Adverse Reactions	Overall % N = 150
Decreased appetite	10
Hyperuricemia	7
Hypercholesterolemia	6
Blood Related Adverse Reactions	
Anemia	5

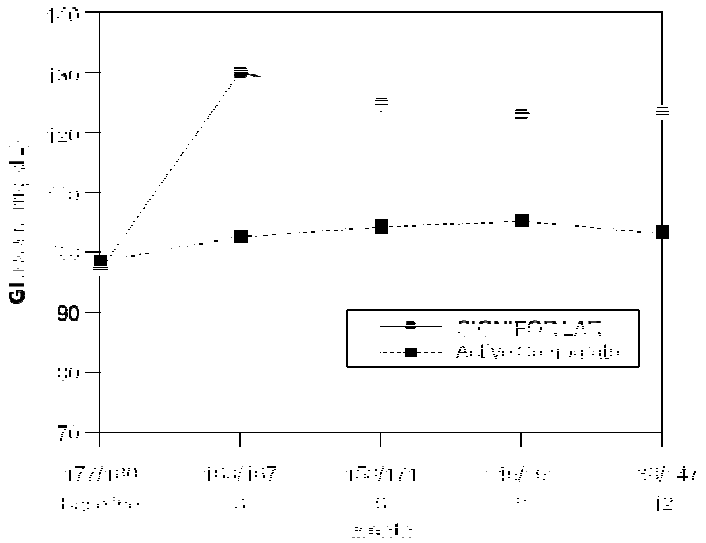
*Diabetes mellitus consists of the two terms: diabetes mellitus and type 2 diabetes mellitus.
**Abdominal pain includes the term abdominal pain upper.
***Sinus bradycardia includes the term bradycardia.
****Fatigue includes the term asthenia.

Other adverse reactions which occurred at a frequency less than 5% were cholestasis (4%), glucose tolerance impaired (3%), aspartate aminotransferase increased (3%), vomiting (3%), lipase increased (3%), injection-site reactions (2%), electrocardiogram QT prolonged (1%), cholecystitis (1%), amylase increased (1%), and prothrombin time prolonged (1%).

Hyperglycemia

The average fasting plasma glucose levels in patients with acromegaly naïve to drug therapy study *[see Clinical Studies (14.1)]* across visits is shown in Figure 2 below.

Figure 2. Mean Fasting Plasma Glucose (mg/dL) by Visit in the Study of Patients With Acromegaly Naïve to Drug Therapy*



*Numbers of patients with a glucose value at the given timepoint in the SIGNIFOR LAR/Active comparator arms are displayed as xxx/xxx on the x axis.

Pancreatic Enzyme Elevation and Pancreatitis

Asymptomatic elevations in lipase and alpha amylase were observed in 30% and 20% of patients receiving SIGNIFOR LAR in the drug naïve study in acromegaly, and in 1% and 3% of patients receiving SIGNIFOR LAR in the study of acromegaly patients previously treated. In the drug-naïve study, 2 acromegaly patients receiving SIGNIFOR LAR developed pancreatitis. In the Cushing's disease study, increased lipase was observed in 4% of patients, and 1 patient developed pancreatitis. Pancreatitis is a potential adverse reaction associated with the use of SIGNIFOR LAR due to the association between cholelithiasis and acute pancreatitis.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of SIGNIFOR LAR. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Cholelithiasis resulting in complications, including cholecystitis and cholangitis, which have sometimes required cholecystectomy

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on SIGNIFOR LAR

Drugs that Prolong QT

Coadministration of drugs that prolong the QT interval with SIGNIFOR LAR may have additive effects on the prolongation of the QT interval. Monitoring effects on the QT interval at 21 days is recommended *[see Warnings and Precautions (5.2)]*.

7.2 Effect of SIGNIFOR LAR on Other Drugs

Cyclosporine

Concomitant administration of cyclosporine with SIGNIFOR LAR may decrease the relative bioavailability of cyclosporine and, therefore, dose adjustment of cyclosporine to maintain therapeutic levels may be necessary.

