Signifor® LAR
(pasireotide) for injectable suspension
20 mg, 40 mg, 60 mg

FOR MEDIA USE ONLY

About Signifor LAR	Signifor® long-acting release (LAR)* (pasireotide) for injectable suspension, for intramuscular use, is approved in the United States (US) for the treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option. Signifor LAR is a next generation somatostatin analog (SSA) that has been studied and found effective in both medically naïve 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 SSAs.
How Signifor LAR Works	Signifor LAR binds to somatostatin receptors, SSTR2 and SSTR5, which are present in high numbers in the pituitary gland, located at the base of the brain, where an excessive amount of growth hormone is produced. By binding to these somatostatin receptors, Signifor LAR reduces the production of growth hormone (GH) and subsequently, insulin-like growth factor-1 (IGF-1).
Key Data	The US Food and Drug Administration (FDA) approval of Signifor LAR in acromegaly was based on two multicenter Phase III studies, C2305 and C2402, which respectively examined medically naïve 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 SSA: • The C2305 study was a multicenter, randomized, double-blind study in patients with active acromegaly who were not previously treated with medication (medically naïve), 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 comparator. ○ The efficacy endpoint of the proportion of patients achieving full GH and IGF-1 biochemical control at month 12 was met. ▪ The percentage of patients achieving biochemical control was 31.3% and 19.2% for Signifor LAR and the active comparator, respectively (*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 arm. ○ 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. ○ Ring size and acromegaly symptoms score (i.e., headache, fatigue, perspiration, paresthesia or tingling sensation in limbs, and osteoarthralgia 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 noted. ○ 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%). • 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 somatostatin analog therapies at maximal or near maximal doses in 198 patients with inadequately controlled acromegaly. o 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 limit. o 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 to 0% in the pre-trial therapy SSA 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, respectively. o 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 assessed by MRI at month 6. o 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%).
Dosing and Administration	Signifor LAR for injectable suspension is a long-acting, intramuscular injection. The recommended starting dose of Signifor LAR is 40 mg once every 4 weeks (every 28 days). The dose may be increased to a maximum of 60 mg for patients whose GH and/or IGF-1 levels are not fully controlled after 3 months of treatment with this initial dose, and who tolerate this dose. Management of suspected adverse reactions or over response to treatment (age- and sex-adjusted IGF-1 less than the lower limit of normal) may require dose reduction of Signifor LAR. The dose may be decreased, either temporarily or permanently, by 20 mg decrements. Signifor LAR should not be used in patients with severe hepatic impairment. Patients with moderate hepatic impairment should start on a 20 mg dose and should not receive higher than a 40 mg dose.
Acromegaly	Acromegaly is a rare, debilitating endocrine disorder caused by a non-cancerous pituitary tumor that produces too much GH. Excess GH, in turn, triggers the overproduction of another hormone, IGF-1. 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 features. 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. In fact, heart disease is responsible for approximately 60% of deaths among people 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 million. 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 million. On average, patients experience a delayed diagnosis of 6 to 10 years from disease onset. 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 levels. Notably, a recent meta-analysis using more sensitive assays and more stringent evaluation criteria showed that up to 45% of patients can still have elevated levels of either GH or IGF-1. Reduction of tumor volume and minimization of clinical manifestations are other important treatment

	goals.
Signifor LAR Important Safety Information	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. The brands listed are the trademarks or registered trademarks of their respective owners and are not trademarks or registered trademarks of Novartis.

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.

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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®.