

## **Isturisa® is now available as a Medical Treatment for Cushing's Syndrome in Germany**

**With the oral cortisol synthesis inhibitor osilodrostat (Isturisa®), a new therapy option for medical treatment of adults with endogenous Cushing's syndrome is now available in Germany as of July 15, 2020.<sup>1</sup> Isturisa® can contribute to alleviate the high burden of this rare but serious and potentially life-threatening disease.<sup>2</sup> Results of the pivotal, multicenter, randomised withdrawal, double-blind phase III study LINC-3 show that osilodrostat led to a rapid and sustained reduction of cortisol levels accompanied by improvements in comorbidities, clinical symptoms and quality of life. Furthermore osilodrostat was well tolerated.<sup>1,3</sup>**

***Puteaux, France, July 16, 2020*** – Cortisol synthesis inhibitor osilodrostat (Isturisa®) is now available in Germany as of July 15, 2020, as a promising new therapy option for medical treatment of adult patients with endogenous Cushing's syndrome (CS).<sup>1,4</sup> Isturisa® was approved by the European Commission on January 9, 2020.

The approval of Isturisa® (osilodrostat) is based on the results of the pivotal phase III study, LINC-3, in which the efficacy and safety of osilodrostat in 137 patients with Cushing's disease were assessed. A significantly higher proportion of patients with Cushing's disease treated with Isturisa® maintained normal mean urinary free cortisol (mUFC) at the end of the 8-week randomized withdrawal period (week 34) versus placebo (86% vs 29%). Cortisol level control is the primary objective in the treatment of patients with Cushing's disease. Thus, the study successfully met its primary and key secondary endpoint.<sup>1,3</sup> Moreover, the results showed that osilodrostat resulted in a rapid and sustained reduction of mean free urine cortisol levels maintained during the 48-week follow-up period. This was accompanied by improvements in clinical symptoms, comorbidity and quality of life.

"Data from the LINC-3 study underline the efficacy and safety of Isturisa® in a prospective setting and represent a significant advance in the treatment of patients with Cushing's disease, a serious and potentially life-threatening rare disease," commented Pr. Rosario Pivonello, Professor of Endocrinology at the Federico II University of Naples (Italy). "I would like to thank all patients who participated in the LINC-3 study and their families who helped make this new and welcome therapy option available for this underserved patient population."

The launch of Isturisa® is an addition to the Recordati Rare Diseases endocrinology portfolio which also includes Signifor®, subcutaneous and intramuscular formulations, available across Europe, indicated for the treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed, and for adult patients with acromegaly for whom surgery is not an option or has not been curative and who are inadequately controlled on treatment with another somatostatin analogue.<sup>5</sup>

### **High Burden of Disease and Impairment of Quality of Life**

Cushing's disease, the most common form of endogenous CS, is associated with high morbidity and burden of disease.<sup>2</sup> As a result, those affected suffer from considerable impairments in their quality of life. In addition, the disease is associated with a large number of significant concomitant diseases as a result of the excessively elevated cortisol levels.<sup>2</sup> These include metabolic syndrome, sleep disorders, osteoporosis, increased susceptibility to infections and/or neuropsychiatric disorders such as depression and anxiety.<sup>2</sup> The mortality rate is correspondingly higher, in particular due to cardiovascular complications. Without proper intervention to normalise cortisol levels, the mortality risk in patients with Cushing's disease is up to five times higher than in the general population.<sup>2</sup> Besides, there are indications that negative physical and psychosocial consequences of chronic hypercortisolism can persist a long time after remission.<sup>2</sup> Because of these potentially life-threatening risks, rapid diagnosis and treatment are necessary.<sup>2,6</sup>

### **Multidisciplinary Treatment with a Need for Optimization**

CS or Cushing's disease require experienced multidisciplinary teams and individual treatment.<sup>2,7</sup> Therapy goals are normalization of cortisol levels, improvement of clinical symptoms and quality of life as well as reduction of comorbidity-related risks.<sup>8,9</sup>

