SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Isturisa 1 mg film-coated tablets
Isturisa 5 mg film-coated tablets
Isturisa 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Isturisa 1 mg film-coated tablets

Each film-coated tablet contains osilodrostat phosphate corresponding to 1 mg osilodrostat.

Isturisa 5 mg film-coated tablets

Each film-coated tablet contains osilodrostat phosphate corresponding to 5 mg osilodrostat.

Isturisa 10 mg film-coated tablets

Each film-coated tablet contains osilodrostat phosphate corresponding to 10 mg osilodrostat.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Isturisa 1 mg film-coated tablets

Pale yellow, round, biconvex with beveled-edge tablets, unscored, debossed with ‘1’ on one side. Approximate diameter 6.1 mm.

Isturisa 5 mg film-coated tablets

Yellow, round, biconvex with beveled-edge tablets, unscored, debossed with ‘5’ on one side. Approximate diameter 7.1 mm.

Isturisa 10 mg film-coated tablets

Pale orange brown, round, biconvex beveled-edge tablets, unscored, debossed with ‘10’ on one side. Approximate diameter 9.1 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Isturisa is indicated for the treatment of endogenous Cushing’s syndrome in adult patients for whom surgery is not an option or has not been curative.

4.2 Posology and method of administration

Treatment should be initiated and supervised by physicians experienced in endocrinology or internal medicine and with access to the appropriate facilities for monitoring of biochemical responses since the dose must be adjusted to meet the patient's therapeutic needs, based on the normalisation of cortisol levels.

Posology

The recommended starting dose is 2 mg osilodrostat twice daily. For patients of Asian ancestry, a reduced starting dose of 1 mg twice daily is recommended (see section 5.2).

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. It is recommended that cortisol levels (e.g. 24-hour urinary free cortisol, serum/plasma cortisol) be monitored every 1-2 weeks until adequate clinical response is maintained. Thereafter, less frequent monitoring may be considered as clinically indicated, unless there are reasons for additional monitoring (see sections 4.4 and 4.5). Increases in dose should not occur more frequently than once every 1-2 weeks and should be guided by the results of cortisol assessments and by the individual clinical response.

The dose of osilodrostat should be decreased or treatment temporarily interrupted if cortisol levels are below the lower limit of normal, or if there is a rapid decrease in cortisol levels to the lower part of the normal range, or if the patient has signs or symptoms suggestive of hypocortisolism (see section 4.4). 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. Management of other suspected adverse reactions at any time during treatment may also require a temporary dose reduction or temporary interruption of treatment.

The usual maintenance dose in clinical studies varied between 2 and 7 mg twice daily.

The maximum recommended dose of Isturisa is 30 mg twice daily.

If a dose is missed, the patient should take the prescribed dose at the next scheduled time; the next dose should not be doubled.

Special populations

Elderly
There is no evidence to suggest that dose adjustment is required in patients aged 65 years or above. However, data on the use of osilodrostat in this population are limited and Isturisa should therefore be used with caution in this age group.

Renal impairment
No dose adjustment is required for patients with renal impairment (see section 5.2). Urinary free cortisol (UFC) levels should be interpreted with caution in patients with moderate to severe renal impairment, due to reduced UFC excretion. Alternative methods for cortisol monitoring should be considered in these patients.

Hepatic impairment
No dose adjustment is required for patients with mild hepatic impairment (Child-Pugh A). For patients with moderate hepatic impairment (Child-Pugh B), the recommended starting dose is 1 mg twice daily. For patients with severe hepatic impairment (Child-Pugh C), the recommended starting dose is 1 mg once daily in the evening, with initial up-titration to 1 mg twice daily (see section 5.2).

Data on use in patients with hepatic impairment is limited. More frequent monitoring of adrenal function may be required in patients with hepatic impairment during dose titration.

Paediatric population
The safety and efficacy of Isturisa in children and adolescents under the age of 18 years of age have not yet

been established.
No data is available.

Method of administration

Oral use.

Isturisa can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypocortisolism

Inhibition of cortisol synthesis by osilodrostat has led to hypocortisolism-related events such as cortisol withdrawal syndrome (symptomatic decrease of cortisol levels, but still above the lower limit of the normal range) and adrenal insufficiency (cortisol levels below the normal range).

