UNDERSTANDING THE APPROPRIATE PATIENT FOR SANDOSTATIN® LAR® (OCTREOTIDE)

The case study presented in this brochure is based on a fictional patient. Individual results may vary.

Indication for Sandostatin® LAR®
Sandostatin® LAR® (octreotide) is indicated for the treatment of patients with acromegaly in whom surgery is inappropriate or ineffective, or in the interim period until radiotherapy becomes fully effective.

Please see Important Safety Information on pages 7-13.
Consider the following patient

**MEET KATIE**

**36-YEAR-OLD WOMAN LIVING WITH ACROMEGALY**

<table>
<thead>
<tr>
<th>Surgical History:</th>
<th>Katie had transsphenoidal surgery about 18 months ago to remove a GH-secreting tumor on her pituitary gland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Condition:</td>
<td>Recent increase in GH and IGF-1 levels indicates the tumor has returned</td>
</tr>
<tr>
<td>GH Level:</td>
<td>7 ng/mL^{3,4}</td>
</tr>
<tr>
<td>IGF-1 Level:</td>
<td>650 ng/mL^{5}</td>
</tr>
<tr>
<td>Symptoms:</td>
<td>Over the past 3 months, Katie has been experiencing a flare-up of past symptoms—headaches and fatigue</td>
</tr>
<tr>
<td>Physician Recommendation:</td>
<td>Initiate medical therapy with Sandostatin® LAR® 20 mg every 4 weeks for 3 months^{7,*}</td>
</tr>
</tbody>
</table>

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**Important Notes:**

Katie has never taken any medicine to control her acromegaly and is unfamiliar with Sandostatin® LAR®

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GH, growth hormone; IGF-1, insulin-like growth factor 1.
WHAT SHOULD THE PATIENT KNOW?

In a case like Katie’s, it’s critical to remind patients that they are not alone. Surgery to remove a tumor does not always cure acromegaly. In fact, nearly 20% to 45% of patients will have their acromegaly return after surgery. It’s important patients talk with their doctor if they begin to experience symptoms, especially those once controlled.

- Katie will need to undergo an oral glucose tolerance test (OGTT) and a blood test to see if her GH and IGF-1 levels are controlled.

- Following surgery, biochemical control is indicated by a GH level of <1.0 ng/mL and an IGF-1 level that is normal for age.

- Based on Katie’s age and the tests being used, her IGF-1 levels should be 54 to 258 ng/mL.

Before starting treatment, remind patients that acromegaly is a chronic illness, like diabetes, and most patients will stay on Sandostatin® LAR®. While a small population do come off treatment, it’s very uncommon.
TREATMENT WITH SANDOSTATIN® LAR®

HOW IT WORKS

Sandostatin® LAR® is a somatostatin analogue. Somatostatin is the hormone in the brain that inhibits GH release. Sandostatin® LAR® stimulates the effects of natural somatostatin working at the tumor site to regulate GH secretion and tumor growth.

IMPORTANT DOSING INFORMATION

Treatment with Sandostatin® LAR® should be initiated at 20 mg every 4 weeks for 3 months.

Patients currently on treatment with subcutaneous Sandostatin® (octreotide acetate) Injection can start treatment with Sandostatin® LAR® the day after the last dose of subcutaneous Sandostatin® Injection.

Upon completing the first 3 months of treatment, dosing adjustments may be needed based on GH levels, IGF-1 levels, and clinical symptoms.

Keep in Mind:

- Patients will only have to come into the office once every 4 weeks to receive their injection
- At each visit, you will need to conduct an OGTT or a blood test to check their GH and IGF-1 levels
- For patients in whom, within this 3-month period, clinical symptoms and biochemical parameters (GH; IGF-1) are not fully controlled (GH concentrations still above 2.5 ng/mL), the dose may be increased to 30 mg every 4 weeks
  - If after 3 months, GH, IGF-1, and/or symptoms are not adequately controlled at a dose of 30 mg, the dose may be increased to 40 mg every 4 weeks
- Once their GH and IGF-1 levels are better controlled, you may then consider dropping patients to a lower dose

COMMON SIDE EFFECTS OF SANDOSTATIN® LAR®

- Diarrhea
- Nausea
- Abdominal pain
- Flatulence
- Headache
- Gallstones
- Hyperglycemia
- Constipation

