Managing Acromegaly: Review of Two Cases

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 25-28.

Please see full Prescribing Information.
Objectives

Follow the cases of two patients with acromegaly to:

• Understand the acromegaly patient journey
• Review the symptoms, diagnosis, and management of acromegaly
• Recognize the role of SIGNIFOR® LAR (pasireotide) for injectable suspension as one available treatment option

Please see the Indication on slide 24 and Important Safety Information on slides 25-28.

Please see full prescribing information.
Case Study 1: Celia, a Newly Diagnosed Patient

• Celia is a 39 year old stay-at-home mom
• She noticed that her wedding ring no longer fit
• She began experiencing pain in her joints during exercise, which worsened over several months
• Over time, her joint pain became almost constant and she suffered from chronic headaches, profuse sweating and fatigue, finally prompting a visit to her primary care physician (PCP)
• Celia’s PCP referred her to an endocrinologist

Reference
Celia: Diagnostic Investigations

• The diagnosis of acromegaly depends on clinical and laboratory findings
• Growth Hormone (GH) and Insulin Growth Factor 1 (IGF-1) testing and pituitary magnetic resonance imaging (MRI) are complementary tools to assist physicians in making a diagnosis
• Celia’s endocrinologist orders the following:
  – Laboratory testing for elevations in GH and IGF-1
  – MRI to confirm presence of pituitary adenoma
  – Visual field testing to assess possible optic chiasm compression
• Celia is anxious to learn the cause of her symptoms

Reference
Celia: Diagnostic Results

Laboratory results confirm acromegaly
• IGF-1 is 3.2 times upper limit of normal (3.2 x ULN) for Celia’s age and sex
• GH is 25 mcg/mL by oral glucose tolerance test [OGTT] (Recommended target is GH <1 mcg/L.)

Imaging results:
• MRI reveals a large sellar mass abutting the optic chiasm and cavernous sinus invasion
• Invasion of the tumor into the cavernous sinus suggests that Celia’s tumor will probably not be able to be completely removed by surgery

Reference
Celia: Treatment Recommendations

- Surgical debulking of the tumor
- Treatment with medical therapy if GH and IGF-1 levels remain elevated

Reference
Celia: Surgical Treatment

- Transsphenoidal surgery is recommended as the primary therapy in most patients
- When total surgical resection is unlikely, surgical debulking is recommended to improve the subsequent response to medical therapy
- Celia undergoes endonasal transsphenoidal surgery to remove the resectable portion of the tumor

Reference
Celia: Postoperative Findings

- Celia reports continued headaches, sweating, arthralgias, and fatigue
- OGTT and laboratory assays reveal elevated GH (8.2 mcg/L) and IGF-1 (2.5 x ULN)
- MRI scan reveals an unresectable residual tumor in the left cavernous sinus
- Visual fields are normal
Treatment With SIGNIFOR LAR

• Celia’s endocrinologist prescribes SIGNIFOR® LAR (pasireotide) for injectable suspension

• SIGNIFOR LAR 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

• Celia will receive an intramuscular injection of 40 mg SIGNIFOR LAR once every 4 weeks, to be administered by a trained health professional – in this case, her nurse

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

Please see Important Safety Information on slides 25-28.
Please see full Prescribing Information.
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.

Please see Important Safety Information on slides 25-28. Please see full Prescribing Information.
Celia: Side Effects of Treatment

- At her second monthly visit for her injection, Celia tells her nurse she has been experiencing gastrointestinal side effects
- Her nurse discusses supportive care to help Celia manage her diarrhea, abdominal pain, and nausea

<table>
<thead>
<tr>
<th>Diarrhea</th>
<th>Abdominal pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nausea</td>
</tr>
</tbody>
</table>

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

Please see Indication on slide 24 and Important Safety Information on slides 25-28.
Please see full Prescribing Information.
Celia: Other Potential Side Effects

- Celia’s nurse is alert to other potential side effects Celia might experience

### Adverse Reactions Occurring in ≥ 10% of Patients

<table>
<thead>
<tr>
<th>Adverse Reaction Type</th>
<th>SIGNIFOR LAR (40-60mg) % N=178</th>
<th>Active Comparator % N=180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>39</td>
<td>45</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>29</td>
<td>8</td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>26</td>
<td>36</td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>Alopecia</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>Blood creatine phosphokinase increased</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Sinus bradycardia(^1)</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Back pain</td>
<td>8</td>
<td>11</td>
</tr>
</tbody>
</table>

\(^1\) Diabetes mellitus includes the following preferred terms (PTs): Diabetes mellitus and type 2 diabetes mellitus

\(^1\) Sinus bradycardia includes the following PTs: Bradycardia and sinus bradycardia

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

Please see Indication on slide 24 and Important Safety Information on slides 25-28.