Cortisol levels should be monitored at regular intervals (see section 4.2), since hypocortisolism-related events can occur at any time during treatment and after treatment discontinuation. 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 osilodrostat exposure (see section 4.5). It is recommended to use laboratory methods that do not exhibit significant cross-reactivity with cortisol precursors such as 11-deoxycortisol that may increase during osilodrostat treatment.

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 osilodrostat considered. After osilodrostat discontinuation, cortisol suppression may persist for months, irrespective of osilodrostat administered dose, and might require additional monitoring. 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.

QTc prolongation

In a thorough QT study, osilodrostat was associated with a dose-dependent QT interval prolongation (mean maximum estimated QTcF increase by +5.3 ms at the highest recommended dose of 30 mg) which may cause cardiac arrhythmias (see section 5.1). Adverse reactions of QT prolongation and clinically relevant ECG findings have been reported in clinical studies.

An electrocardiogram (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 exceeds 480 ms prior to or during treatment, cardiology consultation is recommended. Temporary dose reduction or interruption may be required.

Any hypokalaemia, hypocalcaemia or hypomagnesaemia should be corrected prior to Isturisa administration and electrolyte levels should be monitored periodically during therapy.

Isturisa should be used with caution and the benefit-risk carefully weighed 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 bradyarrhythmias), and
- concomitant medicinal products known to prolong the QT interval (see section 4.5).

If Isturisa is used in patients with these risk factors, more frequent ECG monitoring is recommended.

Corticotroph tumour growth

Discontinuation of osilodrostat treatment should be considered in patients who develop MRI-verified corticotroph tumour invasiveness during treatment.

Concomitant use with strong enzyme inhibitors and inducers

Caution and closer monitoring are advised when co-administered medicinal products that strongly inhibit or induce multiple enzymes are introduced or discontinued during osilodrostat treatment (see section 4.5), as they may affect osilodrostat exposure and may result in a risk of adverse events (due to a potential increase in exposure) or of decreased efficacy (due to a potential decrease in exposure).

Women of childbearing potential

Isturisa may cause foetal harm. Pregnancy status should be verified in women of childbearing potential prior to the initiation of Isturisa, and these patients should be advised of a potential risk to the foetus and of the need to use effective contraception during treatment and for at least one week after stopping treatment (see section 4.6).

Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Potential pharmacodynamic interactions

Co-administration of osilodrostat with other therapies known to affect the QT interval can lead to QT prolongation in patients with known cardiac rhythm disorders (see sections 4.4 and 5.1). A washout period should be considered when switching from other products known to affect the QT interval such as pasireotide or ketoconazole.

Effects of other medicinal products on the pharmacokinetics of osilodrostat

The potential for clinical drug-drug interactions (DDI) with concomitantly administered medicinal products that inhibit transporters or a single CYP or UGT enzyme is low (see section 5.2).

Strong enzyme inhibitors
Caution is advised when co-administered medicinal products that strongly inhibit multiple enzymes are introduced or discontinued during osilodrostat treatment (see section 4.4).

Strong enzyme inducers
Caution is advised when co-administered medicinal products that strongly induce multiple enzymes (e.g. rifampin) are introduced or discontinued during osilodrostat treatment (see section 4.4).

Effects of osilodrostat on the pharmacokinetics of other medicinal products

Because osilodrostat and its major metabolite M34.5 may inhibit and/or induce multiple enzymes and transporters, general caution is advised when osilodrostat is co-administered with sensitive enzyme or transporter substrates with a narrow therapeutic index. Available interaction data is summarised below (see also section 5.2).

Clinical studies
In a healthy volunteer study (n=20) using a single dose of 50 mg osilodrostat and a probe drug cocktail, osilodrostat was found to be a mild inhibitor of CYP2D6 and CYP3A4/5, a mild to moderate inhibitor of CYP2C19, and a moderate inhibitor of CYP1A2.