The primary treatment for Cushing's disease is the surgical resection of the pituitary tumor. However, about a third of the patients do not achieve remission or present with long-term recurrences and, therefore, they require further therapy. Possible therapeutic options are repeat surgery, radiotherapy, bilateral adrenalectomy or medical treatments. The latter act either centrally on the pituitary gland or peripherally on the adrenal gland by inhibiting steroid synthesis. They are also used to bridge the gap between diagnosis of the disease and surgery or radiotherapy or its onset of action, or when surgical treatment is not an option.<sup>2,6,8,9</sup>

However, these medical treatments can only be used to a limited extent and/or can be associated with serious disadvantages and risks. For example, up to 50% of patients with Cushing's syndrome fail to reach normal cortisol levels with the currently available medical treatments, which in up to 28% of cases leads to dose adjustment or therapy discontinuation. Thus, there is an unmet need for more effective pharmacological interventions.<sup>2,8,9</sup>

The introduction of osilodrostat has thus opened up new therapeutic options. The data from prospective studies with a well-planned design indicate that this active ingredient is a promising, effective therapy option which is well tolerated.<sup>3,4</sup>

### **About Cushing's Syndrome**

**Cushing's syndrome (CS)** is caused by inappropriate and chronic exposure to excessive cortisol levels. The source of this excessive cortisol can be endogenous or exogenous (ie medication). Endogenous CS is most commonly caused either by an adrenal gland tumor (approx. 15%), leading to an excessive cortisol secretion, or by a pituitary adenoma (ie a tumor of the pituitary gland located in the brain) secreting excessive adrenocorticotrophic hormone (ACTH), which accounts for about 70% of cases. Remaining 15% of cases are of other (ectopic) origin.<sup>2,10,11</sup> With a prevalence of 40 cases per million inhabitants and an incidence of 1.2 to 2.4 per million per year Cushing's disease is a rare disease.<sup>2,11</sup> Women are affected about three times more often than men.<sup>2,7</sup> The peak age is between the 4th and 6th decade of life.<sup>11</sup> The disease is characterized by various long-term effects of glucocorticoids on organs and tissues and can, therefore, be very heterogeneous. Clinical symptoms include stretch marks on the skin (striae rubrae), obesity, muscle atrophy of the extremities, moon-shaped face, general

weakness, osteoporosis, glucose intolerance, arterial hypertension, wound healing disorders, increased bleeding tendency and thromboembolic complications. However, many symptoms are non-specific and also appear in common diseases such as alcohol addiction, obesity or (poorly controlled) diabetes mellitus. Because of the low specificity of symptoms CS is often diagnosed late in the course of disease.<sup>6,10</sup>

Chronically elevated cortisol levels can lead to serious complications and comorbidities, severe impairment of quality of life and increased mortality.<sup>2,6</sup> Therefore, normalizing cortisol levels is the main therapeutic goal.<sup>8,9</sup> For most forms of CS surgical resection of the causative tumor is the primary treatment option. In case of a residual tumor or relapse irradiation is possible. However, symptoms decrease with a delay of several months to years. Medical treatments are used to bridge the gap between the diagnosis of the disease and surgery or until radiotherapy begins to work, as well as when there is no remission due to these procedures. A distinction is made between steroid synthesis inhibitors, which primarily act on adrenal gland, and substances, acting centrally on pituitary gland.<sup>5,8</sup>

### **About LINC-3**

LINC-3 is a prospective 48-week, phase III, multi-center study to evaluate the safety and efficacy of Isturisa® in patients (N = 137) with persistent or recurrent Cushing's disease or with De Novo disease, who are not eligible for surgical therapy. The study consisted of a 12-week open-label dose titration period, followed by a 12-week maintenance period and an 8-week double-blind, randomized withdrawal phase in which eligible patients were randomized to receive 1: 1 osilodrostat or placebo, followed by another 14-week open-label phase with osilodrostat. The primary endpoint was the proportion of randomized patients who maintained complete response (mUFC ≤ ULN with no dose increase above the level at week 26) at the end of the 8-week randomized withdrawal period (week 34). The key secondary endpoint was the proportion of patients with normal mUFC at week 24 and with no dose increase above the level established at week 12.<sup>1,3</sup>