Bromocriptine

Coadministration of SIGNIFOR LAR with bromocriptine may increase the blood levels of bromocriptine. Dose reduction of bromocriptine may be necessary.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited data with SIGNIFOR LAR in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. In embryo-fetal development studies in rabbits, findings indicating a developmental delay were observed with subcutaneous administration of pasireotide during organogenesis at doses less than the exposure in humans at the highest recommended dose; maternal toxicity was not observed at this dose *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

In embryo-fetal development studies in rats given 1 mg/kg/day, 5 mg/kg/day, and 10 mg/kg/day subcutaneously throughout organogenesis, maternal toxicity was observed at all doses, including the lowest dose tested which had exposures 12 times higher than that at the maximum therapeutic dose based on area under the curve (AUC) comparisons across species. An increased incidence of early/total resorptions and malrotated limbs was observed in rats at 10 mg/kg/day. At 10 mg/kg/day in rats, the maternal systemic exposure (AUC) was 42179 ng*hr/mL, approximately 106 times the exposure in humans at the highest recommended dose of 60 mg SIGNIFOR LAR administered as an intramuscular injection once every 4 weeks.

In embryo-fetal development studies in rabbits given 0.05 mg/kg/day, 1 mg/kg/day, and 5 mg/kg/day subcutaneously through organogenesis, maternal toxicity was observed at 1 mg/kg/day, at a maternal systemic exposure (AUC) of 1906 ng*hr/mL, approximately 5 times higher than the maximum human therapeutic exposure. An increased incidence of unossified forepaw phalanx, indicative of a developmental retardation, was observed in rabbits at 0.05 mg/kg/day, with maternal systemic exposures less than the systemic exposure in humans at the highest recommended dose.

In pre- and post-natal developmental studies in rats given subcutaneous doses of 2 mg/kg/day, 5 mg/kg/day, and 10 mg/kg/day during gestation through lactation and weaning, maternal toxicity was observed at all doses including the lowest dose (9 times higher than the maximum therapeutic dose based on surface area

comparisons across species). Retardation of physiological growth, attributed to GH inhibition was observed at 2 mg/kg/day during a pre- and post-natal study in rats. After weaning, body weight gains in the rat pups (F1 generation) exposed to pasireotide were comparable to controls, showing reversibility of this developmental delay.

8.2 Lactation

Risk Summary

There is no information available on the presence of SIGNIFOR LAR in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Studies show that pasireotide administered subcutaneously passes into the milk of lactating rats; however, due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk *(see Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SIGNIFOR LAR, and any potential adverse effects on the breastfed child from SIGNIFOR LAR or from the underlying maternal condition.

Data

Available data in animals have shown excretion of pasireotide in milk. After a single 1 mg/kg [^{14}C]-pasireotide subcutaneous dose to lactating rats, the transfer of radioactivity into milk was observed. The overall milk:plasma (M/P) exposure ratio of total radioactivity was 0.28, based on $AUC_{0-\infty}$ values.

8.3 Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as the therapeutic benefits of a reduction in growth hormone (GH) levels and normalization of insulin-like growth factor (IGF-1) in acromegalic females treated with pasireotide may lead to improved fertility.

Similarly, the therapeutic benefits of a reduction or normalization of serum cortisol levels in female patients with Cushing's disease treated with pasireotide may also lead to improved fertility.

8.4 Pediatric Use

Safety and effectiveness of SIGNIFOR LAR have not been established in pediatric patients.

8.5 Geriatric Use

Clinical studies of SIGNIFOR LAR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

Dose adjustment is not required in patients with mild impaired hepatic function (Child-Pugh A), but is required for patients with moderately impaired hepatic function (Child-Pugh B). The safety and efficacy of SIGNIFOR LAR have not been established in patients with severe hepatic impairment (Child-Pugh C). No dosage recommendation can be given for patients with severe hepatic impairment (Child-Pugh C) *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Clinical studies of SIGNIFOR LAR in patients with renal impairment have not been conducted. On the basis of studies with pasireotide given subcutaneously, dosage adjustment is not needed in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In the event of overdosage, it is recommended that appropriate supportive treatment be initiated, as dictated by the patient's clinical status, until resolution of the symptoms.

