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NEWS RELEASE

RECORDATI: ISTURISA® (OSILODROSTAT) APPROVED IN JAPAN

Recordati announces Japanese MHLW approval of Isturisa® (osilodrostat), an effective and well-tolerated cortisol synthesis inhibitor, for patients with endogenous Cushing's syndrome.

Milan, Italy, 24 March 2021 – Recordati today announces the Japanese Ministry of Health, Labour and Welfare (MHLW) approval of Isturisa® (osilodrostat) for the treatment of patients with endogenous Cushing's syndrome for whom pituitary surgery is not an option or has not been curative. Isturisa® is a novel treatment option for patients with endogenous Cushing's syndrome, which normalised cortisol levels in most adult patients with Cushing's disease during a Phase III trial (LINC 3), with a manageable safety profile.[1] Results of a Phase II trial in Japanese patients demonstrated that Isturisa also normalised cortisol levels in patients with non-pituitary causes of endogenous Cushing's syndrome.[2]

Isturisa® is authorised for the treatment of adult patients with endogenous Cushing's syndrome in Europe and for the treatment of adult patients with Cushing's disease in the USA for whom pituitary surgery is not an option or has not been curative.[3,4] Isturisa® is a potent, oral inhibitor of 11β-hydroxylase (CYP11B1), the enzyme responsible for the final step of cortisol biosynthesis.[3,4]

"The MHLW's approval of Isturisa® as an effective and generally well-tolerated oral treatment option for patients with Cushing's syndrome constitutes another major milestone for our Endocrinology franchise. We are committed to bringing Isturisa® to all patients who need it," stated Andrea Recordati, CEO. "On behalf of Recordati, I extend my gratitude to the patients who participated in the clinical trials and their families and caregivers who supported them. We also appreciate the hard work of the investigators, clinicians and study staff in bringing this therapy to patients in need."

"Isturisa® is an important and appreciated therapy in treating patients with endogenous Cushing's syndrome including Cushing's disease, a severe, potentially life-threatening rare disease," said Akira Shimatsu, MD, Advanced Medical Care Center, Kusatsu General Hospital/National Hospital Organization Kyoto Medical Center. "Cushing's syndrome results in an increased risk of cardiovascular and cerebrovascular diseases, as well as hypercoagulability, diabetes, infections, depression, and decreased quality of life. If not appropriately treated, patients with Cushing's syndrome have increased mortality. Until now, patients in need of medications to reduce cortisol levels have had few approved options, either with limited efficacy or with too many adverse effects. We now have a well-documented, effective oral treatment that represents a new therapeutic option that will help address the medical needs of this underserved patient population."

The approval is based on data generated by the LINC clinical programme, which demonstrated that Isturisa® leads to normalisation of cortisol levels in the majority of patients, accompanied by improvements in multiple clinical features of the disease.[1] In the Phase III LINC 3 study, a significantly higher proportion of patients treated with Isturisa® maintained normal mean urinary free cortisol (mUFC), a primary objective of treatment for patients with Cushing's disease, at the end of an 8-week randomised-withdrawal period (week 34) versus placebo (86.1% vs 29.4%, Cochran-Mantel-Haenszel exact test 2-sided $p<0.001$).[1] Adverse drug reactions associated with Isturisa® and occurring in at least

10% of patients at any time during the LINC 3 study were adrenal insufficiency, nausea, fatigue, glucocorticoid deficiency, blood corticotrophin increased, asthenia, headache, hormone level abnormal, arthralgia, blood testosterone increased, decreased appetite and vomiting.

Recordati expects Isturisa® to become commercially available in Japan in the third quarter of 2021.

"Recordati Rare Diseases is actively building its commercial, medical, and market access teams for endocrinology to help achieve its mission of supporting patients with Cushing's syndrome and other rare serious conditions. We are excited by the prospect of making Isturisa® – an effective and well-tolerated medical treatment option – available to patients with Cushing's syndrome in Japan and are planning to launch the product in the second half of this year," said Satoshi Fujiwara, General Manager Recordati Rare Diseases Japan.

Important safety information for Isturisa®
Please refer to the full prescribing information (the full prescribing information in Japanese will be available on the PMDA website: https://www.pmda.go.jp/PmdaSearch/iyakuSearch/).

About Cushing's syndrome
Cushing's syndrome is a disorder caused by chronic exposure to excess levels of cortisol from either an exogenous (ie medication) or an endogenous source.[5] It is a rare, serious and difficult-to-treat disease that is estimated to affect up to 5 patients per million per year.[5] There are various causes of endogenous Cushing's syndrome, which include an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma (Cushing's disease), benign or cancerous ACTH-secreting tumours that arise outside the pituitary (ectopic ACTH syndrome), and cortisol-secreting adrenal adenomas or carcinomas.[5] There is often a delay in diagnosing Cushing's syndrome due in part to limited disease awareness, which consequently leads to a delay in treating patients.[5,6] Prolonged exposure to elevated cortisol levels is associated with considerable morbidity, mortality and impaired quality of life as a result of complications and comorbidities.[7] Normalisation of cortisol levels is therefore a primary objective in the treatment of Cushing's syndrome.[8]

About LINC 3
LINC 3 was a prospective, multicentre, 48-week trial with an 8-week, double-blind, randomised-withdrawal phase to evaluate the safety and efficacy of Isturisa® in patients with Cushing's disease.[1] The primary endpoint in the LINC 3 trial was the proportion of patients randomised to Isturisa® and placebo, separately, at week 26 with mUFC not exceeding the upper limit of normal (ULN) at the end of the 8-week randomised-withdrawal period (week 34) and without a dose increase during this period.[1] The key secondary endpoint was the proportion of enrolled patients with mUFC ≤ULN after an initial 24 weeks of open-label treatment with Isturisa® without any dose increase after week 12.[1] LINC 3 involved 137 patients with persistent or recurrent Cushing's disease or those with *de novo* disease who were not candidates for surgery.[1]

About Isturisa®

Isturisa® is a potent oral, reversible inhibitor of 11β-hydroxylase (CYP11B1), the enzyme that catalyses the final step of cortisol biosynthesis in the adrenal gland; it is authorised in the EU and Switzerland for the treatment of adult patients with endogenous Cushing's syndrome and in the USA for the treatment of patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.[3,4] Isturisa® is available in Japan as 1 mg and 5 mg film-coated tablets. Please see the prescribing information for detailed recommendations for the use of this product.

References

1. Pivonello R *et al. Lancet Diabetes Endocrinol* 2020;8:748-61.
2. Tanaka T *et al. Endocr J* 2020;67:841-52.
3. Isturisa® summary of product characteristics. May 2020.
4. Isturisa® prescribing information. March 2020.
5. Lacroix A *et al. Lancet* 2015;386:913-27.
6. Rubinstein G *et al. J Clin Endocrinol Metab* 2020;105.
7. Pivonello R *et al. Lancet Diabetes Endocrinol* 2016;4:611-29.
8. Nieman LK *et al. J Clin Endocrinol Metab* 2015;100:2807-31.

About the 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 4300, dedicated to the research, development, manufacturing and marketing of pharmaceuticals. Headquartered in Milan, Italy, Recordati has operations throughout the whole of Europe (including Russia and Turkey), North Africa, the USA, Canada, Mexico, some South American countries, Japan and Australia. An efficient field force of medical representatives promotes a wide range of innovative pharmaceuticals, proprietary and under licence, in a number of therapeutic areas, including a specialised business dedicated to treatments for rare diseases. Recordati is a partner of choice for new product licences 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 2020 was €1,448.9 million, operating income was €469.0 million, and net income was €355.0 million.

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