*For patients whose GH concentrations are consistently below 1 ng/mL, whose IGF-1 serum concentrations normalized, and in whom most reversible signs/symptoms of acromegaly have disappeared after 3 months of treatment with 20 mg, 10 mg Sandostatin® LAR® may be administered every 4 weeks. However, particularly in this group of patients, it is recommended to closely monitor adequate control of serum GH and IGF-1 concentrations and clinical signs/symptoms at this low dose of Sandostatin® LAR®. For patients on a stable dose of Sandostatin® LAR®, assessment of GH and IGF-1 should be made every 6 months.
NURSING CONSIDERATIONS

Review the following with your patients prior to initiation of Sandostatin® LAR® treatment:

<table>
<thead>
<tr>
<th>Topic</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>What biochemical control means and how Sandostatin® LAR® can help achieve treatment goals</td>
<td>- How biochemical testing is performed and how often</td>
</tr>
<tr>
<td>How biochemical testing is performed and how often</td>
<td>- Factors that may influence biochemical test results</td>
</tr>
<tr>
<td>Factors that may influence biochemical test results</td>
<td>- Sleep, exercise, stress levels, food intake, and blood sugar level</td>
</tr>
<tr>
<td>Treatment schedule</td>
<td>- Sandostatin® LAR® injection every 4 weeks</td>
</tr>
<tr>
<td>Potential for dose changes during treatment</td>
<td></td>
</tr>
<tr>
<td>Importance of continued monitoring and adherence to therapy</td>
<td></td>
</tr>
<tr>
<td>Current symptoms</td>
<td>- Frequency, severity, and management</td>
</tr>
<tr>
<td>Treatment side effects</td>
<td></td>
</tr>
<tr>
<td>Current medication list</td>
<td></td>
</tr>
</tbody>
</table>
Encourage your patients to find a support group with other patients with acromegaly, either online or in their area, if they haven’t done so already. A support group is a place where they can share their feelings and concerns, hear others’ stories, and even help those who are just beginning their own journey.

Acromegaly Community
An international nonprofit support system for patients with acromegaly and their caregivers, featuring extensive disease information and support networking.
www.acromegalycommunity.com | 1-918-786-8209

Hormone Health Network
The public education affiliate of the Endocrine Society and a leading source of hormone-related health information.
www.hormone.org | 1-800-HORMONE

National Organization for Rare Disorders (NORD)
A national organization providing patient advocacy, education, and research support for rare diseases, such as acromegaly.
www.rarediseases.org | 1-800-999-NORD

Pituitary Network Association (PNA)
An international nonprofit organization for patients with pituitary tumors and disorders, their families, loved ones, and the physicians and healthcare providers who treat them.
www.pituitary.org | 1-805-499-9973

*Novartis Pharma AG may make donations to these support groups and organizations. However, Novartis AG has no control over third-party websites and makes no representation as to the accuracy, completeness, adequacy, or any other aspects of the information contained on such websites.
SANDOSTATIN® LAR® IMPORTANT SAFETY INFORMATION

Contraindications
Known hypersensitivity to octreotide or to any of the excipients (see list of excipients).

Special warnings and precautions for use

General
As GH-secreting pituitary tumors may sometimes expand, causing serious complications (e.g., visual field defects), it is essential that all patients be carefully monitored. If evidence of tumor expansion appears, alternative procedures may be advisable.

The therapeutic benefits of a reduction in growth hormone (GH) levels and normalization of insulin-like growth factor 1 (IGF-1) concentration in female acromegalic patients could potentially restore fertility. Female patients of childbearing potential should be advised to use adequate contraception if necessary during treatment with octreotide (see Fertility, pregnancy and lactation).

Thyroid function should be monitored in patients receiving prolonged treatment with octreotide. Hepatic function should be monitored during octreotide therapy.

Cardiovascular related events
Common cases of bradycardia have been reported. Dose adjustment of medicinal products such as beta blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may be necessary (see Interaction with other medicinal products and other forms of interaction).

Gallbladder and related events
Cholelithiasis is a very common event during Sandostatin® treatment and may be associated with cholecystitis and biliary duct dilatation (see Undesirable effects). Ultrasonic examination of the gallbladder before and at about 6-monthly intervals during Sandostatin® LAR® therapy is recommended.

Glucose metabolism
Because of its inhibitory action on growth hormone, glucagon, and insulin release, Sandostatin® LAR® may affect glucose regulation. Post-prandial glucose tolerance may be impaired. As reported for patients treated with s.c. Sandostatin®, in some instances, the state of persistent hyperglycemia may be induced as a result of chronic administration. Hypoglycemia has also been reported.

