

Novartis gains FDA approval for Signifor® LAR to treat patients with acromegaly, a rare and life-threatening hormonal disorder

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- Acromegaly is an endocrine disorder caused by elevated growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels⁽¹⁾
- Signifor LAR, a next-generation somatostatin analog, provides a new option for patients with acromegaly with inadequately controlled disease⁽²⁾
- Signifor LAR FDA approval is based on two Phase III studies showing efficacy in medically naive patients and those inadequately controlled on standard of care⁽²⁾

EAST HANOVER, N.J., Dec. 16, 2014 /PRNewswire/ -- Novartis announced today that the US Food and Drug Administration (FDA) has approved Signifor® long-acting release (LAR)* (pasireotide) for injectable suspension, for intramuscular use, for the treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option. The approval of Signifor LAR, a next-generation somatostatin analog (SSA), helps address a critical unmet need among the acromegaly patient population. Signifor LAR has been studied and found effective in both medically naive patients with acromegaly who have had prior surgery or for whom surgery was not an option, as well as patients whose disease is not fully controlled on first generation SSAs².

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Acromegaly is a rare, debilitating endocrine disorder caused by the excess production of growth hormone (GH) and insulin-like growth factor-1 (IGF-1)^{1,3}. In the majority of cases, the disease is caused by a non-cancerous tumor on the pituitary gland. Prolonged exposure to GH and IGF-1 may cause patients to experience extreme physical changes including the enlargement of hands, feet and facial features¹. Acromegaly is also associated with two- to three-fold increased mortality rates and serious health complications, including heart disease, hypertension, diabetes, arthritis and colon cancer^{1,4,5}. In fact, heart disease is responsible for approximately 60% of deaths among people with acromegaly⁶.

"Treating acromegaly can be extremely challenging and the consequences of inadequate normalization of hormone levels can be serious for patients," said Dr. Monica Gadelha, Professor, Federal University of Rio de Janeiro and pivotal trial study author. "With the approval of Signifor LAR, physicians now have a new acromegaly therapy that provides an enhanced mechanism to address elevated hormone levels. This is a significant achievement and much welcomed news for patients with acromegaly."

Worldwide, the prevalence of acromegaly is estimated to be 60 cases per million, with an annual incidence of 3 to 4 new cases per million¹. However, recent studies suggest that pituitary adenomas may be more prevalent than previously thought, and that the prevalence of acromegaly may be between 115 and 295 cases per million³. On average, patients experience a delayed diagnosis of 6 to 10 years from disease onset⁷. Once diagnosed, the primary objective when treating acromegaly is to achieve biochemical control of the disease, as measured by both the reduction of GH levels and normalization of IGF-1 levels⁸. Notably, a recent meta-analysis using more sensitive assays and more stringent evaluation criteria showed that 45% of patients with acromegaly fail to achieve recommended levels of GH or normalized levels of IGF-1⁹. Reduction of tumor volume and minimization of clinical manifestations are other important treatment goals⁸.

This FDA approval was based on two multicenter Phase III studies, C2305 and C2402, which respectively examined medically naive patients who have had prior surgery or for whom surgery was not an option and patients with acromegaly inadequately controlled on first generation SSAs. In both studies, higher rates of full biochemical control (defined as mean GH level <2.5mcg/L and normal IGF-1 levels) were achieved with Signifor LAR compared to a first generation SSA².

"The FDA approval of Signifor LAR for acromegaly marks an important day for physicians and patients living with difficult-to-treat pituitary conditions and underscores our continued commitment to helping patients manage rare diseases," said Bruno Strigini, President, Novartis Oncology. "We are pleased that a new treatment option is now available to help address the serious impact of uncontrolled acromegaly, and are optimistic about providing this much needed treatment to other patients worldwide in the near future."

Signifor LAR is an SSA administered intramuscularly once-monthly that exerts its pharmacological activity via binding to somatostatin receptors (SSTRs). Signifor LAR has the potential to stimulate both SSTR2 and SSTR5 subtype receptors, which are relevant for inhibition of GH and IGF-1 secretion, making Signifor LAR a more effective treatment for acromegaly compared to other SSAs currently used to treat this disease².

In the US, Signifor LAR has orphan drug designation for acromegaly. Orphan drug designation is granted for products that treat a condition that affects fewer than 200,000 people in the US^{10,11}. In November 2014, the European Medicines Agency (EMA) approved Signifor* to treat

adult patients with acromegaly for whom surgery is not an option or has not been curative and who are inadequately controlled on treatment with a first-generation SSA. Novartis has also submitted additional regulatory applications for Signifor LAR worldwide.

About study C2305

The C2305 study was a multicenter, randomized, double-blind study in patients with active acromegaly who were not previously treated with medication (medically naive), and had persistent disease despite prior surgery or were ineligible for surgery. Patients were randomized to receive either Signifor LAR (starting dose of 40 mg with possibility to up-titrate to 60 mg) or the active comparator².

The efficacy endpoint of proportion of patients achieving full GH and IGF-1 biochemical control at month 12 was met. Specifically, the percentage of patients achieving biochemical control was 31.3% for Signifor LAR and 19.2% for the active comparator, ($P < .01$ for treatment difference). Biochemical control was achieved early in the study (i.e., month 3) by 30.1% of patients in the Signifor LAR arm².

Ninety-eight percent of patients treated with Signifor LAR had either a reduction or no change in tumor volume from baseline as assessed by MRI at month 12. Additionally, ring size and acromegaly symptoms score (i.e., headache, fatigue, perspiration, paresthesia or tingling sensation in limbs, and osteoarthritis or joint pain) were followed. At month 12, reductions in ring size and in symptom severity scores in both treatment groups compared to baseline were noted².

