.0%**) • Headache (**34.2%**) • Dizziness (**30.1%**)

LINC 3: Long-term changes in mean mUFC and median (IQR) osilodrostat dose over time[9]



Mean mUFC, n=	137	135	131	125	130	130	125	125	124	125	119	37	85	44	92	109	115	114	108	103	96
Dose, n=		135	135	131	132	127	128	127	122	122	119	36	86	42	96	108	111	112	110	100	97

Data are reported up to week 204; values up to week 72 are displayed here
Adapted from: Fleseriu M, Newell-Price J, Pivonello R et al. Long-term outcomes of osilodrostat in Cushing's disease: LINC 3 study extension. Eur J Endocrinol 2022;187:531–41.

HYPOCORTISOLISM-RELATED ADVERSE EVENTS

As with all steroidogenesis inhibitors, AEs related to hypocortisolism are expected during Isturisa® treatment because of its potent inhibition of 11β-hydroxylase.[5]

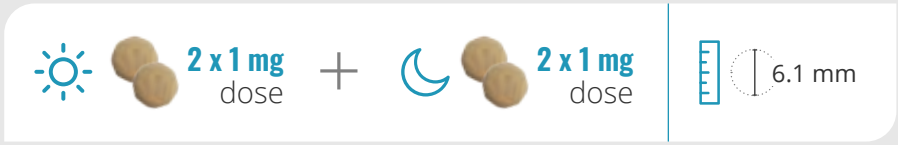
	LINC 3[9]	LINC 4[5,8]
	Median (range) exposure: **130** (1–245) **weeks**	Median (range) exposure: **87** (2–127) **weeks**
FREQUENCY	**54.0%** of patients experienced hypocortisolism-related AE Most common during **first 26 weeks**	**24.7%**† of patients experienced hypocortisolism-related AE Most common during **first 48 weeks**
REPORTED AS*	Adrenal insufficiency: **29.2%** Glucocorticoid deficiency: **20.4%**	Adrenal insufficiency: **24.7%**† Acute adrenocortical insufficiency, steroid withdrawal syndrome: **Both 1.4%**†
MANAGEMENT	Dose reduction: **60.3%** Temporary dose interruption: **48.9%** Glucocorticoid therapy: **22.6%** Discontinuation: **3.6%**	Dose adjustment‡: **30.0%**† Temporary dose interruption: **75.0%**† Glucocorticoid therapy: **65.0%**† Discontinuation: **10.0%**†

- In the LINC clinical development programme, a higher occurrence of hypercortisolism-related AEs (adverse events) were described during the dose titration period in LINC 3 than LINC 4.[5,9]
- Isturisa® dose titration was slower in LINC 4 (every 3 weeks) than in LINC 3 (every 2 weeks), suggesting that increased dose intervals could mitigate the risk of hypocortisolism-related AEs,[8] but this did not impact its ability to normalise cortisol levels in patients with Cushing's disease.[5]
- Very few patients discontinued Isturisa® because of hypocortisolism-related AEs[5]. Instead, these AEs were well managed with Isturisa® dose reduction or temporary interruption and/or with additional glucocorticoid therapy.[9]

*Hypocortisolism-related AEs were assessed by investigators based on their clinical judgement and not a formal diagnosis
†Data from the LINC 4 core study
‡Dose increase or decrease not specified

How do you initiate Isturisa® in routine clinical practice?

Isturisa® should be initiated at 2 mg bid.[1,2] For patients of Asian ancestry, a reduced starting dose of 1 mg bid is recommended.[1,2]



Isturisa® can be taken with or without food.
The dose can be gradually titrated (initially by dose increments of 1 or 2 mg) based on individual response and tolerability, with the aim to achieve normal cortisol levels.[1]

Isturisa® can be considered in all patients with Cushing's syndrome, regardless of the aetiology and severity of hypercortisolism.[5,6,14]

Treatment with Isturisa® should be initiated and supervised by:[1]

- Physicians experienced in endocrinology or internal medicine.
- Physicians with access to the appropriate facilities to monitor the patient's biochemical response, so that the dose is adjusted to meet the patient's therapeutic needs based on normalisation of cortisol levels.

