Managing Acromegaly: Biochemical Control with SIGNIFOR LAR (pasireotide)

INDICATION AND USAGE
SIGNIFOR® LAR (pasireotide) for injectable suspension is a somatostatin analog indicated for the treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option.

HIGHLIGHTS OF IMPORTANT SAFETY INFORMATION
- Hyperglycemia and diabetes, sometimes severe, may occur with initiation of SIGNIFOR LAR therapy. A majority of patients, including those with normal glucose tolerance, pre-diabetes and diabetes, experienced increased glucose levels within the first 2 to 3 months of treatment with SIGNIFOR LAR. Glucose monitoring should be assessed prior to starting treatment with SIGNIFOR LAR. Blood glucose monitoring should be done weekly for the first 3 months after initiating SIGNIFOR LAR and the first 4 to 6 weeks after dose increases. Periodic monitoring should continue thereafter, as clinically appropriate. Patients who develop significant hyperglycemia may require initiation or adjustment in the dose or type of anti-diabetic treatment per standard of care.
- The optimal treatment for the management of SIGNIFOR LAR-induced hyperglycemia is not known. If hyperglycemia cannot be controlled despite medical management, the dose of SIGNIFOR LAR should be reduced or SIGNIFOR LAR should be discontinued.

Please see additional Important Safety Information on slides 16-20.
Please see full Prescribing Information.
Objectives

- Understand the roles of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) in acromegaly
- Recognize the goal of treatment and importance of biochemical control of GH and IGF-1
- Know how the use of SIGNIFOR® LAR (pasireotide) for injectable suspension may help provide biochemical control
- Identify opportunities for nurses to support patients through counseling and interventions
SIGNIFOR LAR Indication

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Reference
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Highlights of Important Safety Information

- Hyperglycemia and diabetes, sometimes severe, may occur with initiation of SIGNIFOR LAR therapy. A majority of patients, including those with normal glucose tolerance, pre-diabetes and diabetes, experienced increased glucose levels within the first 2 to 3 months of treatment with SIGNIFOR LAR.

- Glucose monitoring should be assessed prior to starting treatment with SIGNIFOR LAR. Blood glucose monitoring should be done weekly for the first 3 months after initiating SIGNIFOR LAR and the first 4 to 6 weeks after dose increases. Periodic monitoring should continue thereafter, as clinically appropriate.

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Acromegaly Overview

- Acromegaly is a rare hormonal disorder caused by hypersecretion of growth hormone (GH) and insulin-like growth factor 1 (IGF-1)\(^1\)
  - Majority of cases are due to benign pituitary adenomas
- Time to diagnosis from onset of symptoms is 7 to 10 years\(^2\)
  - Most (77%) patients present with macroadenoma at time of diagnosis\(^1\)
- Surgery is first-line treatment for initial management in most patients\(^1\)

References:
Long-Term Impact of Uncontrolled Acromegaly

• GH stimulates the liver to produce the hormone IGF-1
  – IGF-1 causes tissue growth in the body

• If the tumor on the pituitary gland continues to overproduce GH, IGF-1 levels will also continue to rise

• Elevated GH and IGF-1 levels result in an increased risk of health complications

References:
Goals of Treatment

• Biochemical normalization
• Attenuation of symptoms, such as headache, fatigue, perspiration, paresthesia, and osteoarthralgia
• Control of tumor mass
• Maintenance of pituitary function

Reference
Goal of Treatment: Biochemical Control

• Recommended biochemical target goals:
  - Age-normalized IGF-1 value
  - Random GH < 1.0 mcg/L

• During treatment, GH and IGF-1 should be measured with the same assay throughout management
  - GH is measured by taking multiple random serum samples or after an oral glucose tolerance test (OGTT)
  - IGF-1 requires only a random blood sample

Reference

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Goal of Treatment: Biochemical Control (continued)

• Pituitary surgery is the primary treatment for patients with microadenomas and noninvasive macroadenomas
  - Surgery results in an initial remission rate of 40-50% for macroadenomas and >85% for microadenomas
  - Most patients with acromegaly (~77%) have macroadenomas

• If surgery fails to achieve biochemical control, medical therapy is recommended
  - Somatostatin analogs (SSAs) are recommended for most patients requiring medical therapy

Reference
SIGNIFOR LAR (pasireotide)

- SIGNIFOR\textsuperscript{®} LAR (pasireotide) for injectable suspension is a somatostatin analog indicated 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 was studied in two Phase 3 clinical trials:
  - A prospective, randomized, double-blind, multicenter, 12-month study in drug-naive patients with acromegaly.
  - A prospective, multicenter, randomized parallel-group trial comparing 2 doses of pasireotide to continued open-label therapy in patients with acromegaly who were inadequately controlled with other somatostatin analogs.