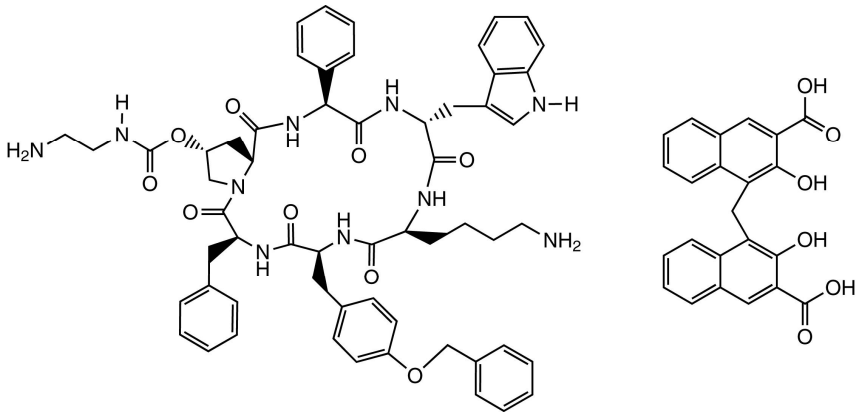
Up-to-date information about the treatment of overdose can be obtained from a certified Regional Poison Center. In the event of an overdose, contact the National Capital Poison Center at 1-800-222-1222 or www.poison.org.

11 DESCRIPTION

SIGNIFOR LAR (pasireotide) for injectable suspension is a long-acting release form of pasireotide pamoate, as powder to be suspended in the provided diluent immediately prior to intramuscular injection. SIGNIFOR LAR contains pasireotide, a somatostatin analog in the form of pasireotide pamoate (pamoic acid salt). Pasireotide is a cyclohexapeptide with pharmacologic properties mimicking those of the natural hormone somatostatin. Pasireotide pamoate has a chemical name of (2-Aminoethyl) carbamic acid (2R,5S,8S,11S,14R,17S,19aS)-11-(4-aminobutyl)-5-benzyl-8-(4-benzyloxybenzyl)-14-(1H-indol-3-ylmethyl)-4,7,10,13,16,19-hexaoxo-17-phenyloctadecahydro-3a,6,9,12,15,18-hexaazacyclopentacyclooctadecen-2-yl ester pamoic acid salt.

The molecular formula of pasireotide pamoate is $C_{58}H_{66}N_{10}O_9 \bullet C_{23}H_{16}O_6$ and the molecular weight is 1435.58.

The structural formula is:



The drug product consists of pasireotide pamoate uniformly distributed within microspheres which are made of biodegradable copolymers of poly (D,L-lactide-co-glycolide) acids (PLGA).

SIGNIFOR LAR is available in a vial containing the sterile pasireotide pamoate, PLGA microspheres powder, 10 mg, 20 mg, 30 mg, 40 mg and 60 mg to be reconstituted with the provided 2 mL sterile diluent.

Each vial contains:

	10 mg	**20 mg**	**30 mg**	**40 mg**	**60 mg**
Pasireotide pamoate	13.71 mg*	27.42 mg*	41.13 mg*	54.84 mg*	82.26 mg*
Poly(D,L-lactide-co-glycolide) [50-60:40-50]	13.15 mg	26.29 mg	39.44 mg	52.58 mg	78.87 mg
Poly(D,L-lactide-co-glycolide) [50:50]	13.15 mg	26.29 mg	39.44 mg	52.58 mg	78.87 mg

*Corresponds to 10 mg, 20 mg, 30 mg, 40 mg and 60 mg of pasireotide base, respectively.

Each diluent prefilled syringe contains:

Mannitol	90 mg
Carboxymethylcellulose sodium	14 mg
Poloxamer 188	4 mg
Water for injections	add to 2 mL

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SIGNIFOR LAR is an injectable cyclohexapeptide, somatostatin analog. Pasireotide exerts its pharmacological activity via binding to somatostatin receptors (SSTR). There are 5 known human somatostatin receptor subtypes: SSTR 1, 2, 3, 4, and 5. These receptor subtypes are expressed in different tissues under normal physiological conditions. Somatostatin analogs bind to SSTRs with different potencies. Pasireotide binds with high affinity to 4 of the 5 SSTRs (see Table 4).

Table 4 – Binding Affinities of Somatostatin (SRIF-14) and Pasireotide to the Five Human SSTR Subtypes (SSTR 1-5)

Compound	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Somatostatin (SRIF-14)	0.93 ± 0.12	0.15 ± 0.02	0.56 ± 0.17	1.5 ± 0.4	0.29 ± 0.04
Pasireotide	9.3 ± 0.1	1.0 ± 0.1	1.5 ± 0.3	> 100	0.16 ± 0.01

Results are the mean + SEM of IC_{50} values expressed as nmol/l (nM).

12.2 Pharmacodynamics

Somatostatin receptors are expressed in many tissues including neuroendocrine tumors (e.g., growth hormone or adrenocorticotropic hormone secreting pituitary adenomas).