- CYP2D6 – area under the curve (AUC) geometric mean ratio of 1.5 for dextromethorphan (CYP2D6 substrate) when dosed with osilodrostat compared to when dosed alone.
- CYP3A4 – AUC geometric mean ratio of 1.5 for midazolam (CYP3A4 substrate) when dosed with osilodrostat compared to when dosed alone.
- CYP2C19 –AUC geometric mean ratio of 1.9 for omeprazole (CYP2C19 substrate) when dosed with osilodrostat compared to when dosed alone. However, an *in vitro* signal of time-dependent inhibition has been observed, thus the consequence following repeated dosing is unclear. Osilodrostat should be used with caution when co-administered with sensitive CYP2C19 substrates with a narrow therapeutic index.
- CYP1A2 –AUC geometric mean ratio of 2.5 for caffeine (CYP1A2 substrate) when dosed with osilodrostat compared to when dosed alone. However, an *in vitro* signal of CYP1A2 induction has been observed, thus the consequence following repeated dosing is unclear. Osilodrostat should be used with caution when co-administered with sensitive CYP1A2 substrates with a narrow therapeutic index such as theophylline and tizanidine.

In a healthy volunteer study (n=24), osilodrostat (30 mg twice daily for 7 days before concomitant administration with a combined oral contraceptive containing 0.03 mg ethinyl oestradiol and 0.15 mg levonorgestrel and continued for another 5 days) did not have a clinically meaningful effect on the AUC and maximum serum concentration (C_{max})of ethinyl estradiol (geometric mean ratio: 1.03 and 0.88, respectively) and AUC of levonorgestrel (geometric mean ratio: 1.02). The C_{max} of levonorgestrel fell slightly outside the bioequivalence acceptance range (geometric mean ratio: 0.86; 90% confidence interval : 0.737-1.00). The effects of a longer induction period and an interaction with other hormonal contraceptives have not been studied (see also sections 4.4 and 4.6).

In vitro data
In vitro data for osilodrostat and its major metabolite M34.5 suggest a potential for both inhibition and induction for CYP1A2, CYP2B6 and CYP3A4/5, a potential for time-dependent inhibition of CYP2C19, and an inhibitory potential for CYP2E1 and UGT1A1. It cannot be excluded that osilodrostat may affect the exposure of sensitive substrates for these enzymes.

In vitro data for osilodrostat and its major metabolite M34.5 suggest an inhibitory potential for OATP1B1, OCT1, OCT2, OAT1, OAT3 and MATE1. It cannot be excluded that osilodrostat may affect the exposure of sensitive substrates for these transporters.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Based on preclinical data, osilodrostat may cause foetal harm when administered to a pregnant woman. A pregnancy test before initiating treatment is recommended in women of childbearing potential. Women of childbearing potential have to use effective contraception during and for at least one week after treatment. If hormonal contraceptives other than the oral combination of ethinylestradiol and levonorgestrel are used, an additional barrier method of contraception is recommended (see section 4.5). Isturisa should not be used in women of childbearing potential not using contraception.

Pregnancy

There are no or limited amount of data from the use of osilodrostat in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Isturisa should not be used during pregnancy.

Breast-feeding

It is unknown whether osilodrostat/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Isturisa and for at least one week after treatment.

Fertility

There is no information on the effect of osilodrostat on human fertility. Animal studies have shown effects on the menstrual cycle and reduced female fertility in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Isturisa has minor influence on the ability to drive and use machines. Patients should be warned about the potential for dizziness and fatigue (see section 4.8) and should be advised not to drive or use machines if these symptoms occur.

4.8 Undesirable effects

Summary of the safety profile

A total of 210 patients with Cushing´s disease has been treated with osilodrostat in the pivotal Phase III studies.
The most frequent (incidence ≥10%) adverse reactions reported in the pivotal Phase III studies (C2301 and C2302) with Isturisa were adrenal insufficiency (see section 4.4 Warnings and precaution), fatigue, oedema, vomiting, nausea, decreased appetite, headache, dizziness, hypotension, arthralgia, myalgia, tachycardia and blood testosterone increased.
The safety profile of Isturisa was generally consistent across all types of Cushing's syndrome studied in clinical trials.

