New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Isturisa® (osilodrostat) [Recordati S.p.A]**
Dosage Formulations:	1mg, 5mg, and 10mg oral tablets
FDA Approval Date: **FDB File Date:**	FDA: March 6, 2020 FDB: April 19, 2020
Indication:	For the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative
Mechanism of Action:	Cortisol synthesis inhibitor – inhibits 11beta-hydroxylase (CYP11B1) which is responsible for the final step of cortisol biosynthesis in the adrenal gland

Dose/ Administration:	• Initial Dose: 2mg twice daily administered orally with or without food
	• Titrate dose by 1-2mg twice daily, no more frequently than every 2 weeks based on rate of cortisol changes, individual tolerability and improvement in signs and symptoms
	• Maximum Dose: 30mg twice daily
	• Patients with hepatic impairment:
	  ○ Recommended initial dose for Child-Pugh B: 1mg twice daily
	  ○ Recommended initial dose for Child-Pugh C: 1mg once daily in the evening

Drug Clinical Highlights:	• FDA granted Orphan Drug designation
	• First FDA approved agent with this mechanism of action (MOA) for this disease (metyrapone has same MOA but only used off label for Cushing's syndrome)
	• No documented contraindications
	• Warnings/Precautions:
	  ○ Hypocortisolism: dosage reduction or interruption may be necessary
	  ○ QTc prolongation: perform electrocardiogram and use with caution in patients with risk factors for QTc prolongation (congenital long QT syndrome, congestive heart failure, bradyarrythmias, uncorrected electrolyte abnormalities and concomitant medications known to prolong the QT interval)
	  ○ Elevations in adrenal hormone precursors and androgens: monitor for hypokalemia, worsening of hypertension, edema and hirsutism
	• The most common adverse reactions reported in the clinical trials were adrenal insufficiency (43.1%), fatigue (38.7%), nausea (37.2%), headache (30.7%) and edema (21.2%)
	• Drug interactions include CYP2B6 inducers, CYP3A4 inhibitors and inducers
	• Breastfeeding is not recommended during treatment and for at least one week after treatment
	• Core Period Clinical Trial:
	  ○ Study population: Cushing's disease patients aged 18 to 75 years with persistent or recurrent disease despite pituitary surgery (88%) or de novo patients for whom surgery was not indicated or who had refused surgery; 96% of patients had received previous treatments for Cushing's disease prior to the study
	  ○ 48 week, multicenter, quadruple masking study,
	  ○ Period 1 (n=137): 12 week, open-label, dose titration period
	  ▪ During this period, patients were started on 2mg twice daily and their dose was titrated as needed
	  ▪ To move to Period 2 (the maintenance phase), mean urine free cortisol (mUFC) had to be ≤ upper limit of normal (ULN) and patients had to tolerate therapy
	  ○ Period 2 (n=130): 12-week, open-label, maintenance treatment period

- During this period, patients were continued on their dose at the end of Period 1 and assessed based on their need to increase this dose
- Patients were considered responders in Period 2 if they were able to maintain a mUFC within the normal range without the need for a dosage increase and moved onto Period 3
- Maintenance dosage varied between 2 and 7mg twice daily

- Period 3 (n=71): 8-week, double-blind, placebo-controlled, randomized, withdrawal treatment period (provides data for the primary efficacy endpoint)
  - Half of the patients who were eligible to continue past Periods 1 and 2 (had continued normal mUFC) continued taking Isturisa while the other half switched to placebo
  - Period 3 assessed the percentage of patients who had normal cortisol levels at the end of 8 weeks versus the patients who received placebo
  - Primary efficacy endpoint: compare percentage of complete responders at the end of Period 3 (mUFC ≤ULN)

Primary Endpoint	Isturisa (N=36)	Placebo (N=34)	Complete Responder Rate Difference
Complete responder rate at the end of the 8-week randomized withdrawal period (Period 3)	31 (86%) 95% CI (71,95)	10 (29%) 95% CI (15,47)	Osilodrostat vs placebo 57 (38, 76) 2-sided p-value <0.001

- Period 4: open-label treatment period of 14 to 24 weeks duration
  - Patients who had maintained benefit while receiving Isturisa were given the option to enter an open-label extension period

Disease State Clinical Highlights:

- Cushing's syndrome is rare condition that occurs when there is an increase of cortisol in the body regardless of the cause.
- Cushing's disease occurs in the presence of pituitary adenomas that produce high levels of adrenocorticotropin hormone (ACTH). With this oversecretion of ACTH, it leads to an overproduction of cortisol by the adrenal glands.
- Cushing's syndrome has an estimated prevalence of 1 per 26,000 – of these, about 70% have Cushing's disease.
- Symptoms include rounding of the face, a pad of fatty tissue between the shoulders and neck and thin skin with bruises and stretch marks.
- Hypercortisolism can be diagnosed with a 24-hour urinary free cortisol, midnight plasma cortisol, late-night salivary cortisol or low-dose dexamethasone suppression test.
- Cushing's disease mainly affects those between the ages of 20 and 50, with females have a higher incidence rate at 70% of all cases.