Acromegaly

Pasireotide binds to SSTR2 and SSTR5 subtype receptors which may be relevant for inhibition of GH secretion. *In vivo* studies show that SIGNIFOR LAR lowers GH and IGF-1 levels in patients with acromegaly.

Cushing's Disease

Corticotroph tumor cells from Cushing's disease patients frequently over-express SSTR5 whereas the other receptor subtypes are often not expressed or are expressed at lower levels. Pasireotide binds and activates the SSTRs resulting in inhibition of ACTH secretion, which leads to decreased cortisol secretion.

Cardiac Electrophysiology

Individually corrected QT (QTcI) interval was evaluated in a randomized, blinded, crossover study in healthy subjects investigating pasireotide subcutaneous doses of 0.6 mg and 1.95 mg twice daily, respectively. The maximum mean (95% upper confidence bound) placebo-subtracted QTcI change from baseline was 12.7 (14.7) ms and 16.6 (18.6) ms, respectively. Both pasireotide doses decreased heart rate, with a maximum mean (95% lower confidence bound) placebo-subtracted change from baseline of -10.9 (-11.9) beats per minute (bpm) observed at 1.5 hours for pasireotide 0.6 mg twice daily, and -15.2 (-16.5) bpm at 0.5 hours for pasireotide 1.95 mg twice daily.

The predicted pasireotide peak concentration (25.8 ng/mL) following SIGNIFOR LAR 60 mg dose in acromegaly patients is similar to the observed peak concentration (24.3 mg/mL) of the subcutaneous SIGNIFOR 0.6 mg twice daily dose and below the observed peak concentration (80.6 ng/mL) of the subcutaneous SIGNIFOR 1.95 mg twice daily dose. The predicted pasireotide peak concentration for the SIGNIFOR LAR dose of 40 mg in Cushing's disease patients is 14 ng/mL.

12.3 Pharmacokinetics

Pasireotide for intramuscular use is formulated as microspheres for long-acting release. After a single injection, the plasma pasireotide concentration shows an initial burst release on the injection day, followed by a dip from Day 2 to Day 7, then a slow increase to the maximum concentration around Day 21, and a slow declining phase over the next weeks, concomitant with the terminal degradation phase of the polymer matrix of the dosage form.

Absorption and Distribution:

No studies have been conducted to evaluate the absolute bioavailability of pasireotide in humans. Food effect is unlikely to occur since SIGNIFOR LAR is administered via a parenteral route.

In healthy volunteers, pasireotide administered as SIGNIFOR LAR is widely distributed with large apparent volume of distribution (V_z/F > 100 L). Distribution between blood and plasma is concentration-independent and shows that pasireotide is primarily located in the plasma (91%). Plasma protein binding is moderate (88%) and independent of concentration.

Pasireotide has low passive permeability and is likely to be a substrate of P-gp (P-glycoprotein), but the impact of P-gp on the ADME (absorption, distribution, metabolism, excretion) of pasireotide is expected to be low. In clinical testing in healthy volunteers, P-gp inhibition did not affect the rate or extent of pasireotide availability *[see Drug Interactions (7.1)]*. At therapeutic dose levels, pasireotide is not expected to be a substrate of BCRP (breast cancer resistance protein), OCT1 (organic cation transporter 1), or OATP (organic anion-transporting polypeptides) 1B1, 1B3, or 2B1.

Elimination:

Metabolism and Excretion:

Pasireotide was shown to be highly metabolically stable in human liver and kidney microsomes.References In healthy volunteers, pasireotide in its unchanged form is the predominant form found in plasma, urine and feces. Somatropin may increase CYP450 enzymes and, therefore, suppression of growth hormone secretion by somatostatin analogs including pasireotide may decrease the metabolic clearance of compounds metabolized by CYP450 enzymes.

Pasireotide is eliminated mainly via hepatic clearance (biliary excretion) with a small contribution of the renal route. In a human ADME study with subcutaneous SIGNIFOR with a single dose 0.6 mg, 55.9 ± 6.63% of the radioactivity dose was recovered over the first 10 days post dosing, including 48.3 ± 8.16% of the radioactivity in feces and 7.63 ± 2.03% in urine.

The apparent clearance (CL/F) of SIGNIFOR LAR in healthy volunteers is on average 4.5–8.5 liters/hour.

