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Novartis drug Signifor® gains FDA approval as the first medication to treat Cushing's disease, a serious endocrine disorder

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- - As the only pituitary-directed therapy, Signifor represents a novel therapeutic approach by addressing the underlying mechanism of Cushing's disease(1)
- - In the Phase III trial, most patients experienced a sustained decrease in mean urinary-free cortisol levels, a key measure of disease, with a subset normalizing(2)
- - In the EU, Signifor has been previously approved for the treatment of adult patients with Cushing's disease; other worldwide regulatory filings are underway

EAST HANOVER, N.J., Dec. 14, 2012 /PRNewswire/ -- Novartis announced today that the US Food and Drug Administration (FDA) has approved Signifor® (pasireotide) injection for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative[3]. Signifor is the first medicine to be approved in the US that addresses the underlying mechanism of Cushing's disease, a serious, debilitating endocrine disorder caused by the presence of a non-cancerous pituitary tumor which ultimately leads to excess cortisol in the body[1,4]. This approval follows a unanimous recommendation from the FDA Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) in support of the use of Signifor.

"The FDA approval of Signifor for Cushing's disease brings a novel pituitary-directed therapy to patients with limited treatment options," said Herve Hoppenot, President, Novartis Oncology. "Today's milestone reinforces Novartis' commitment to addressing unmet needs and advancing treatments for rare pituitary-related disorders."

Cushing's disease most commonly affects adults as young as 20 to 50 years and affects women three times more often than men. It may present with weight gain, central obesity, a round, red full face, severe fatigue and weakness, striae (purple stretch marks), high blood pressure, depression and anxiety. Cushing's disease can cause severe illness and death with mortality up to four times higher than in the healthy population[1,4,5,6,7].

The approval is based on data from PASPORT-CUSHINGS (PASireotide clinical trial PORTfolio - CUSHING'S disease), the largest randomized Phase III study to evaluate a medical therapy in patients with Cushing's disease[3]. Results from the PASPORT-CUSHINGS study found that a decrease in mean urinary-free cortisol (UFC), the key measure of biochemical control of the disease, was sustained during the treatment period in most patients, with a subset of patients reaching normal levels. The study also showed that certain clinical manifestations of Cushing's disease tended to improve[2].

"Patients with Cushing's disease may suffer from debilitating manifestations, and there are many serious health complications associated with the disease," said Mary Andrews, CEO and Co-Founder of the US non-profit, The MAGIC Foundation. "The FDA approval of Signifor offers the option of a medical therapy that may help certain patients with Cushing's disease."

In April 2012, the European Commission approved Signifor for the treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed. Other worldwide regulatory filings for pasireotide for this use are also underway.

About Cushing's disease
Cushing's syndrome is an endocrine disorder caused by excessive cortisol, a vital hormone that regulates metabolism, maintains cardiovascular function and helps the body respond to stress. Cushing's disease is a form of Cushing's syndrome, in which excess cortisol production is triggered by a pituitary adenoma secreting excess adrenocorticotropic hormone (ACTH). It is a rare but serious disease that affects approximately one to two patients per million per year. The first line and most common treatment approach for Cushing's disease is surgical removal of the tumor[4,6,8].

About PASPORT-CUSHINGS
PASPORT-CUSHINGS is a prospective, randomized, double-blind, Phase III study conducted at 68 sites in 18 countries. The study evaluated the efficacy and safety of Signifor in 162 adult patients with persistent or recurrent Cushing's disease, as well as in patients with newly diagnosed Cushing's disease who were not candidates for surgery[2].

Patients with UFC levels greater than 1.5 times the upper limit of normal (ULN) were randomized to receive Signifor subcutaneous (sc) injection in doses of 0.9 mg (n=80) or 0.6 mg (n=82) twice daily[2].

The primary endpoint, the proportion of patients who achieved normalization of UFC after six months without dose up-titration relative to randomized dose, was met in patients treated with 0.9 mg twice daily. Mean UFC levels were normalized in 26% and 15% of the patients randomized to receive Signifor 0.9 mg and 0.6 mg, respectively, at month six[2].

The median reduction in mean UFC from baseline to month six was around 47% in both dose groups. Reductions in UFC were observed after one month of treatment with Signifor and were sustained during the treatment period in most patients. In addition, 34% and 41% of patients experienced a reduction in mean UFC from baseline less than or equal to ULN or greater than or equal to 50% in the 0.6 mg and 0.9 mg groups, respectively[2].

Decreases in blood pressure, weight, body mass index and waist circumference were observed during the study. Limited conclusions can be drawn on these decreases due to variability of response across patients and the absence of a control group[2].

The most common adverse events (AE) (greater than or equal to 20%) occurring in patients in either dose group receiving Signifor were diarrhea, nausea, hyperglycemia, cholelithiasis, headache, abdominal pain, fatigue and diabetes mellitus. The safety profile of Signifor was similar to that of other somatostatin analogs with the exception of the greater degree of hyperglycemia[2].

About Signifor (pasireotide)
Signifor® (pasireotide) is approved in the US for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative, and in the European Union for the treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed.