The most common adverse events (AEs) with Signifor LAR versus the active comparator were diarrhea (39% vs. 45%), cholelithiasis (26% vs. 36%), hyperglycemia (29% vs. 8%) and diabetes mellitus (26% vs. 4%)².

About study C2402

The C2402 study was a randomized study evaluating the efficacy and safety of double-blind Signifor LAR (40 mg and 60 mg) versus continued open-label pre-trial SSA therapies at maximal or near maximal doses in 198 patients with inadequately controlled acromegaly. Inadequate control was defined as mean GH level >2.5 mcg/L and IGF-1 >1.3 times the sex- and age-adjusted upper normal limit².

The efficacy endpoint of the proportion of patients achieving biochemical control, as defined by GH and IGF-1 levels, at 6 months with Signifor LAR 40 mg or 60 mg versus continued pre-trial SSA therapy, was met for both Signifor LAR doses. Specifically, 15.4% and 20.0% of patients treated with Signifor LAR 40 mg and 60 mg, respectively, achieved full GH and IGF-1 biochemical control at 6 months compared with 0% in the pre-trial SSA therapy control arm. Biochemical control was achieved by month 3 in 15.4% and 18.5% of patients in the Signifor LAR 40 mg and 60 mg arms, respectively².

Eighty-one percent and 70% of patients treated with Signifor LAR 40 mg and 60 mg, respectively, had either a reduction or no change in tumor volume from baseline as assessed by MRI at month 6².

The most common AEs associated with Signifor LAR 40 mg, 60 mg and pre-trial SSA therapies were hyperglycemia (33%, 30%, 14%) and diabetes mellitus (21%, 31%, 9%)².

About Signifor LAR

Signifor long-acting release (LAR) (pasireotide) for injectable suspension, for intramuscular use, is now approved by the US Food and Drug Administration (FDA) for the treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option.

The safety and efficacy profile of Signifor LAR has not yet been established in countries outside the US or the EU in patients with acromegaly. For various reasons, including the uncertainty of clinical trials, there is no guarantee that Signifor LAR will become commercially available for acromegaly anywhere else in the world.

Information about Novartis clinical trials for pasireotide can be obtained by healthcare professionals at www.clinicaltrials.gov.

Important safety information about Signifor LAR

Signifor LAR can cause serious side effects such as high blood sugar levels. Patients should tell their doctor right away if they experience signs and symptoms such as excessive thirst, high urine output, increased appetite with weight loss, and tiredness. Patients will be asked to monitor their blood glucose levels and may be given medicine to lower their blood sugar.

Signifor LAR can cause a patient's heart to beat slower or cause problems with the heart's electrical system. Patients should tell their doctor right away if they experience weakness, dizziness, and/or fainting since these can be signs of a slow heart beat or electrical problem with the heart. Patients should have their heart monitored by ECG testing before and during Signifor LAR treatment.

Signifor LAR can cause elevations in liver function tests. Patients' liver function may be monitored during treatment.

Signifor LAR may affect patient's gallbladder. Patients should be monitored periodically to check for gallstones.

Signifor LAR may affect a patient's pituitary hormones. Patients may have their pituitary hormones monitored (such as thyroid, adrenal, gonadal) during treatment with Signifor LAR. Signifor LAR may cause symptoms associated with adrenal insufficiency.

Signifor LAR side effects include diarrhea, gallstones, high blood sugar, and diabetes mellitus.

Signifor LAR may interact with certain drugs and patients should tell their doctor about all of their medications. Potential drug interactions with

Signifor LAR may include drugs to control heart beat (anti-arrhythmics), medicines that affect the electrical system in the heart, medicines to control blood pressure (beta-blockers or calcium channel blockers), medicines to control the electrolyte levels in the blood, cyclosporine (Gengraf[®], Neoral[®], Restasis[®], Sandimmune[®]), and bromocriptine (Cycloset[®], Parlodel[®]).

Please see full Prescribing Information for Signifor LAR.

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Disclaimer

The foregoing release contains forward-looking statements that can be identified by words such as "can," "suggest," "may," "continued," "commitment," "optimistic," "in the near future," or similar terms, or by express or implied discussions regarding potential new indications or labeling for Signifor LAR, or regarding potential future revenues from Signifor LAR. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that Signifor LAR will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that Signifor LAR will be commercially successful in the future. In particular, management's expectations regarding Signifor LAR and could be affected by, among other things, the uncertainties inherent in research and development, including unexpected clinical trial results and additional analysis of existing clinical data; unexpected regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain proprietary intellectual property protection; general economic and industry conditions; global trends toward health care cost containment, including ongoing pricing pressures; unexpected manufacturing issues, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. 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

Novartis Pharmaceuticals Corporation researches, develops, manufactures and markets innovative prescription drugs used to treat a number of diseases and conditions, including cardiovascular, dermatological, central nervous system, bone disease, cancer, organ transplantation, psychiatry, infectious disease and respiratory. The company's mission is to improve people's lives by pioneering novel healthcare solutions.

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, over-the-counter and animal health products. Novartis is the only global company with leading positions in these areas. In 2013, the Group achieved net sales of USD 57.9 billion, while R&D throughout the Group amounted to approximately USD 9.9 billion (USD 9.6 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 133,000 full-time-equivalent associates and sell products in more than 150 countries around the world. For more information, please visit <http://www.novartis.com>.

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* In the European Union, the long-acting release formulation of pasireotide for the treatment of acromegaly has been approved under the trade name Signifor®.

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