What tests would you perform to guide your decision to prescribe treatment with Isturisa®?[1,2,7,10,12]

ASSESSMENTS PRIOR TO ISTURISA® INITIATION[1,2,12]

Hypercortisolism	Clinical parameters	Biochemical parameters	Procedural examinations
Standard tests: • 24-hour urinary free cortisol (24-h UFC) • Morning serum cortisol (MSC) • Adrenocorticotropic hormone (ACTH) • Late-night salivary cortisol (LNSC)	Including but not restricted to: • Hypertension • Diabetes	Including but not restricted to: • Fasting plasma glucose • Glycated haemoglobin (HbA_{1c}) • Potassium	• Electrocardiogram (ECG) • Dual-energy X-ray absorptiometry • Magnetic resonance imaging (MRI) • Computed tomography

Other tests (if not already performed):

- Midnight serum cortisol
- Testosterone (males and females)
- Calcium (in some cases)
- Magnesium
- Kidney function tests
  - Creatinine
  - Sodium
  - Urea
  - Estimated glomerular filtration rate (eGFR)
- Luteinising hormone (LH)
- Follicle-stimulating hormone (FSH)
- Testosterone
- Oestradiol
- Liver function tests
  - Alanine aminotransfewrase (ALT) and aspartate aminotransferase (AST)
  - Gamma-glutamyltransferase (GGT)
  - Alkaline phosphatase (ALP)
- Thyroid function tests
  - Thyroid-stimulating hormone (TSH)
  - Free triiodothyronine (FT3)
  - Free thyroxine (FT4)

These tests comprise part of the full treatment pathway

How do you titrate the dose of Isturisa® in routine clinical practice?

Treatment with Isturisa® allows flexible dosing to suit a patient's individual needs. Three strengths of Isturisa® are available: 1, 5 and 10 mg.[1,2]

Multiple dosing options allow you to adjust therapy for each patient's unique needs during titration and maintenance.[1,2]

The dose can be gradually titrated by 1 or 2 mg bid, no more frequently than every 2 weeks.. In some patients, the dose may not need to be increased this often; the frequency of dose titration can be adapted to each patient's clinical response and tolerability.[1,2]

Improvements in signs and symptoms of Cushing's syndrome

If a patient tolerates 10 mg twice daily and continues to have 24-hour UFC levels above the ULN, the dosage can be up-titrated by 5 mg twice daily every 2 weeks.[2]

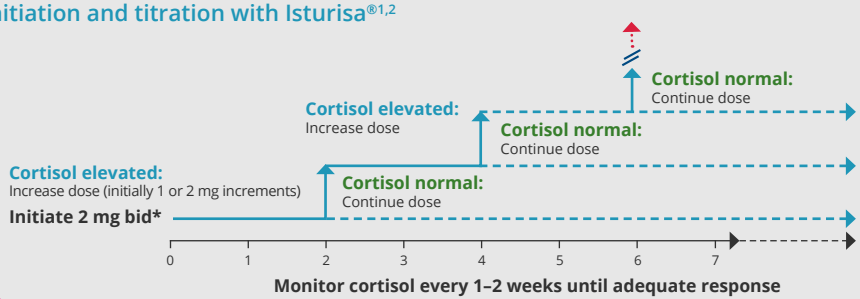
The maintenance dosage of Isturisa® is individualised and determined by titration based on cortisol levels and patient's signs and symptoms.[2]

- Note: Although the maximum maintenance dosage of Isturisa® is 30 mg twice daily, the maintenance dosage in clinical trials was between 2–7 mg twice daily.[2]

Laboratory tests to monitor cortisol levels are essential as these help to guide decisions about dose titration:[1,2]

- Cortisol levels (eg 24-hour UFC, serum cortisol) should be monitored every 1–2 weeks until cortisol is maintained at a normal level.[1,2]

Initiation and titration with Isturisa®[1,2]



*A reduced starting dose of 1 mg bid is recommended for patients of Asian ancestry.

Sensitivity to Isturisa® varies between people and does not appear to be related to the severity of hypercortisolism; no correlation has been identified between mUFC level at treatment initiation and dose received at first normalisation.[5,13,14]

There are no studies assessing dose equivalence between Isturisa® and other medical treatments; when making the switch to Isturisa®, dose initiation and titration should be performed according to manufacturer recommendations, with a starting dose of 2 mg bid.[1,2,18]