Reference
SIGNIFOR LAR [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2014.

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Biochemical Control in Drug-Naive Patients

Proportion of patients achieving GH < 2.5 μg/L and normal IGF-1 for age and sex at 12 months

<table>
<thead>
<tr>
<th>Proportion</th>
<th>SIGNIFOR LAR</th>
<th>Active Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH&lt;2.5 mcg/L and normalized IGF-1</td>
<td>31.3%</td>
<td>19.2%</td>
</tr>
<tr>
<td>GH&lt;2.5 mcg/L and IGF-1 ≤ULN</td>
<td>35.8%</td>
<td>20.9%</td>
</tr>
<tr>
<td>Normalized IGF-1</td>
<td>28.4%</td>
<td>23.6%</td>
</tr>
<tr>
<td>GH&lt;2.5 mcg/L</td>
<td>48.3%</td>
<td>51.6%</td>
</tr>
</tbody>
</table>

* P<0.01 SIGNIFOR LAR vs Active Comparator in the overall population.
* The maximum dose approved for use in the United States was not used in this trial but the majority of patients were receiving the dose most commonly used in the United States to treat acromegaly.

Results at Month 12

Biochemical control was achieved in postsurgery patients in 39.4% of the SIGNIFOR LAR group (n=71) and 21.8% of the Active Comparator group (n=76).

Biochemical control was achieved in de novo patients in 25.7% of the SIGNIFOR LAR group (n=105) and 17.3% of the Active Comparator group (n=104).

Patients were 63% more likely to achieve biochemical control with pasireotide LAR.

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Biochemical Control in Inadequately Controlled Patients

• Inadequate control was defined as GH > 2.5 mcg/L (mean of 5 samples over 2 hr) and sex- and age-adjusted IGF-1 > 1.3 x ULN

A secondary endpoint of biochemical control was achieved by Month 3 in 15.4% and 18.5% of patients in the SIGNIFOR® LAR (pasireotide) for injectable suspension 40 mg and 60 mg arms, respectively.

Reference
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Highlights of Important Safety Information

• Bradycardia and QT Prolongation:
  Bradycardia
  Bradycardia has been reported with the use of SIGNIFOR LAR. Patients with cardiac disease and/or risk factors for bradycardia, such as history of clinically significant bradycardia, high-grade heart block, or concomitant use of drugs associated with bradycardia, should be monitored. Adjustments in the dose of drugs known to slow the heart rate (e.g., beta-blockers, calcium channel blockers) and correction of electrolyte disturbances, maybe necessary when initiating or during the course of SIGNIFOR LAR treatment

  QT Prolongation
  SIGNIFOR LAR is associated with QT prolongation and should be used with caution in patients who are at significant risk of developing prolongation of the QT interval. A baseline ECG is recommended prior to initiating therapy with SIGNIFOR LAR and periodically while on treatment. Hypokalemia or hypomagnesemia must be corrected prior to initiating SIGNIFOR LAR and should be monitored periodically during therapy

Reference
SIGNIFOR LAR [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2014.

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Nurse’s Role in Treating Patients With Acromegaly

• Reinforce the importance of adequate biochemical control with each patient
• Discuss the patient’s concerns with the extended healthcare team
• Encourage patient to track his or her GH and IGF-1 levels
Treating to Goal: Summary

• Acromegaly is caused by a benign tumor on the pituitary gland that leads to the excessive secretion of GH and IGF-1

• Biochemical control of GH and IGF-1 levels may be achieved with the use of SIGNIFOR® LAR (pasireotide) for injectable suspension

• Nurse interaction can help patients:
  – Recognize the importance of biochemical control
  – Track their GH and IGF-1 levels
Important Safety Information

SIGNIFOR® LAR (pasireotide) for injectable suspension, for intramuscular use

INDICATION

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Important Safety Information

Warnings and Precautions:

• Hyperglycemia and Diabetes: SIGNIFOR LAR can cause increases in blood glucose levels which are sometimes severe. Patients with poor baseline glycemic control are at higher risk of developing severe hyperglycemia.