Please see full Prescribing Information.
Celia: Monitoring

- Celia is on a stable dose of SIGNIFOR® LAR (pasireotide) for injectable suspension to keep her GH and IGF-1 levels controlled
- Her GH and IGF-1 levels are monitored regularly
- She is also monitored for important safety parameters, including:
  - Fasting plasma glucose and hemoglobin A1c
  - Potassium and magnesium levels
  - Liver function
  - Gallbladder function
  - Pituitary function

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

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Please see full Prescribing Information.
Celia: Asymptomatic Gallstones

- Celia develops gallstones after being on SIGNIFOR® LAR (pasireotide) for injectable suspension for 12 months
- Her gallstones are asymptomatic
- SIGNIFOR LAR is continued at the same dosage, but she is monitored with ultrasounds more frequently

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

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Please see full Prescribing Information.
The Nurse’s Role: Helping Celia Beyond Therapy

- Celia’s nurse cultivated an open nurse-patient relationship through active listening and consistent follow-up.
- Celia’s nurse helped her understand the rarity of her condition and the importance of staying positive.
- Celia was encouraged to identify with others by joining a local support group in the community or seeking online sources of support for patients with acromegaly.
Case Study 2: Robert, an Inadequately Controlled Patient

- Robert is a 44-year-old married electrician
- He suffers from acromegaly related symptoms, and their cause has remained undiagnosed
- Robert’s wife sees a news article about acromegaly and recognizes many of the signs and symptoms
- She discusses what she learned with Robert and they schedule an appointment with an endocrinologist

Reference
Robert: Diagnosis

- Based on Robert’s symptom history and physical signs, Robert’s endocrinologist agrees that acromegaly is a distinct possibility
- IGF-1 and GH testing confirm a diagnosis of acromegaly
- Pituitary MRI reveals a macroadenoma
Robert: Initial Treatment

• Transsphenoidal surgery is only partially successful and significant unresected tumor remains
• Despite some improvement, Robert’s postsurgical biochemical levels remain elevated
• No radiotherapy is performed
• Robert’s endocrinologist prescribes a first-generation somatostatin analog (SSA) to achieve biochemical control of GH and IGF-1 levels
• After 9 months of medical treatment, tumor volume remains unchanged and Robert’s biochemical levels are not adequately controlled (GH 5.8 mcg/L, IGF-1 2.4 x ULN)
Robert: Treatment With SIGNIFOR LAR

• Robert’s endocrinologist prescribes SIGNIFOR® LAR (pasireotide) for injectable suspension

• SIGNIFOR LAR 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

• Robert’s nurse will administer an intramuscular injection of 40 mg SIGNIFOR LAR once every 4 weeks

• Prior to starting treatment with SIGNIFOR LAR, Robert’s fasting plasma glucose and hemoglobin A1c are assessed
  – His endocrinologist also performs liver function tests, an electrocardiogram, and also assesses his serum potassium and magnesium levels

• Blood glucose monitoring will be done weekly for the first 3 months and the first 4 to 6 weeks after dose increases

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

Please see Important Safety Information on slides 25-28.
Please see full Prescribing Information.
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

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

Please see Important Safety Information on slides 25-28.
Please see full Prescribing Information.
Robert: Ongoing Medical Management

- After 24 weeks of treatment, Robert’s biochemical levels are controlled on a stable dose of SIGNIFOR® LAR (pasireotide) for injectable suspension (GH is 2.5 mcg/L and IGF-1 is normalized)
- His GH and IGF-1 levels continue to be monitored regularly
- Additional monitoring is performed as recommended in the SIGNIFOR LAR Prescribing Information
- Robert’s nurse assesses his symptoms and inquires about side effects during his monthly visits for his SIGNIFOR LAR injection

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

Please see Indication on slide 24 and Important Safety Information on slides 25-28.
Please see full Prescribing Information.
The Nurse’s Role: Helping Robert Beyond Therapy

• From month to month, the nurse continued building a relationship with Robert and his wife as a trusted care partner
• His nurse was proactive in assessing Robert’s symptoms and asking about any possible side effects
• Robert and his wife were provided with information to help them connect with the acromegaly community to share experiences and access resources
Summary

• Patients with acromegaly can present with a variety of signs and symptoms, and the journey to diagnosis can be a long and frustrating one

• The primary treatment strategy for acromegaly is surgical intervention, but medical therapy with SIGNIFOR® LAR (pasireotide) for injectable suspension may be indicated for some patients

• Nurse interaction can help patients understand and cope with acromegaly

Please see Indication on slide 24 and Important Safety Information on slides 25-28.

Please see full Prescribing Information.
Important Safety Information

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

INDICATION

SIGNIFOR LAR 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.

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

Please see full Prescribing Information.
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
SIGNIFOR LAR [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2014.

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

• 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.

Please see full Prescribing Information.
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
SIGNIFOR LAR [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2014.

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

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