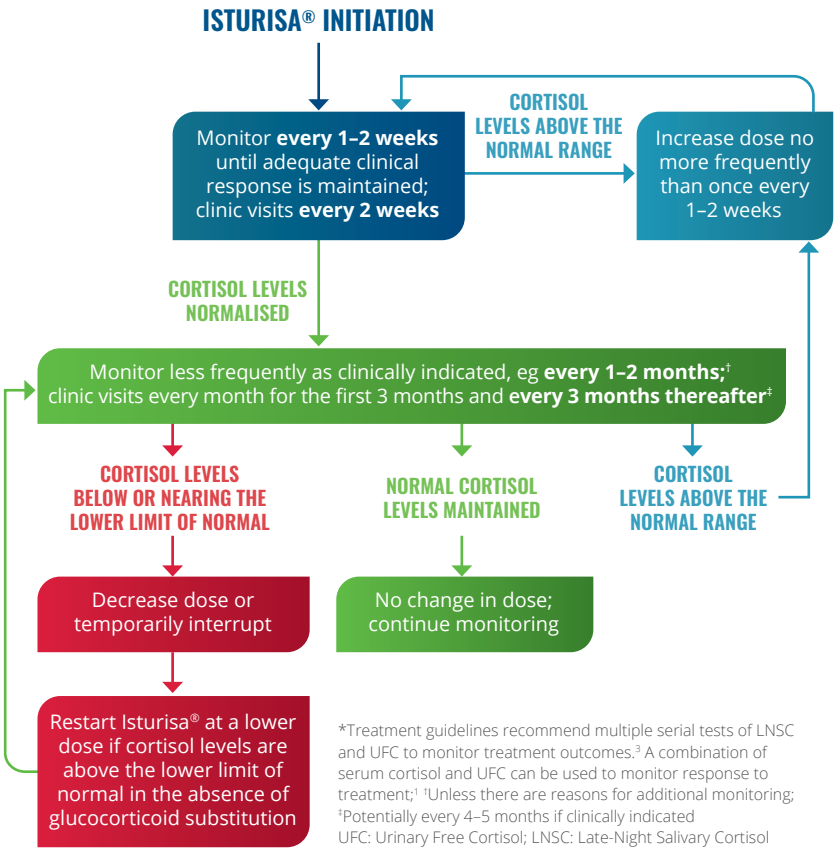
What to cover when couselling your patients before Isturisa® initiation?

Counselling the patient on what to expect during Isturisa® treatment, on recognising the signs and symptoms of hypocortisolism, and on situations in which hypocortisolism is likely to occur (eg infection, illness, stress) is a vital step in the early identification of patients in need of additional management.[15] Patients should always contact their healthcare provider if they are experiencing such symptoms.[16]

- ☑ Highlight that Isturisa® is one of the medical treatments that has been most studied in clinical trials; as a consequence, many patients have been treated with the drug.
- ☑ Explain what Isturisa® is, how it works and how to recognise that the drug is effective.
- ☑ Describe the potential side effects so that the patient knows what to expect, particularly the signs and symptoms of hypocortisolism, and educate on situations in which hypocortisolism is likely to occur (eg infection, illness, stress).
- ☑ Advise that there may be a need to take glucocorticoid replacement therapy if the patient's cortisol levels fall rapidly or during times of stress or illness.
- ☑ Advise patients to read the Isturisa® patient information leaflet and Isturisa® patient package. Clarify that this can be shared with their GP (general practitioner), who may not be as familiar with the disease as they are.

How do you monitor your patients' response to Isturisa®?

Monitoring cortisol (UFC or serum cortisol)* levels is recommended during initiation and maintenance of Isturisa® treatment[1,2]



*Treatment guidelines recommend multiple serial tests of LNSC and UFC to monitor treatment outcomes.[3] A combination of serum cortisol and UFC can be used to monitor response to treatment;[1] [1]Unless there are reasons for additional monitoring; [‡]Potentially every 4–5 months if clinically indicated
UFC: Urinary Free Cortisol; LNSC: Late-Night Salivary Cortisol

Each patient should be considered on an individual basis. Several biochemical and clinical parameters, including physical signs and symptoms of hypercortisolism, can be used to monitor a patient's response to Isturisa® treatment.[15]

THE PRIMARY GOAL OF TREATMENT IS TO REDUCE AND MAINTAIN UFC (AND/OR SERUM CORTISOL) AT NORMAL LEVELS[10]

- Once UFC normalisation has been achieved, it can also be useful to assess and monitor late-night salivary cortisol, with the intention of normalising this parameter as well.[12,21]
- Once stable cortisol normalisation has been achieved, it is important to continue monitoring each patient at regular intervals.[1,2]
- If cortisol levels are nearing the LLN, the dose of Isturisa® may need to be down-titrated, even several months after the start of treatment.[1,15]
- If cortisol levels are above the ULN, the dose of Isturisa® may need to be up-titrated to bring cortisol levels within the normal range.[1]
- Spontaneous fluctuations in cortisol levels can occur in patients; the degree of fluctuation varies between individuals.[17]
- If there is no improvement in cortisol levels or signs and symptoms of hypercortisolism despite dose titration, this suggests that the patient is not responding to treatment, and an alternative treatment strategy should be considered.[12,18]