Tabulated list of adverse reactions

Adverse reactions (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first.
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1 Adverse reactions

System organ class	**Frequency category**	**Preferred term***
Endocrine disorders	Very common	Adrenal insufficiency
Metabolism and nutrition disorders	Very common	Hypokalaemia, decreased appetite
Nervous system disorders	Very common	Dizziness, headache
	Common	Syncope
Cardiac disorders	Very common	Tachycardia
Vascular disorders	Very common	Hypotension
Gastrointestinal disorders	Very common	Vomiting, nausea, diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders	Very common	Rash, hirsutism**, acne**
Musculoskeletal and connective tissue disorders	Very common	Myalgia, arthralgia
General disorders and administration site conditions	Very common	Fatigue, oedema
	Common	Malaise

Investigations	Very common	Blood testosterone increased**, blood corticotrophin increased
	Common	Electrocardiogram QT prolonged, transaminases increased
* Some terms denote grouped term of two or more MedDRA preferred terms that were considered clinically similar. The term "adrenal insufficiency" includes the terms "glucocorticoid deficiency", "adrenocortical insufficiency acute", "steroid withdrawal syndrome", "urine free cortisol decreased", "cortisol decreased". ** Observed in female patients.		

Description of selected adverse reactions

CYP11B1 inhibition by osilodrostat is associated with adrenal steroid precursor accumulation and testosterone increases. In a clinical study with osilodrostat, mean testosterone levels in female patients increased from high normal at baseline to above the upper limit of the normal range. The increases reversed when treatment was interrupted. The testosterone increase was associated with mild to moderate cases of hirsutism or acne in a subset of patients.

Adrenocorticotropic Hormone (ACTH) values above 10-fold upper limit of normal were observed in some Cushing's disease patients treated with osilodrostat in the clinical studies (see section 5.1) and may be associated with cortisol values below the lower limit of normal.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

Overdosage may result in severe hypocortisolism. Signs and symptoms suggestive of hypocortisolism may include nausea, vomiting, fatigue, low blood pressure, abdominal pain, loss of appetite, dizziness and syncope.

In case of suspected overdosage, Isturisa should be interrupted, cortisol levels checked, and if necessary corticosteroid supplementation 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anticorticosteroids, ATC code: H02CA02

Mechanism of action

Osilodrostat is a cortisol synthesis inhibitor. It potently inhibits 11β-hydroxylase (CYP11B1), the enzyme responsible for the final step of cortisol biosynthesis in the adrenal gland.

CYP11B1 inhibition is associated with the accumulation of precursors such as 11-deoxycortisol and acceleration of adrenal biosynthesis including androgens. In Cushing's disease, the fall in plasma cortisol concentration also stimulates ACTH secretion, via the feedback mechanism which accelerates steroid biosynthesis (see section 4.8).

Pharmacodynamic effects

In a thorough QT study (n=86 male and female healthy volunteers) with osilodrostat, the maximum QTcF interval duration differences to placebo were 1.73 ms (90% CI: 0.15, 3.31) at the 10 mg dose and 25.38 ms (90% CI: 23.53, 27.22) at a supratherapeutic dose of 150 mg. Based on an interpolation of these results, the mean maximum prolongation at the highest recommended dose of 30 mg is estimated to be +5.3 ms.

Clinical efficacy and safety

The efficacy and safety of osilodrostat in patients with endogenous Cushing's syndrome in adults were evaluated in two phase III multicenter studies (study C2301 and C2302).

Study C2301 is a randomised withdrawal (RW) study, and Study C2302 is, a double-blind, randomised study of osilodrostat vs placebo.

Study C2301

The study C2301 consisted of a 26-week open-label period of single-arm osilodrostat treatment period, followed by an 8-week double-blind randomised withdrawal period in which patients were randomised in 1:1 ratio to either osilodrostat or placebo and a subsequent osilodrostat 14-week open-label period. Patients who maintained clinical benefit on osilodrostat could continue in a long-term extension period until last patient achieved week 72, in order to collect further efficacy and safety data.

The eligibility criteria included Cushing's disease (with confirmation of the pituitary source of excess adrenocorticotrophic hormone), and a mean urinary free cortisol (mUFC, derived from three 24-hour urine collections) value greater than 1.5 times the upper limit of normal (ULN) at screening.

A total of 137 adult patients were enrolled. The mean age of the patients was 41.2 years, and the majority were female (77%). Seven patients were aged 65 years or older. Prior therapy included pituitary surgery in 88% of patients and prior medical therapy in 75% of patients. The mean and median baseline mUFC levels were 1006.0 nmol/24 h (7 x ULN) and 476.4 nmol/24 h (3 x ULN), respectively (ULN: 138 nmol/24 h). Co-morbidities at baseline included hypertension (67.9% of patients), obesity (29.9%), diabetes mellitus (21.9%) and osteoporosis (27.7%).