Signifor is expected to be available in the US by March 2013 and will be dispensed exclusively through a single specialty pharmacy. For more information about

Signifor distribution, doctors and patients can contact Patient Assistance Now Endocrinology (PAN Endo) at 1-877-503-3377 (Press Option 3 for Signifor) or visit www.Signifor.us for more information. PAN Endo also offers quick and easy access to information about the many reimbursement and support programs available for its endocrinology medicines. Enrollment into PAN Endo will begin in January 2013.

For the treatment of Cushing's disease, Signifor has been studied as a twice-daily subcutaneous (sc) injection and is currently being evaluated as a long-acting release (LAR), once-monthly intramuscular (IM) injection as part of a global Phase III program in Cushing's disease and acromegaly. Signifor is a multireceptor targeting somatostatin analog that binds with high affinity to four of the five somatostatin receptor subtypes (sst 1, 2, 3 and 5)[6,9,10].

Important Safety Information about Signifor

Treatment with Signifor leads to suppression of adrenocorticotropic hormone (ACTH) secretion in Cushing's disease patients. Suppression of ACTH may lead to a decrease in circulating levels of cortisol and potentially hypocortisolism. Patients need to be monitored and instructed how to monitor for signs and symptoms of hypocortisolism. Temporary exogenous steroid (glucocorticoid) replacement therapy and/or dose reduction or interruption of Signifor therapy may be necessary.

Elevations in blood glucose levels have been frequently reported in healthy volunteers and patients treated with Signifor. Cushing's disease patients with poor glycemic control may be at higher risk of developing severe hyperglycemia and associated complications. Glycemic status should be assessed prior to starting treatment with Signifor. Patients need to be closely monitored for hyperglycemia; if hyperglycemia develops, the initiation or adjustment of antidiabetic treatment is recommended. Dose reduction or treatment discontinuation should be considered if uncontrolled hyperglycemia persists. After treatment discontinuation, glycemic monitoring (e.g., FPG or HbA1c) should be done according to clinical practice.

Bradycardia has been reported with use of Signifor. Patients with cardiac disease and/or risk factors for bradycardia need to be closely monitored. Signifor is associated with QT prolongation. Caution should be exercised in patients who have or may develop QT prolongation. Hypokalemia or hypomagnesemia must be corrected prior to initiating therapy and monitored thereafter. A baseline electrocardiogram should be performed prior to the start of Signifor therapy and monitoring for an effect on QTc interval is advisable during therapy.

Elevations in AST (aminotransferases) or ALT (alanine aminotransferase) were reported with the use of Signifor. Monitoring of liver function is recommended prior to starting treatment with Signifor. Liver function should be monitored again after one or two weeks on treatment, then monthly for the first three months and every six months thereafter. Therapy should be discontinued if AST or ALT increase five times the upper limit of normal or greater.

Cholelithiasis has been frequently reported with the use of Signifor. Ultrasonic evaluation of the gallbladder prior to treatment, and thereafter at six and 12 month intervals is recommended.

Monitoring of pituitary hormones is recommended prior to initiating treatment and periodically thereafter as clinically appropriate.

Signifor should not be used during pregnancy unless medically necessary. Breast feeding should be discontinued during treatment with Signifor.

Signifor may affect the way other medicines work, and other medicines can affect how Signifor works. Caution should be exercised with the concomitant use of bromocriptine, cyclosporine, anti-arrhythmic medicines or drugs that may lead to QT prolongation.

The most common adverse events (AE) (greater than or equal to 20%) occurring in patients in either dose group receiving Signifor were diarrhea, nausea, hyperglycemia, cholelithiasis, headache, abdominal pain, fatigue and diabetes mellitus.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by terminology such as "underway," "commitment," "will," "expected," "can," or similar expressions, or by express or implied discussions regarding potential additional marketing approvals for Signifor or regarding potential future revenues from Signifor. You should not place undue reliance on these statements. Such forward-looking statements reflect the current views of management regarding future events, and involve known and unknown risks, uncertainties and other factors that may cause actual results with Signifor to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that Signifor will be approved for sale in any additional markets, or at any particular time. Nor can there be any guarantee that Signifor will achieve any particular levels of revenue in the future. In particular, management's expectations regarding Signifor could be affected by, among other things, unexpected regulatory actions or delays or government regulation generally; unexpected clinical trial results, including unexpected new clinical data and unexpected additional analysis of existing clinical data; competition in general; government, industry and general public pricing pressures; unexpected manufacturing issues; the company's ability to obtain or maintain patent or other proprietary intellectual property protection; the impact that the foregoing factors could have on the values attributed to the Novartis Group's assets and liabilities as recorded in the Group's consolidated balance sheet, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those anticipated, believed, estimated or expected. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis

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Located in East Hanover, New Jersey, Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG, which provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, eye care, cost-saving generic pharmaceuticals, preventive vaccines and diagnostic tools, over-the-counter and animal health products. Novartis is the only global company with leading positions in these areas. In 2011, the Group's continuing operations achieved net sales of USD 58.6 billion, while approximately USD 9.6 billion (USD 9.2 billion excluding impairment and amortization charges) was invested in R&D throughout the Group. Novartis Group companies employ approximately 127,000 full-time-equivalent associates and operate in more than 140 countries around the world. For more information, please visit http://www.novartis.com.

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