Steady-State Pharmacokinetics:

PK steady-state for SIGNIFOR LAR is achieved after 3 monthly doses. Following multiple intramuscular doses every 4 weeks (every 28 days), SIGNIFOR LAR demonstrates approximately dose-proportional PK exposures (steady-state trough; Ctrough, ss) in the dose range of 10 mg to 60 mg every 4 weeks.

Special Populations:

Population PK analyses of SIGNIFOR LAR suggest that race, gender and body weight do not have clinically relevant influence on circulating levels of pasireotide. No dose adjustment is required for demographics.

Pediatric Patients

No studies have been performed in pediatric patients *[see Use in Specific Populations (8.4)]*.

Geriatric Patients

Age is not a significant covariate in the population PK analysis. Therefore age is not expected to significantly impact circulating levels of pasireotide.

Efficacy and safety data on patients older than 65 years are limited *[see Use in Specific Populations (8.5)]*.

Hepatic Impairment

In a clinical study with a single subcutaneous dose of 600 µg pasireotide in subjects with impaired hepatic function (Child-Pugh A, B and C), subjects with moderate and severe hepatic impairment (Child-Pugh B and C) showed significantly higher exposures than subjects with normal hepatic function. Upon comparing with the control group, AUC_{inf} was increased by 12%, 56%, and 42%; and C_{max} was increased by 3%, 46%, and 33% respectively, in the mild, moderate, and severe hepatic impairment groups *[see Use in Specific Populations (8.6), Dosage and Administration (2.5)]*.

Renal Impairment

Clinical studies have not been performed in patients with renal impairment. However, renal clearance has a minor contribution to the elimination of pasireotide in humans. Renal function (creatinine clearance and estimated glomerular filtration rate) is not a covariate in the population PK analysis. Therefore, renal function is not expected to significantly impact the circulating levels of pasireotide *[see Use in Specific Populations (8.7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

A lifetime carcinogenicity study was conducted in rats and transgenic mice. Rats were given daily subcutaneous doses of pasireotide at 0.01 mg/kg/day, 0.05 mg/kg/day, and 0.3 mg/kg/day for 104 weeks. There were no drug-related tumors in rats at exposures up to 5-times higher than the maximum recommended clinical exposure of

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

SIGNIFOR LAR for injectable suspension is supplied in a single-use kit containing the following:

- One 6-mL brownish glass vial with a grey rubber stopper of SIGNIFOR LAR containing slightly yellow to yellow powder with a flip-off cap
- One 3-mL glass barrel/grey rubber stopper prefilled syringe containing 2 mL of clear, colorless to slightly yellow/brown diluent solution for reconstitution
- One sterile 20G x 1.5" stainless steel, polypropylene safety injection needle
- One vial adapter made of polycarbonate for drug product reconstitution

SIGNIFOR LAR kits are available in the following strengths:

SIGNIFOR LAR Kit	Final Concentration When Reconstituted (total product strength per total volume)	Final Concentration When Reconstituted (per mL)	Flip-off Cap Color	NDC
10 mg	10 mg/2 mL	5 mg/mL	Brown	0078-0748-81
20 mg	20 mg/2 mL	10 mg/mL	Gray	0078-0641-81
30 mg	30 mg/2 mL	15 mg/mL	Lilac	0078-0741-81
40 mg	40 mg/2 mL	20 mg/mL	Red	0078-0642-81
60 mg	60 mg/2 mL	30 mg/mL	Orange	0078-0643-81

16.2 Storage and Handling

Store at 2°C to 8°C (36°F-46°F). Do not freeze.

SIGNIFOR LAR should be stored at refrigerated temperatures between 2°C to 8°C (36°F-46°F) until the time of use. SIGNIFOR LAR drug product kit should remain at room temperature for a minimum of 30 minutes before reconstitution, but should not exceed 24 hours at room temperature. However, after preparation of the drug suspension, it must be administered immediately.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- Instruct patients on the importance of adhering to their return visit schedule.
- Advise patients that SIGNIFOR LAR should only be administered by a trained healthcare professional.

Hyperglycemia and Diabetes

- Advise patients to assess fasting plasma glucose and HbA1c prior to starting treatment with SIGNIFOR LAR and advise patients to consistently monitor blood glucose levels, particularly after the start of treatment or after dose changes, so that appropriate action can be taken *[see Warnings and Precautions (5.1)]*.