Patients received a starting dose of 2 mg osilodrostat twice daily and the dose could be up-titrated based on individual response and tolerability during an initial 12-week period. Patients with no further dose increases during the following 12 weeks and with a mUFC ≤ULN at week 24 were randomised in a 1:1 ratio at week 26 to receive either osilodrostat or matching placebo for 8 weeks (double-blind randomised withdrawal period), followed by open-label osilodrostat for the remainder of the study. At week 26, 71 patients were randomised in a 1:1 ratio to continue receiving osilodrostat (n=36) or to switch to placebo (n=35). Patients who were not eligible for randomisation at week 24 (n=47) continued on open-label osilodrostat treatment. Nineteen patients discontinued prior to week 26. 113 patients completed week 48 and 106 patients entered the extension phase. An additional 8 patients discontinued between week 48 and week 72.

The primary objective was to compare the proportion of complete responders at week 34 (the end of the 8-week randomised withdrawal period) between patients randomised to continued active treatment and placebo. For the primary endpoint, a complete response was defined as a mUFC value ≤ULN at week 34. Patients whose dose was increased during the randomised withdrawal period or who discontinued randomised treatment were considered non-responders. The key secondary endpoint was to assess the complete response rate at week 24. Patients with dose increases between weeks 12 and 24 and patients with no valid mUFC assessment at week 24 were counted as non-responders for the key secondary endpoint.

Results

The study C2301 met its primary and key secondary endpoints (Table 2).

Median mUFC levels decreased to 62.5 nmol/24 h (-84.1% change from baseline, n=125) at week 12, to

75.5 nmol/24 h (-82.3%, n=125) at week 24 and to 63.3 nmol/24 h (-87.9%, n=108) at week 48 and to 64 nmol/24h (-86.6%, n=96) at week 72.

Median time to first normal mUFC, with the dose escalation used in the study was 41 days.

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

	Osilodrostat n=36	**Placebo n=34**	
Primary endpoint: Proportion of responders at the end of the randomised withdrawal period (week 34) n (%) (95% CI)	31 (86.1) (70.5, 95.3)	10 (29.4) (15.1, 47.5)	
Response rate difference (odds ratio): osilodrostat vs. placebo	13.7 (3.7, 53.4) 2-sided p value <0.001		
Secondary endpoints			**All patients N=137**
Key secondary endpoint: Proportion of patients with mUFC ≤ULN at week 24 and no dose increase after week 12 (95% CI)			72 (52.6%) (43.9, 61.1)
Complete mUFC response rate (mUFC ≤ULN) at week 48 (95% CI)			91 (66.4%) (57.9, 74.3)
Complete mUFC response rate (mUFC ≤ULN) at week 72 (95% CI)			86 (62.8%) (54.1, 70.9)
mUFC: mean urinary free cortisol; ULN: upper limit of normal; CI: confidence interval; response: mUFC ≤ULN.			

Improvements were observed in cardiovascular and metabolic parameters (Table 3) and 85.6% of patients with available assessments showed an improvement in at least one physical feature of Cushing's disease at week 48. With the longer follow up, improvements in cardiovascular and metabolic parameters and physical features of Cushing's disease were maintained.

Table 3 Cardiovascular and metabolic parameters

	Baseline	**Week 24**	**Week 48**
Systolic blood pressure (mmHg)	132.2	124.9 (-4.1%)	121.7 (-6.8%)
Diastolic blood pressure (mmHg)	85.3	81.0 (-3.8%)	78.9 (-6.6%)
Body weight (kg)	80.8	77.3 (-3.0%)	75.5 (-4.6%)
Waist circumference (cm)	103.4	99.1 (-2.6%)	97.4 (-4.2%)
HbA1c (%)	6.0	5.6 (-4.6%)	5.6 (-5.4%)

Osilodrostat treatment also resulted in an improvement in patient-reported outcomes. Improvements from baseline above the established minimal important difference (MID) were observed for Cushing's QoL (total score, Physical Problems subscale and Psychosocial Issues subscale), EQ-5D Utility index and BDI-II (depression) scores. The mean Cushing QoL total score improved from 42.2 at baseline to 58.2 (+14.0; +52.3% change from baseline) at week 48. The improvements observed during the core phase were maintained during the extension phase.