In patients with concomitant Type I diabetes mellitus, Sandostatin® LAR® is likely to affect glucose regulation, and insulin requirements may be reduced. In non-diabetics and type II diabetics with partially intact insulin reserves, Sandostatin® s.c. administration may result in increases in post-prandial glycemia. It is therefore recommended to monitor glucose tolerance and antidiabetic treatment.

In patients with insulinomas, octreotide, because of its greater relative potency in inhibiting the secretion of GH and glucagon than that of insulin, and because of the shorter duration of its inhibitory action on insulin, may increase the depth and prolong the duration of hypoglycemia. These patients should be closely monitored.
SANDOSTATIN® LAR® IMPORTANT SAFETY INFORMATION (cont)

Nutrition
Octreotide may alter absorption of dietary fats in some patients.
Depressed vitamin B₁₂ levels and abnormal Schilling’s tests have been observed in some patients receiving octreotide therapy. Monitoring of vitamin B₁₂ levels is recommended during therapy with Sandostatin® LAR® in patients who have a history of vitamin B₁₂ deprivation.

Sodium content
Sandostatin® LAR® contains less than 1 mmol (23 mg) sodium per dose, i.e., is essentially “sodium-free.”

Interaction with other medicinal products and other forms of interaction
Dose adjustment of medicinal products such as beta blockers, calcium channel blockers, or agents to control fluid and electrolyte balance may be necessary when Sandostatin® LAR® is administered concomitantly (see Special warnings and precautions for use).

Dose adjustments of insulin and antidiabetic medicinal products may be required when Sandostatin® LAR® is administered concomitantly (see Special warnings and precautions for use).

Octreotide has been found to reduce the intestinal absorption of ciclosporin and to delay that of cimetidine.

Concomitant administration of octreotide and bromocriptine increases the bioavailability of bromocriptine.

Limited published data indicate that somatostatin analogues might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that octreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g. quinidine, terfenadine) should therefore be used with caution.

Fertility, pregnancy and lactation
Pregnancy
There is a limited amount of data (less than 300 pregnancy outcomes) from the use of octreotide in pregnant women, and in approximately one third of the cases the pregnancy outcomes are unknown. The majority of reports were received after post-marketing use of octreotide and more than 50% of exposed pregnancies were reported in patients with acromegaly. Most women were exposed to octreotide during the first trimester of pregnancy at doses ranging from 100-1200 micrograms/day of Sandostatin® s.c. or 10-40 mg/month of Sandostatin® LAR®. Congenital anomalies were reported in about 4% of pregnancy cases for which the outcome is known. No causal relationship to octreotide is suspected for these cases.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see Preclinical safety data).

As a precautionary measure, it is preferable to avoid the use of Sandostatin® LAR® during pregnancy (see Special warnings and precautions for use).
Breastfeeding
It is unknown whether octreotide is excreted in human breast milk. Animal studies have shown excretion of octreotide in breast milk. Patients should not breastfeed during Sandostatin® LAR® treatment.

Fertility
It is not known whether octreotide has an effect on human fertility. Late descent of the testes was found for male offsprings of dams treated during pregnancy and lactation. Octreotide, however, did not impair fertility in male and female rats at doses of up to 1 mg/kg body weight per day (see Preclinical safety data).

Effects on ability to drive and use machines
Sandostatin® LAR® has no or negligible influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines if they experience dizziness, asthenia/fatigue, or headache during treatment with Sandostatin® LAR®.

Undesirable effects
Summary of the safety profile
The most frequent adverse reactions reported during octreotide therapy include gastrointestinal disorders, nervous system disorders, hepatobiliary disorders, and metabolism and nutritional disorders.

The most commonly reported adverse reactions in clinical trials with octreotide administration were diarrhea, abdominal pain, nausea, flatulence, headache, cholelithiasis, hyperglycemia and constipation.

Other commonly reported adverse reactions were dizziness, localized pain, biliary sludge, thyroid dysfunction (e.g., decreased thyroid stimulating hormone [TSH], decreased total T4, and decreased free T4), loose stools, impaired glucose tolerance, vomiting, asthenia, and hypoglycemia.