Signs and symptoms of hypercortisolism that can be monitored to assess response to Isturisa® treatment[1,2,12,15]

- Blood pressure
- Weight
- Blood glucose
- BMI
- Potassium
- Bone density
- Distribution of fat deposition
- Muscle strength
- Facial rubor

It can take several weeks to see improvements in some of these parameters.[15]

Hypocortisolism: prevention, monitoring and management

During the Phase III trials of osilodrostat in patients with Cushing's disease, the most frequently observed AEs overall (>25% of patients) were:[5,6]

Decreased appetite	Arthralgia	Nausea	Fatigue
Adrenal insufficiency	Headache	Myalgia	Dizziness

AEs were mostly mild to moderate in severity and mainly occurred during the dose-titration period.[6]

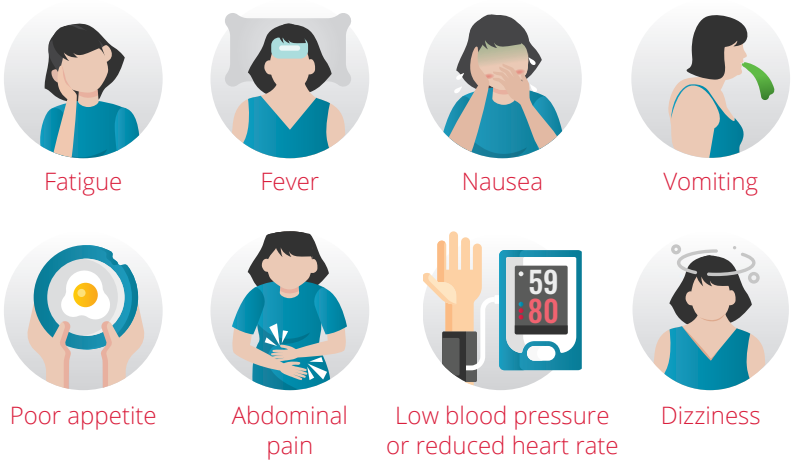
During long-term treatment, the frequency of AEs was lower than during the earlier stages of treatment.[8]

These AEs have also been reported with other steroidogenesis inhibitors.[12]

How do you prevent hypocortisolism and manage patients who experience signs of hypocortisolism in clinical practice?

As with all steroidogenesis inhibitors, there is a risk of hypocortisolism-related events, including adrenal insufficiency.[5,6,12,18]

Signs and symptoms of hypocortisolism



Fatigue · Fever · Nausea · Vomiting

Poor appetite · Abdominal pain · Low blood pressure or reduced heart rate · Dizziness

PREVENTION OF HYPOCORTISOLISM

In addition to appropriate dose titration and regular monitoring for signs and symptoms of hypocortisolism,[15] education of patients and doctors, including local clinicians and general practitioners, is extremely important and should cover the following topics:

- WHAT IS CUSHING'S SYNDROME?
- SIGNS AND SYMPTOMS ASSOCIATED WITH HYPOCORTISOLISM
- SITUATIONS IN WHICH HYPOCORTISOLISM-RELATED EVENTS MAY OCCUR (EG TIMES OF STRESS OR ILLNESS)
- HOW ISTURISA® WORKS

Following the initial consultation, it can be helpful to regularly remind patients during clinic visits about:

- How to recognise the signs and symptoms of hypocortisolism.
- What to do should they suspect that their cortisol levels are too low.
- Always seeking advice from their doctor if symptoms do occur.[15]

Patients with adrenal insufficiency are usually given a kit that contains instructions and a syringe for injection of glucocorticoids if needed. A prescription for oral glucocorticoids can also be provided for administration at home.[15,16,19,20]

MONITORING FOR HYPOCORTISOLISM

Cortisol levels (eg serum cortisol measured at 08:00) should be monitored at regular intervals as hypocortisolism-related events can occur at any time during dose-titration and maintenance periods with Isturisa® treatment.[21] This can help determine whether a patient is at risk of adrenal insufficiency, or whether the patient is experiencing glucocorticoid-withdrawal symptoms.