Study C2302
Study C2302 used a double-blind, placebo-controlled design in 74 adult patients (of whom 73 were treated) with Cushing's disease. The study was comprised of a core phase of 12 weeks of a double-blind, placebo-controlled period, followed by a 36-week open-label treatment period with osilodrostat. The eligibility criteria included a mean urinary free cortisol value ((mUFC), derived from three 24-hour urine collections) greater than 1.3 times the upper limit of normal (ULN=138 nmol/24h) at screening, and a confirmation of the pituitary source of excess ACTH.

The mean age of the enrolled patients was 41.2 years, and 84% of them were female. Overall, 87.7% had undergone surgery prior to study entry and 12.3% of patients had received radiotherapy prior to

study start. The following relevant comorbidities were reported in the medical history of enrolled patients: hypertension (61.6%), obesity (13.7%), diabetes mellitus (16.4%), and osteoporosis (26.0%). The median and mean baseline mUFC levels were 340.3 nmol/24h (2.5 x ULN) and 431.7 nmol/24h (3 x ULN), respectively.

At Baseline patients were randomly allocated in a 2:1 fashion to receive either osilodrostat 2 mg bid or matching-placebo; the dose could be gradually increased at 3-week intervals up to 20 mg bid. At the end of the 12-week double-blind randomised period, all patients were treated with open-label osilodrostat. The starting dose was 2 mg bid. Patients receiving daily dose <2mg bid during the 12-week double-blind randomised, placebo-controlled phase, were continued with their last dose from period 1 regardless of treatment.

The primary objective of the study was to compare the proportion of complete responders (mUFC< ULN) at the end of the 12-week placebo-controlled period between patients randomised to osilodrostat and the ones randomised to placebo.. Patients who discontinued the randomised treatment or discontinued the study during the placebo-controlled period were considered non-responders. The key secondary objective was to assess the proportion of complete responders in both arms combined at week 36 (mUFC< ULN) in patients receiving osilodrostat. Dose reductions and temporary dose interruptions for safety reasons do not preclude patients from being counted as a complete responder for the key secondary endpoint.

Results
In study C2302 the primary efficacy endpoint (proportion of complete responders at the end of the 12-weeks placebo-controlled period) was met.

Table 4 Results of the primary endpoint - Phase III study (C2302)

	Osilodrostat n=48	**Placebo n=25**	
Primary endpoint: Complete response rate at the end of 12-weeks placebo-controlled period (95% CI*)	37 (77.1) (62.7, 88.0)	2 (8.0) (1.0, 26.0)	
Response rate difference (odds ratio): osilodrostat vs. placebo	43.4 (7.1, 343.2) 2-sided p-value < 0.0001		
Secondary endpoints			**All patients N=73**
Key secondary endpoint: Proportion of complete responder after 36-week treatment with osilodrostat in both arms combined (95% CI)			59/73 (80.8%) (69.9, 89.1)
mUFC: mean urinary free cortisol; ULN: upper limit of normal; CI: confidence interval; response: mUFC ≤ULN.			

Overall, mUFC consistently decreased during treatment with osilodrostat. Median mUFC was reduced from 342.2 nmol/24h (2.5 x ULN) at baseline to 49.2 nmol/24h (0.4xULN; change from baseline -83.6%) at week 12 in patients treated with osilodrostat while placebo patients median mUFC went from 297.6 nmol/24h (2.2 x ULN) at baseline to 305.5 nmol/24h (2.2 x ULN; change from baseline +4.5%).

Median time to first normal mUFC, with the dose escalation used in the study was 35 days in patients treated with osilodrostat.

Osilodrostat treatment showed an improvement in cardiovascular-related clinical and metabolic parameters (e.g. fasting glucose, systolic blood pressure (SBP), diastolic blood pressure (DBP), weight, and waist circumference) associated with Cushing's disease. The improvement in these

parameters was already observed at the end of the placebo-controlled period (week 12) and maintained during the open-label treatment period (Week 12 to 48).

During the placebo-controlled period, there was a trend for more patients in the osilodrostat arm experiencing improvement in their physical features of Cushing's disease, relative to the placebo arm. The exceptions were in the domains of facial rubor, striae, and proximal muscle atrophy.