Price Per Unit (WAC):

- 1mg - $110 per tablet
- 5mg - $400 per tablet
- 10mg - $475 per tablet
- Initial dose of 2mg twice daily - $158,400 per year ($13,200 per month)
- Average maintenance dose in clinical trial of 7mg twice daily - $446,400 per year ($37,200 per month)
- Max dose of 30mg twice daily - $1.026 million per year ($85,500 per month)

Therapeutic Alternatives:

- Nonpharmacological treatments:
  - Surgical resection of the offending tumor (1st line)
    - Success rate of this option is about 70-90%
  - Pituitary irradiation
  - Laparoscopic adrenalectomy
- Pharmacotherapy treatments:
  - Used as secondary treatments in preoperative patients or as adjunctive therapy in postoperative patients awaiting response

	Isturisa	Korlym	Signifor	Signifor LAR
Mechanism of Action	Cortisol synthesis inhibitor	Progesterone and glucocorticoid receptor antagonist	Cyclohexapeptide somatostatin analog	Cyclohexapeptide somatostatin analog
Indication	Treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative	Hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing syndrome who have type 2 DM or glucose intolerance and have failed surgery or are not candidates for surgery	Treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative	Treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative Treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option
Dosage Forms	1mg, 5mg, and 10 mg oral tablets	300mg oral tablets	0.3mg, 0.6mg, and 0.9mg SC ampules	10mg, 20mg, 30mg, 40mg, and 60mg IM vials
Contra-indications	None	- Pregnancy - Coadmin with simvastatin, lovastatin, CYP3A4 substrates - Concomitant tx with systemic corticosteroids for life-saving purposes - Hx of unexplained vaginal bleeding - Endometrial hyperplasia with atypia or endometrial carcinoma	None	None
Daily Dose	2mg to 30mg twice daily	600mg daily	0.6mg twice daily	10mg to 60mg every 28 days
WAC	$110 per 1mg tab $400 per 5mg tab $475 per 10mg tab - Annual cost: $158,400 per year to $1.024 million	$524 per tab - Annual cost: $377,280	$232.33 per 1 mL ampule - Annual cost: $167,277	$13,058.40 per vial - Annual cost: $156,700

- Other pharmacotherapy treatments include ketoconazole, metyrapone, mitotane, cabergoline, and etomidate however, these agents are not FDA approved for Cushing's disease.

Prior Authorization Approval Criteria:

Must meet the following criteria:

Initial Therapy:

- Participants aged 18 years or older **AND**
- Prescribed by or in consultation with an endocrinologist or other specialist for the treated disease state **AND**
- Documented diagnosis of Cushing's disease (ICD10 E24.0, E24.3, E24.8, E24.9) **AND**
- Documentation of all the following:
  - Baseline electrocardiogram **AND**
  - Baseline potassium levels, magnesium levels, and cortisol levels
- Documentation of failed pituitary surgery **OR**
- Contraindication to pituitary surgery
- Initial approval of prior authorization is 3 months

	Continuation of Therapy: • Documentation of recent cortisol levels demonstrating mUFC ≤ULN • Documentation of recent electrocardiogram **Additional Provider Diagnostic/Monitoring Criteria, if desired:** • Repeat electrocardiogram within one week after treatment initiation and as clinically indicated thereafter • Continuously monitor potassium, magnesium and cortisol levels, along with blood pressure and hirsutism development • ≥ 2, 24-hour urine free cortisol collections every 1-2 weeks until adequate clinical response is maintained

Implication to State Medicaid Program:	• LOE: May 2033
	• Phase 3 trials underway of Strongbridge Biopharma's levoketoconazole (Recorlev), a cortisol synthesis inhibitor (similar MOA to ketoconazole) – data expected Q2 2020
	• 38 unique Missouri participants were identified to have Cushing's disease over a 1-year timeframe
	  ○ Success rate of 1st line surgery is 70-90%, leaving roughly 4-12 potential participants
	  ○ Potential yearly increase in budget: $1.8 to $5.4 million (using average clinical trial dose of 7mg twice daily)

References:

1. Isturisa (osilodrostat) [package insert]. Lebanon, NJ: Recordati Rare Disease Inc; 2020.
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4. Signifor LAR (pasireotide) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2019.
5. Cabergoline [package insert]. North Wales, PA: Teva Pharmaceuticals USA Inc; 2016.
6. IPD Analytics. Isturisa (osilodrostat). https://secure.ipdanalytics.com/User/Pharma/Drug/Isturisa#91a1e77c-cfee-4b91-8720-41b4502647c7
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