- Patients with hypercortisolism should be monitored at least every 1–2 weeks until adequate clinical response is maintained.
- Patients with normal cortisol levels should be monitored every 1–2 months unless there is a need for additional monitoring.[1,2]

Additional monitoring is required during conditions of increased cortisol demand, which may trigger hypocortisolism-related safety events such as:[1,22]

Physical stress	Major psychological stress	Infection
Flu	Fever	Trauma
During changes in concomitant medications that may affect Isturisa® exposure, eg products that strongly inhibit or induce multiple enzymes[1,2]		

MANAGEMENT OF HYPOCORTISOLISM

Patients exhibiting signs and symptoms of hypocortisolism should be monitored for:[1,2]

Hypotension	Hyponatraemia	Hyperkalaemia	Hypoglycaemia

Cortisol levels should be measured; if cortisol levels are low, consider:[1,2,15]

- Temporary Isturisa® dose reduction.
- Temporary interruption of Isturisa® (the half-life of Isturisa® is approximately 4 hours).
- Initiation of glucocorticoid replacement therapy, if necessary.

Isturisa® may be resumed at a lower dose after resolution of symptoms, provided that cortisol levels are above the LLN in the absence of glucocorticoid substitution.[1,2]

HOW TO **RECOGNISE** AND **MANAGE** ADRENAL INSUFFICIENCY[20–25]

Isturisa rapidly decreases cortisol levels because of its pharmacology. Patients who are receiving medical therapy for Cushing's syndrome can experience glucocorticoid withdrawal syndrome (GWS) or adrenal insufficiency.[26]

GWS is when a patient has symptoms of a rapid decrease in cortisol levels but levels are still in the normal range or above the ULN.[1] GWS occurs after extended, elevated cortisol exposure is withdrawn, such as after surgery or while taking medical therapy for Cushing's syndrome. It can occur even during glucocorticoid replacement therapy, so cortisol levels and symptoms must be continuously monitored.[1,26]

Isturisa® can cause a patient's cortisol levels to become too low; this is known as adrenal insufficiency. Adrenal insufficiency is most common during dose titration in the early stages of treatment; however, adrenal insufficiency can occur at any time. This is an expected side effect because of Isturisa's® pharmacology.

Cortisol levels and symptoms must be monitored regularly so that adrenal insufficiency can be detected early and treated to bring cortisol levels back to normal.

HOW TO TELL THE DIFFERENCE BETWEEN GWS AND ADRENAL INSUFFICIENCY

Symptoms of adrenal insufficiency can overlap with those for GWS. The following table can help to understand the difference between symptoms of adrenal insufficiency, GWS and Cushing's syndrome.[26]

If the patients' symptoms worsen, they must consult their doctor or visit the nearest emergency departement

		CUSHING'S SYNDROME	GLUCOCORTICOID WITHDRAWAL SYNDROME	ADRENAL INSUFFICIENCY
BRAIN	Depression and mood changes	☑	☑	–
	Difficulty sleeping	☑	–	–
	Difficulty staying awake	–	☑	–
CARDIOVASCULAR	High blood pressure	☑	–	–
	Blood clots	☑	–	–
	Low blood pressure	–	–	☑
GLUCOSE METABOLISM	High blood sugar	☑	–	–
	Low blood sugar		–	☑
GASTROINTESTINAL	Poor appetite	–	☑	☑
	Vomiting	–	–	☑
	Increased appetite	☑	–	–
ADIPOSE TISSUE	Central obesity	☑	–	–
	Deposits of fat on the upper back and collarbone	☑	–	–
	Weight loss	–	☑	☑
REPRODUCTIVE SYSTEM	Lack of sex hormone production	☑	–	–
	Reduced or infertility	☑	–	–
SKIN	Red cheeks	☑	–	–
	Red-purple stretch marks	☑	–	–
	Thin skin and bruising	☑	–	–
BONE	Loss of bone density	☑	–	–
	Osteoporosis	☑	–	–
MUSCULOSKELETAL	Muscle loss	☑	☑	–
	Muscle and bone discomfort	☑	☑	☑
	Tiredness	☑	☑	☑

Adapted from He *et al.* 2022[2]

The **Cushing's patient adrenal insufficiency prevention card** is available for patients. Please contact Recordati Rare Diseases Benelux to obtain this card.

In complex or life-threatening situations, patients should be referred to a specialist centre.