Other causes of Cushing's syndrome

The efficacy of osilodrostat was also assessed in 9 adult Japanese patients with other causes of Cushing's syndrome (adrenal adenoma, ectopic corticotropin syndrome and ACTH independent macronodular adrenal hyperplasia; study C1201). At week 12 (primary endpoint), a complete response (mUFC ≤ULN) was observed in 6 patients (66.7%) and a partial response (mUFC decrease by at least 50%) in one additional patient (11.1%). The median average dose used in the study was 2.6 mg/day (range 1.3-7.5 mg/day). The mean duration of treatment in this study was 24 weeks, and long-term exposure was limited.

5.2 Pharmacokinetic properties

Absorption

Osilodrostat is a highly soluble, highly permeable compound (BCS class 1). It is rapidly absorbed (t_{max} ~1 h) and oral absorption in humans is assumed to be nearly complete. Steady state is reached by day 2.

Co-administration with food did not affect absorption to a clinically significant extent. In a healthy volunteer study (n=20), the administration of a single dose of 30 mg osilodrostat with a high-fat meal resulted in a modest reduction of AUC and C_{max} by 11% and 21%, respectively, and the median t_{max} was delayed from 1 to 2.5 hours.

No clinically relevant accumulation was observed in clinical studies. An accumulation ratio of 1.3 was estimated for the 2 to 30 mg dose range.

Distribution

The median apparent volume of distribution (V_z/F) of osilodrostat is approximately 100 litres. Protein binding of osilodrostat and of its major metabolite M34.5 is low (less than 40%) and concentration-independent. The osilodrostat blood-to-plasma concentration ratio is 0.85.

Osilodrostat is not a substrate for OATP1B1 or OATP1B3 transporters.

Biotransformation

In a human ADME study in healthy subjects following the administration of a single dose of 50 mg [^{14}C]-osilodrostat, metabolism was deemed the most important clearance pathway for osilodrostat since ~80% of the dose was excreted as metabolites. The three main metabolites in plasma (M34.5, M16.5 and M24.9) represented 51%, 9% and 7% of the dose, respectively. Both M34.5 and M24.9 have longer half-lives than osilodrostat and some accumulation is expected with twice-daily dosing. The decrease in the contribution of osilodrostat to the radioactivity AUC with time post-dose was found to coincide closely with a corresponding increase in the contribution of M34.5.

Thirteen metabolites were characterised in the urine, with the three main metabolites being M16.5, M22 (an M34.5 glucuronide) and M24.9, with 17, 13 and 11% of the dose, respectively. The formation of the major urinary metabolite M16.5 (direct N-glucuronide) was catalysed by UGT1A4, 2B7 and 2B10. Less than 1% of the dose was excreted as M34.5 (di-oxygenated osilodrostat) in the urine but 13% of the dose was identified as M22 (M34.5-glucuronide). The formation of M34.5 was non-CYP-mediated.

Multiple CYP enzymes and UDP glucuronosyltransferases contribute to osilodrostat metabolism and no single enzyme contributes more than 25% to the total clearance. The main CYP enzymes involved in osilodrostat metabolism are CYP3A4, 2B6 and 2D6. Total CYP contribution is 26%, total UGT contribution is 19% and non-CYP non-UGT mediated metabolism was shown to contribute to ~50% of total clearance. In addition, osilodrostat showed a high intrinsic permeability, low efflux ratio and modest impact of inhibitors on the efflux ratio *in vitro*. This suggests that the potential for clinical drug-drug interactions (DDI) with concomitantly administered medicinal products that inhibit transporters or a single CYP or UGT enzyme is low.

In vitro data indicate that the metabolites do not contribute to the pharmacological effect of osilodrostat.

Elimination

The elimination half-life of osilodrostat is approximately 4 hours.

In an ADME study, the majority (91%) of the radioactive dose of osilodrostat was eliminated in the urine, with only a minor amount eliminated in the faeces (1.6% of dose). The low percentage of the dose eliminated in the urine as unchanged osilodrostat (5.2%) indicates that metabolism is the major clearance pathway in humans.

Linearity/non-linearity

Exposure (AUC_{inf} and C_{max}) increased more than dose-proportionally over the therapeutic dose range.

Drug-drug interactions (see also section 4.5)

In vitro data indicate that neither osilodrostat nor its major metabolite M34.5 inhibits the following enzymes and transporters at clinically relevant concentrations: CYP2A6, CYP2C8, CYP2C9, UGT2B7, P-gp, BCRP, BSEP, MRP2, OATP1B3 and MATE2-K. Since the exposure of M34.5 has not yet been determined after repeated dosing, the clinical relevance of the *in vitro* drug-drug interaction results for M34.5 is unknown.