The primary study endpoint was reached: significantly more patients in the osilodrostat group maintained a normal mUFC value without dose increase than in the placebo group (86% vs. 29%;  $p < 0.001$ ) at the end of the 8-week randomized phase (week 34). More than half of the patients (53%) reached the key secondary endpoint of a normal mUFC value after the first 24 weeks of open therapy with osilodrostat, without increasing the dose after week 12. Two thirds (66%) of the patients had a normal mUFC at the end of the 48-week study. The reduction in cortisol levels was accompanied by improvements in cardiovascular and metabolic parameters (body weight, waist size, HbA1c, blood pressure). At week 48, 86% of the patients for whom data were available showed improvement in at least one physical characteristic of M. Cushing.<sup>1,3</sup>

Osilodrostat was well tolerated.<sup>3</sup> The most commonly observed side effects in LINC-3 were nausea (42%), headache (34%), fatigue (44%) and adrenal insufficiency (51%).<sup>1</sup>

### **About Isturisa®**

Isturisa® is a potent inhibitor of 11 $\beta$ -hydroxylase (CYP11B1), the enzyme responsible for the final step of cortisol synthesis in the adrenal gland. Isturisa® is taken twice daily and is available as 1 mg, 5 mg and 10 mg film-coated tablets. Please see the prescribing information for detailed recommendations for the use of this product.<sup>1</sup>

### **About Recordati Rare Diseases**

The company's EMEA-headquarters is located in Puteaux, France, and its global headquarters is based in Milan, Italy.

For a complete list of products, visit [www.recordatirarediseases.com/products](http://www.recordatirarediseases.com/products).

You can find more information on our website at [www.recordati.com](http://www.recordati.com) and <https://www.recordatirarediseases.com/> or follow us on LinkedIn or Twitter for the latest company news.

### **About Recordati Group**

Recordati, established in 1926, is an international pharmaceutical group, listed on the Italian Stock Exchange (Reuters RECI.MI, Bloomberg REC IM, ISIN IT 0003828271), with a total staff of more than 4,300, dedicated to the research, development, manufacturing and marketing of pharmaceuticals. Headquartered in Milan, Italy, Recordati has operations throughout the whole of Europe, including Russia, Turkey, North Africa, the United States of America, Canada, Mexico, some South American countries, Japan and Australia. An efficient field force of medical representatives promotes a wide range of innovative pharmaceuticals, both proprietary and under license, in several therapeutic areas including a specialized business dedicated to treatments for rare diseases. Recordati is a partner of choice for new product licenses for its territories. Recordati is committed to the research and development of new specialties with a focus on treatments for rare diseases. Consolidated revenue for 2019 was € 1,481.8 million, operating income was € 465.3 million and net income was € 368.9 million.

The source language in which the original text is published is the official and authorized version. Translations are included for a better understanding. Only the version that was published in the original language is legally valid. Therefore, compare the translated version with the original language version of the publication.

### **For additional information:**

#### **Company Contact:**

Claudia Limberger

Franchise Head Endocrinology - Germany

E-Mail: [limberger.c@recordati.com](mailto:limberger.c@recordati.com)

Tel.: +49 1522 8897110

#### **References:**

- <sup>1</sup> Isturisa® Fachinformation, Mai 2020
- <sup>2</sup> Pivonello R et al. *Endocrine* 2017; 56: 10–18
- <sup>3</sup> Biller BMK et al. *Journal of the Endocrine Society* 2019; 3 (Supplement 1): OR16-2
- <sup>4</sup> Ferriere A, Tabarin A. *Best Pract Res Clin Endocrinol Metab* 2020; 34 (2): 101381
- <sup>5</sup> Signifor® and Signifor® LAR Fachinformation, Juni 2018
- <sup>6</sup> Petersen S. Diagnostik und Therapie des Cushing-Syndroms. In: *Endokrinologie Informationen; Sonderheft März* 2017: 38-43
- <sup>7</sup> Lacroix A et al. *Lancet* 2015; 386: 913
- <sup>8</sup> Nieman LK et al. *J Clin Endocrinol Metab* 2015; 100: 2807
- <sup>9</sup> Broersen LHA et al. *Pituitary* 2018; 21: 631
- <sup>10</sup> Nieman LK et al. *Am J Med* 2005; 118: 1340–1346
- <sup>11</sup> Pivonello R et al. *Endocrine Reviews* 2015; 36: 385–486