Bradycardia and QT Prolongation

- Advise patients that an ECG will be taken before treatment and periodically thereafter. Advise patients with cardiac disease and with risk factors for QT prolongation and bradycardia that adjustments in cardiac medications may be made and electrolyte disturbances may require correction *[see Warnings and Precautions (5.2)]*.

Liver Test Elevations

- Advise patients that liver function will be assessed prior to starting treatment with SIGNIFOR LAR and will be closely monitored for the first three months of treatment and thereafter as clinically indicated *[see Warnings and Precautions (5.3)]*.

Cholelithiasis and Complications of Cholelithiasis

- Inform patients that cholelithiasis and complications of cholelithiasis have been reported with the use of SIGNIFOR LAR [*see Warnings and Precautions (5.4)*].
- Advise patients to contact their healthcare provider if they experience signs or symptoms of gallstones (cholelithiasis) or complications of cholelithiasis (e.g., cholecystitis or cholangitis) [*see Warnings and Precautions (5.4)*].
- Advise patients that the gallbladder will be monitored by ultrasound periodically *[see Warnings and Precautions (5.4)]*.

Pituitary Hormone Deficiency(ies)

- Advise patients that monitoring of anterior pituitary function will be performed periodically *[see Warnings and Precautions (5.5)]*.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

Patient Information
SIGNIFOR® LAR (sig-na-for L.A.R.)
(pasireotide)
for injectable suspension, for intramuscular use

Read this Patient Information before you start receiving SIGNIFOR LAR, and each time you receive it. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is SIGNIFOR LAR?

SIGNIFOR LAR is a prescription medicine used to treat people with:

- acromegaly for whom surgery has not worked well enough or who cannot have surgery.
- Cushing's disease for whom surgery has not worked well enough or who cannot have surgery.

It is not known if SIGNIFOR LAR is safe and effective for use in children.

What should I tell my healthcare provider before receiving SIGNIFOR LAR?

Before you receive SIGNIFOR LAR, tell your healthcare provider about all of your medical conditions, including if you:

- have high blood sugar (hyperglycemia).
- have diabetes.
- have or have had heart problems, including an abnormal heart rate or rhythm or problems with the electrical system of your heart (QT prolongation).
- have a low level of potassium or magnesium in your blood.
- have liver problems.
- have gallstones (cholelithiasis).
- are pregnant or plan to become pregnant. It is not known if SIGNIFOR LAR will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if SIGINFOR LAR passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take SIGNIFOR LAR.

Treatment with SIGNIFOR LAR may result in improved fertility and the possibility of unplanned pregnancy in females who have acromegaly or Cushing's disease and have not gone through menopause. Talk to your healthcare provider about birth control methods that may be right for you during treatment with SIGNIFOR LAR.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

SIGNIFOR LAR and other medicines may affect each other, causing side effects. SIGNIFOR LAR may affect the way other medicines work, and other medicines may affect how SIGNIFOR LAR works. Your healthcare provider may need to change your dose of SIGNIFOR LAR or your other medicines. Especially tell your healthcare provider if you take:

- medicines to control your heart beat (antiarrhythmics)
- medicines to control your blood pressure (such as beta-blockers or calcium channel blockers)
- medicines to control the potassium and magnesium (electrolytes) levels in your body
- medicines that may affect the way the electrical system of your heart works (QT prolongation)
- cyclosporine
- bromocriptine

Ask your healthcare provider for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

How will I receive SIGNIFOR LAR?

- SIGNIFOR LAR must be given by a trained healthcare provider as an injection into the muscle of your buttocks (intramuscularly).
- Your healthcare provider will tell you how much SIGNIFOR LAR you will receive and when you will receive it.
- Your healthcare provider may change your dose of SIGNIFOR LAR or the length of time between your injections. Your healthcare provider will tell you how long you need to receive SIGNIFOR LAR.
- Before you receive SIGNIFOR LAR for the first time, your healthcare provider should do a blood test to check your fasting blood sugar level, hemoglobin A1c level, electrolyte levels, and your liver function.
- You will need to check your blood sugar levels during treatment with SIGNIFOR LAR, especially after you start treatment with SIGNIFOR LAR and after your dose is increased. Your healthcare provider will tell you how often you should check your blood sugar levels.
- Before you receive SIGNIFOR LAR for the first time and during your treatment, your healthcare provider should do a test to check your heart (electrocardiogram).
- If you miss a dose of SIGNIFOR LAR, you may receive your missed dose up to 14 days before your next dose.
- It is important that you keep your scheduled appointments with your healthcare provider during treatment with SIGNIFOR LAR.