NON-LIFE-THREATENING SITUATION

- Examine for signs of adrenal insufficiency (nausea, vomiting, fatigue, abdominal pain, poor appetite, dizziness).[19,24]
- Measure morning serum cortisol levels.[25]
- Monitor for hypotension, hyponatraemia, hyperkalaemia and hypoglycaemia.[19]
- If diagnosis of adrenal insufficiency is confirmed:
  - Administer glucocorticoid replacement therapy.[23]
  - Notify the treating physician who prescribed the steroidogenesis inhibitor for advice on management of adrenal insufficiency and temporarily reduce or interrupt the treatment.[2]

ACUTE ADRENAL INSUFFICIENCY (ADRENAL CRISIS)

- Assess for the following symptoms: extreme fatigue, weight loss, nausea or vomiting, dehydration, hypotension, loss of consciousness, coma.[24]
- Hospitalise immediately (in the emergency department or department that is monitoring the patient).[22,24]
- Treat with glucocorticoid replacement therapy, such as IV hydrocortisone, and administer rehydration therapy (sodium chloride 0.9%);[25] the dose of glucocorticoid replacement therapy depends on the product administered.
- Notify the treating physician to assist with the management plan before the patient is discharged.[20]

NOTES

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Abbreviations

AE, adverse event
ACTH, adrenocorticotropic hormone
bid, twice daily
BMI, body mass index
CD, Cushing's disease
GP, general practitioner
GWS, glucocorticoid withdrawal syndrome
IQR, interquartile range
IV, intravenous
LLN, lower limit of normal
LNSC, late-night salivary cortisol
mUFC, mean urinary free cortisol
QR, quick-response
SmPC, summary of product characteristics
UFC, urinary free cortisol
ULN, upper limit of normal