Special populations

Hepatic impairment
In a phase I study in 33 subjects with varying degrees of hepatic function using a single dose of 30 mg osilodrostat, AUC_{inf} was 1.4- and 2.7-fold higher in the moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment cohorts, respectively. C_{max} was 15 and 20% lower in the moderate and severe cohorts. The terminal half-life increased to 9.3 hours and 19.5 hours in the moderate and severe cohorts. Mild hepatic impairment (Child-Pugh A) did not influence exposure to any significant extent. The absorption rate was not affected by the degree of hepatic impairment.

Renal impairment
In a phase I study in 15 subjects with varying degrees of renal function using a single dose of 30 mg osilodrostat, comparable systemic exposure was seen in subjects with severe renal impairment, end-stage renal disease and normal renal function.

Race/ethnicity and bodyweight
The relative bioavailability was approximately 20% higher in Asian patients compared to other ethnicities. Body weight was not shown to be a major determinant of this difference.

Age and gender
Age and gender had no significant impact on osilodrostat exposure in adults. The number of elderly patients in clinical studies was limited (see section 4.2).

5.3 Preclinical safety data

Repeat dose toxicity

In repeat dose toxicity studies conducted in mice, rats and dogs, the central nervous system, liver, female reproductive organs, and the adrenal gland were the primary target organs. The NOAEL for hepatic, reproductive organ and adrenal effects in long-term (26- and 39-week) studies was at least four-fold human clinical exposure based on AUC. CNS findings (aggression, hypersensitivity to touch and increased or decreased activity) were noted in the rat, mouse and dog. The NOAEL for the CNS effects was approximately 2-fold human free C_{max} based on the most sensitive species.

Carcinogenicity and mutagenicity

Genotoxicity assays conducted *in vitro* in bacterial systems and *in vitro* and *in vivo* in mammalian systems with and without metabolic activation do not indicate a relevant risk in humans. In rat and mice carcinogenicity studies, an increased incidence of hepatocellular adenoma/carcinoma (at lower doses in males than females), and neoplastic changes of thyroid follicular adenoma/carcinoma (in male rats only) were observed. The findings are likely rodent specific and considered not relevant to humans.

Fertility and reproductive toxicity

Reproductive studies in rabbits and rats demonstrated embryotoxicity, foetotoxicity (increased resorptions and decreased foetal viability, decreased foetal weights, external malformations, and visceral and skeletal variations) and teratogenicity at maternally toxic doses. The NOAEL was 10-fold human exposure (AUC) in a pre- and postnatal developmental study, and 8- to 73-fold human exposure (AUC) in a rat fertility and early embryonic development study. The maternal and foetal NOAEL in the rabbit embryofoetal development study was 0.6-fold human exposure (AUC).

Juvenile toxicity

The findings in juvenile rat toxicity studies were largely consistent with those observed in adult rat studies. Delayed sexual maturation was noted at high doses with no effects on overall reproductive performance or parameters after a 6-week recovery period. There were no effects on long bone growth or behavioural performance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Cellulose, microcrystalline
Mannitol
Croscarmellose sodium
Magnesium stearate
Silica, colloidal anhydrous

Film coat

Hypromellose
Titanium dioxide (E171)
Macrogol 4000
Talc

1 mg tablet
Iron oxide yellow (E172)
Iron oxide red (E172)

5 mg tablet
Iron oxide yellow (E172)

10 mg tablet
Iron oxide yellow (E172)
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Alu/Alu blister of 10 tablets.
Packs containing 60 tablets (6 blisters of 10 tablets).

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Recordati Rare Diseases
Puteaux
France

8. LICENSE HOLDER

Medison Pharma Ltd.
10 Hashiloach St.,
POB 7090 Petach Tikva
Israel

9. REGISTRATION NUMBERS

Isturisa 1 mg film-coated tablets: 171-12-37207
Isturisa 5 mg film-coated tablets: 171-13-37208
Isturisa 10 mg film-coated tablets: 171-14-37209

Revised in January 2025 according to MoH guidelines

Isturisa 1 mg, 5 mg, 10 mg-SPC-0125-V1