A majority of patients, including those with normal glucose tolerance, pre-diabetes, and diabetes, experienced increased glucose levels within the first 2 to 3 months of treatment with SIGNIFOR LAR.

Fasting plasma glucose and hemoglobin A1c should be assessed prior to starting treatment with SIGNIFOR LAR. In patients with poorly controlled diabetes mellitus, anti-diabetic treatment should be optimized before SIGNIFOR LAR treatment is started. Blood glucose monitoring should be done weekly for the first 3 months after initiating SIGNIFOR LAR and the first 4 to 6 weeks after dose increases. Periodic monitoring should continue thereafter, as clinically appropriate.

Patients who develop significant hyperglycemia on SIGNIFOR LAR may require initiation of anti-diabetic therapy(ies) or adjustment in the dose or type of anti-diabetic therapy(ies) per standard of care. The optimal treatment for the management of SIGNIFOR LAR-induced hyperglycemia is not known. If hyperglycemia cannot be controlled, despite medical management, the dose of SIGNIFOR LAR should be reduced or discontinued.

After treatment discontinuation, fasting plasma glucose and hemoglobin A1c should be assessed if indicated. Patients on anti-diabetic therapy discontinuing SIGNIFOR LAR may require more frequent blood glucose monitoring and anti-diabetic dose adjustment to mitigate the risk of hypoglycemia.

Reference
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Please see full Prescribing Information.
Bradycardia and QT Prolongation

Bradycardia
Bradycardia has been reported with the use of SIGNIFOR LAR. Patients with cardiac disease and/or risk factors for bradycardia, such as history of clinically significant bradycardia, high-grade heart block, or concomitant use of drugs associated with bradycardia, should be monitored. Adjustments in the dose of drugs known to slow the heart rate (e.g., beta-blockers, calcium channel blockers) and correction of electrolyte disturbances, maybe necessary when initiating or during the course of SIGNIFOR LAR treatment.

QT Prolongation
SIGNIFOR LAR is associated with QT prolongation and should be used with caution in patients who are at significant risk of developing prolongation of the QT interval. A baseline ECG is recommended prior to initiating therapy with SIGNIFOR LAR and periodically while on treatment. Hypokalemia or hypomagnesemia must be corrected prior to initiating SIGNIFOR LAR and should be monitored periodically during therapy.

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Please see full Prescribing Information.
Important Safety Information (continued)

- **Liver Test Elevations**
  Increases in liver enzymes have been observed with SIGNIFOR LAR. ALT or AST elevation greater than 3 times the upper limit of normal (ULN) were observed in 3% of patients and ALT or AST elevation greater than 5 times the upper limit of normal (ULN) were observed in 1% of patients treated with SIGNIFOR LAR.

  Assessment of liver function is recommended prior to treatment with SIGNIFOR LAR, and after the first 2 to 3 weeks, then monthly for 3 months. Thereafter, liver function should be monitored as clinically indicated. Patients who develop increased transaminase levels should be monitored until values return to pre-treatment levels. Treatment with SIGNIFOR LAR should be discontinued if signs or symptoms suggestive of clinically significant liver impairment develop.

*Reference*
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Please see full Prescribing Information.
Important Safety Information (continued)

- **Cholelithiasis**: Cholelithiasis was reported in up to 33% of patients treated with SIGNIFOR LAR in clinical trials. Patients should be monitored periodically.

- **Pituitary Hormone Deficiency(ies)**: Suppression of pituitary hormones other than GH/IGF-1, may occur on SIGNIFOR LAR. Monitoring pituitary function (e.g., thyroid, adrenal, gonadal) prior to initiation of therapy with SIGNIFOR LAR, as well as periodically during treatment, as clinically appropriate, is recommended. Patients should be monitored for and instructed on the signs and symptoms of adrenal insufficiency during therapy. If adrenal insufficiency is suspected it should be confirmed and treated per standard of care with exogenous glucocorticoids at replacement doses.

**Adverse Reactions**

Adverse reactions associated with SIGNIFOR LAR and occurring in >20% of patients were diarrhea, cholelithiasis, hyperglycemia, and diabetes mellitus.

**Drug Interactions**

Caution is advised when co-administering drugs that prolong the QT interval with SIGNIFOR LAR.

The following drugs may require monitoring and possible dose adjustment when used with SIGNIFOR LAR: cyclosporine and bromocriptine.

**Contraindications**

None

**Please see full Prescribing Information**

Reference

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