NAAM VAN HET GENEESMIDDEL Isturisa 1 mg – 5 mg – 10 mg filmomhulde tabletten. **KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING** Elke filmomhulde tablet bevat osilodrostatfosfaat overeenkomend met respectievelijk 1 mg – 5 mg – 10 mg osilodrostat. **FARMACEUTISCHE VORM** Filmomhulde tablet (tablet). Isturisa 1 mg filmomhulde tabletten Lichtgele, ronde, biconvexe tabletten met schuine randen, zonder breukstreep, met op één zijde een '1' in reliëf. De diameter bedraagt ongeveer 6,1 mm. Isturisa 5 mg filmomhulde tabletten Gele, ronde, biconvexe tabletten met schuine randen, zonder breukstreep, met op één zijde een '5' in reliëf. De diameter bedraagt ongeveer 7,1 mm. Isturisa 10 mg filmomhulde tabletten Lichtoranjebruine, ronde, biconvexe tabletten met schuine randen, zonder breukstreep, met op één zijde een '10' in reliëf. De diameter bedraagt ongeveer 9,1 mm. **THERAPEUTISCHE INDICATIES** Isturisa is geïndiceerd voor de behandeling van het endogene syndroom van Cushing bij volwassenen. **CONTRA-INDICATIES** Overgevoeligheid voor de werkzame stof of voor een van de hulpstoffen. **BIJZONDERE WAARSCHUWINGEN EN VOORZORGEN BIJ GEBRUIK** Hypocortisolisme Remming van de cortisolsynthese door osilodrostat heeft geleid tot hypocortisolisme-gerelateerde voorvallen, zoals cortisolonttrekkingssyndroom (symptomatische daling van cortisolspiegels, maar nog wel boven de ondergrens van de normale waarden) en bijnierinsufficiëntie (cortisolspiegels beneden de normale waarden). De cortisolspiegel moet met regelmatige tussenpozen gecontroleerd worden, aangezien hypocortisolisme-gerelateerde voorvallen op elk moment tijdens de behandeling en na stopzetting van de behandeling kunnen optreden. Aanvullende monitoring is aanbevolen met name tijdens omstandigheden met een verhoogde vraag naar cortisol, zoals lichamelijke of psychische stress, of tijdens veranderingen van gelijktijdig gebruikte geneesmiddelen die de blootstelling aan osilodrostat kunnen beïnvloeden. Het wordt aanbevolen laboratoriummethoden te gebruiken die geen significante kruisreactiviteit vertonen met precursoren van cortisol zoals 11-deoxycortisol die tijdens behandeling met osilodrostat kunnen toenemen. Patiënten moeten geattendeerd worden op de tekenen en symptomen die in verband worden gebracht met hypocortisolisme (bijv. nausea, braken, vermoeidheid, abdominale pijn, verminderde eetlust en duizeligheid). Symptomatische patiënten moeten gecontroleerd worden op hypotensie, hyponatriëmie, hyperkaliëmie en/of hypoglykemie. Indien hypocortisolisme wordt vermoed, moet de cortisolspiegel worden bepaald en een tijdelijke verlaging van de dosis of een tijdelijke onderbreking van Isturisa worden overwogen. Na stopzetting van de behandeling met osilodrostat kan cortisolonderdrukking maanden aanhouden, ongeacht de toegediende dosis osilodrostat, en kan aanvullende monitoring nodig zijn. Indien nodig, dient corticosteroïdsubstitutie te worden gestart. Na het verdwijnen van de symptomen kan osilodrostat worden hervat met een lagere dosis, mits de cortisolspiegel boven de ondergrens van normaal ligt in afwezigheid van glucocorticoïdsubstitutie. QTc-verlenging In een grondig QT-onderzoek werd osilodrostat in verband gebracht met een dosisafhankelijke verlenging van het QT-interval (gemiddelde toename van de maximale geschatte QTcF met +5,3 ms bij de hoogste aanbevolen dosis van 30 mg), wat hartaritmieën kan veroorzaken. QT-verlenging en klinisch relevante ECG bevindingen zijn als bijwerking gemeld in klinisch onderzoek. Er moet een elektrocardiogram (ECG) worden gemaakt voorafgaand aan de start van de behandeling met Isturisa, binnen één week na het instellen van de behandeling en daarna waar dit klinisch aangewezen is. Indien het QTc-interval voorafgaand aan of tijdens de behandeling langer is dan 480 ms, wordt aanbevolen een cardioloog te raadplegen. Tijdelijke dosisverlaging of onderbreking kan nodig zijn. Elke hypokaliëmie, hypocalciëmie en/of hypomagnesiëmie moet(en) vóór toediening van Isturisa worden gecorrigeerd en tijdens de behandeling moeten de elektrolytspiegels periodiek worden gecontroleerd. Isturisa moet met voorzichtigheid worden gebruikt en de risico/batenanalyse moet zorgvuldig worden beoordeeld bij patiënten met risicofactoren voor QT-verlenging zoals: congenitaal lang-QT-syndroom, significante hart- en vaatziekte (inclusief congestief hartfalen, recent myocardinfarct, instabiele angina pectoris, aanhoudende ventriculaire tachycardie, tweede- en derdegraads hartblok en klinisch belangrijke bradyaritmieën) en gelijktijdig gebruik van geneesmiddelen waarvan bekend is dat ze het QT-interval verlengen. Als Isturisa wordt gebruikt bij patiënten met deze risicofactoren, worden frequentere ECG-controles aanbevolen. Corticotrofe tumorgroei Stopzetting van de behandeling met osilodrostat moet worden overwogen bij patiënten die tijdens de behandeling door MRI geverifieerde corticotrofe tumorinvasiviteit ontwikkelen. Gelijktijdig gebruik met sterke enzymremmers of enzyminductoren Voorzichtigheid en nauwlettende controle worden geadviseerd wanneer gelijktijdig toegediende