What are the possible side effects of SIGNIFOR LAR?
SIGNIFOR LAR may cause serious side effects, including:

- **high blood sugar (hyperglycemia) and diabetes.** High blood sugar and diabetes are serious but common side effects of SIGNIFOR LAR. Your healthcare provider should check your blood sugar level before you start receiving SIGNIFOR LAR and while you receive it. Tell your healthcare provider if you have any of these symptoms:
  - feel very thirsty
  - urine more than usual
  - increased appetite with weight loss
  - tiredness

  If you get hyperglycemia while receiving SIGNIFOR LAR, your healthcare provider may give you another medicine to lower your blood sugar. Your healthcare provider may also change your dose of SIGNIFOR LAR or advise you to stop receiving it.
- **slow heart rate (bradycardia).** SIGNIFOR LAR can cause your heart to beat slower. People who have, or have had heart problems, or take certain medicines used to treat slow heart rate or that may cause a slow heart rate, are at higher risk for bradycardia. Tell your healthcare provider if you get any of these symptoms:
  - weakness
  - dizziness
  - fainting or near fainting spells
- **changes in the electrical system of your heart (QT interval prolongation).** Tell your healthcare provider if you get any of these symptoms:
  - weakness
  - dizziness
  - fainting or near fainting spells
- **higher than normal liver function tests.** Your healthcare provider should do blood tests to check your liver while you receive SIGNIFOR LAR.
- **gallstones (cholelithiasis) and complications that can happen if you have gallstones.** Gallstones are a serious but common side effect of SIGNIFOR LAR. Possible complications of gallstones include inflammation and infection of the gall bladder. Your healthcare provider should do a test (ultrasound) to check your gall bladder before and during your treatment with SIGNIFOR LAR. Tell your healthcare provider if you get any of these symptoms:
  - sudden pain in your upper right stomach area (abdomen)
  - sudden pain in your right shoulder or between your shoulder blades
  - yellowing of your skin and whites of your eyes
  - fever with chills
  - nausea
- **low levels of pituitary hormones (pituitary insufficiency).** SIGNIFOR LAR may reduce the pituitary hormones in your body. Your healthcare provider should do a blood test to check your pituitary hormone levels before you start receiving SIGNIFOR LAR and while you receive it. Tell your healthcare provider if you get any of these symptoms:
  - nausea and vomiting
  - tiredness
  - dizziness
  - diarrhea
  - low blood sugar levels
  - loss of appetite
  - weight loss

The most common side effects of SIGNIFOR LAR include:

- diarrhea
- headache
- stomach-area pain
- hair loss
- stuffy nose and sore throat
- low blood sugar
- limb swelling
- loss of appetite
- nausea
- increase in the level of an enzyme in your blood called creatine phosphokinase (CPK)
- tiredness
- stomach bloating
- high blood pressure
- back pain

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of SIGNIFOR LAR. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1–800–FDA–1088.

How should I store SIGNIFOR LAR?

- Store SIGNIFOR LAR in the refrigerator between 36^{O}F to 46^{O}F (2^{O}C to 8^{O}C).
- **Do not** freeze SIGNIFOR LAR.
- Take SIGNIFOR LAR out of the refrigerator at least **30 minutes** before you will receive it to allow it to come to room temperature.
- **Do not** use SIGNIFOR LAR if it has been out of the refrigerator and at room temperature for more than 24 hours.
- Your healthcare provider should give you SIGNIFOR LAR right away after it is mixed.

Keep SIGNIFOR LAR and all medicines out of the reach of children.

General information about the safe and effective use of SIGNIFOR LAR.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use SIGNIFOR LAR for a condition for which it was not prescribed. Do not give SIGNIFOR LAR to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about SIGNIFOR LAR. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about SIGNIFOR LAR that is written for health professionals.

For more information go to www.SIGNIFORLAR.com or call 1-888-NOW-NOVA.

What are the ingredients in SIGNIFOR LAR?

Active ingredient: pasireotide pamoate

Inactive ingredients:

Vial: Poly(D,L-lactide-co-glycolide)

Prefilled syringe: Mannitol, carboxymethylcellulose sodium, poloxamer 188, water for injections

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This Patient Information has been approved by the U.S. Food and Drug Administration. Revised:4/2019