geneesmiddelen worden geïntroduceerd of gestaakt die meerdere enzymen sterk remmen of induceren tijdens de behandeling met osilodrostat, omdat deze de blootstelling aan osilodrostat kunnen beïnvloeden en kunnen leiden tot een risico op bijwerkingen (als gevolg van een mogelijke toename van de blootstelling) of tot een verminderde werkzaamheid (vanwege een mogelijke afname van de blootstelling). Vrouwen die zwanger kunnen worden Isturisa kan schadelijk zijn voor de foetus. Voordat de behandeling met Isturisa wordt gestart, moet de zwangerschapsstatus worden gecontroleerd bij vrouwen die zwanger kunnen worden, en deze patiënten moeten ingelicht worden over een potentieel risico voor de foetus en over de noodzaak om effectieve anticonceptie te gebruiken tijdens de behandeling en gedurende ten minste één week na het stoppen met de behandeling. Gehalte aan natrium Dit middel bevat minder dan 1 mmol natrium (23 mg) per tablet, dat wil zeggen dat het in wezen 'natriumvrij' is. **BIJWERKINGEN** Samenvatting van het veiligheidsprofiel In totaal zijn 210 patiënten met de ziekte van Cushing behandeld met osilodrostat in de fase III-hoofdonderzoeken. De vaakst voorkomende (incidentie ≥ 10%) bijwerkingen gemeld in de fase III-hoofdonderzoeken (C2301 en C2302) met Isturisa waren bijnierinsufficiëntie, vermoeidheid, oedeem, braken, nausea, verminderde eetlust, hoofdpijn, duizeligheid, hypotensie, artralgie, myalgie, tachycardie en bloed testosteron verhoogd. Het veiligheidsprofiel van Isturisa was over het algemeen consistent voor alle typen van het syndroom van Cushing die in klinische onderzoeken zijn onderzocht. Lijst van bijwerkingen uit klinische onderzoeken De bijwerkingen staan vermeld per **systeem/orgaanklasse** volgens gegevensbank MedDRA. Binnen elke systeem/orgaanklasse zijn de bijwerkingen gerangschikt naar frequentiecategorie met de meest voorkomende eerst. Binnen elke frequentiecategorie worden de bijwerkingen gerangschikt naar afnemende ernst. Daarnaast is de overeenkomstige frequentiecategorie voor elke bijwerking gebaseerd op de volgende internationale afspraak: zeer vaak (≥ 1/10); vaak (≥ 1/100, < 1/10); soms (≥ 1/1.000, < 1/100); zelden (≥ 1/10.000, < 1/1.000); zeer zelden (< 1/10.000). Systeem/orgaanklasse Frequentiecategorie Voorkeursterm*. **Endocriene aandoeningen** *Zeer vaak:* Bijnierinsufficiëntie. **Voedings- en stofwisselingsstoornissen** *Zeer vaak:* Hypokaliëmie, verminderde eetlust. **Zenuwstelselaandoeningen** *Zeer vaak:* Duizeligheid, hoofdpijn; *Vaak:* Syncope. **Hartaandoeningen** *Zeer vaak:* Tachycardie. **Bloedvataandoeningen** *Zeer vaak:* Hypotensie. **Maagdarmstelselaandoeningen** *Zeer vaak:* Braken, nausea, diarree, abdominale pijn. **Huid- en onderhuidaandoeningen** *Zeer vaak:* Rash, hirsutisme**, acne**. **Skeletspierstelsel- en bindweefselaandoeningen** *Zeer vaak:* Myalgie, artralgie. **Algemene aandoeningen en toedieningsplaatsstoornissen** *Zeer vaak:* Vermoeidheid, oedeem; *Vaak:* Malaise. **Onderzoeken** *Zeer vaak:* Bloed testosteron verhoogd**, bloed corticotrofine verhoogd; *Vaak:* Elektrocardiogram QT verlengd, transaminasen verhoogd. * Sommige termen geven een gegroepeerde term aan voor twee of meer MedDRA-voorkeurstermen die klinisch gelijkaardig werden geacht. De term "bijnierinsufficiëntie" omvat de termen "glucocorticoïdendeficiëntie", "acute bijnierschorsinsufficiëntie", "steroïdontrekkingssyndroom", "vrij cortisol in urine verlaagd", "cortisol verlaagd". ** Waargenomen bij vrouwelijke patiënten. Beschrijving van geselecteerde bijwerkingen CYP11B1-remming door osilodrostat gaat gepaard met een accumulatie van precursoren van bijniersteroïden en een verhoogde testosteronspiegel. In een klinisch onderzoek met osilodrostat steeg de gemiddelde testosteronspiegel bij vrouwelijke patiënten van hoog- normaal bij baseline tot boven de bovengrens van de normale waarden. De gestegen waarden liepen terug toen de behandeling werd onderbroken. De testosteronstijging ging gepaard met lichte tot matige gevallen van hirsutisme of acne in een subgroep patiënten. Adrenocorticotroop hormoon (ACTH)-waarden boven de tienvoudige bovengrens van normaal werden waargenomen bij sommige patiënten met de ziekte van Cushing die in de klinische onderzoeken met osilodrostat werden behandeld en kunnen gepaard gaan met cortisolwaarden beneden de ondergrens van normaal. Melding van vermoedelijke bijwerkingen Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het Nederlands Bijwerkingen Centrum Lareb, Website: www.lareb.nl. **FARMACOTHERAPEUTISCHE CATEGORIE** Anti-corticosteroïden, ATC-code: H02CA02. **HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN** Recordati Rare Diseases, Tour Hekla, 52 avenue du Général de Gaulle, 92800 Puteaux, France. **AFLEVERINGSWIJZE** U.R. **DATUM VAN HERZIENING VAN DE TEKST** 12/2024.

To report an adverse reaction, please contact the pharmacovigilance department at Recordati Rare Diseases:
RRDPharmacovigilance@recordati.com

You can also report side effects using the national reporting system:
www.lareb.nl

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