Tabulated list of adverse reactions
The following adverse drug reactions, listed in Table 1, have been accumulated from clinical studies with octreotide:

Adverse drug reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.
Table 1 Adverse drug reactions reported in clinical studies

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th>Very common: Diarrhea, abdominal pain, nausea, constipation, flatulence.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
<td>Dyspepsia, vomiting, abdominal bloating, steatorrhea, loose stools, discoloration of feces.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>Very common: Headache.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
<td>Dizziness.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endocrine disorders</th>
<th>Common: Hypothyroidism, thyroid disorder (e.g., decreased TSH, decreased total T4, and decreased free T4).</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Hepatobiliary disorders</th>
<th>Very common: Cholelithiasis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
<td>Cholecystitis, biliary sludge, hyperbilirubinemia.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
<th>Very common: Hyperglycemia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
<td>Hypoglycemia, impaired glucose tolerance, anorexia.</td>
</tr>
<tr>
<td>Uncommon:</td>
<td>Dehydration.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
<th>Very common: Injection site reactions.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
<td>Asthenia.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Common: Elevated transaminase levels.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th>Common: Pruritus, rash, alopecia.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Respiratory disorders</th>
<th>Common: Dyspnea.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
<th>Common: Bradycardia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon:</td>
<td>Tachycardia.</td>
</tr>
</tbody>
</table>
Post-marketing
Spontaneously reported adverse reactions, presented in Table 2, are reported voluntarily and it is not always possible to reliably establish frequency or a causal relationship to drug exposure.

Table 2 Adverse drug reactions derived from spontaneous reports

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Thrombocytopenia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Anaphylaxis, allergy/hypersensitivity reactions.</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Urticaria.</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Acute pancreatitis, acute hepatitis without cholestasis, cholestatic hepatitis, cholestasis, jaundice, cholestatic jaundice.</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Arrhythmias.</td>
</tr>
<tr>
<td>Investigations</td>
<td>Increased alkaline phosphatase levels, increased gamma glutamyl transferase levels.</td>
</tr>
</tbody>
</table>

Description of selected adverse reactions

Gallbladder and related reactions
Somatostatin analogues have been shown to inhibit gallbladder contractility and decrease bile secretion, which may lead to gallbladder abnormalities or sludge. Development of gallstones has been reported in 15 to 30% of long-term recipients of s.c. Sandostatin®. The incidence in the general population (aged 40 to 60 years) is about 5 to 20%. Long-term exposure to Sandostatin® LAR® of patients with acromegaly or gastroentero-pancreatic tumors suggests that treatment with Sandostatin® LAR® does not increase the incidence of gallstone formation, compared with s.c. treatment. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery.

Gastrointestinal disorders
In rare instances, gastrointestinal side effects may resemble acute intestinal obstruction, with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding. The frequency of gastrointestinal adverse events is known to decrease over time with continued treatment.

Hypersensitivity and anaphylactic reactions
Hypersensitivity and allergic reactions have been reported during post-marketing experience. When these occur, they mostly affect the skin, rarely the mouth and airways. Isolated cases of anaphylactic shock have been reported.
Injection site reactions
Injection site related reactions including pain, redness, hemorrhage, pruritus, swelling or induration were commonly reported in patients receiving Sandostatin® LAR®; however, these events did not require any clinical intervention in the majority of the cases.

Metabolism and nutrition disorders
Although measured fecal fat excretion may increase, there is no evidence to date that long-term treatment with octreotide has led to nutritional deficiency due to malabsorption.

Pancreatic enzymes
In very rare instances, acute pancreatitis has been reported within the first hours or days of Sandostatin® s.c. treatment and resolved on withdrawal of the drug. In addition, cholelithiasis-induced pancreatitis has been reported for patients on long term Sandostatin® s.c. treatment.

Cardiac disorders
Bradycardia is a common adverse reaction with somatostatin analogues. In both acromegalic and carcinoid syndrome patients, ECG changes were observed such as QT prolongation, axis shifts, early repolarization, low voltage, R/S transition, early R wave progression, and nonspecific ST-T wave changes. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac diseases (see Special warnings and precautions).

Thrombocytopenia
Thrombocytopenia has been reported during post-marketing experience, particularly during treatment with Sandostatin® (i.v.) in patients with cirrhosis of the liver, and during treatment with Sandostatin® LAR®. This is reversible after discontinuation of treatment.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

Overdose
A limited number of accidental overdoses of Sandostatin® LAR® have been reported. The doses ranged from 100 mg to 163 mg/month of Sandostatin® LAR®. The only adverse event reported was hot flushes. Cancer patients receiving doses of Sandostatin® LAR® up to 60 mg/month and up to 90 mg/2 weeks have been reported. These doses were in general well tolerated; however, the following adverse events have been reported: frequent urination, fatigue, depression, anxiety, and lack of concentration. The management of overdosage is symptomatic.
List of excipients

Powder (Vial):
Poly(DL-lactide-co-glycolide)
Mannitol (E421)

Solvent (Prefilled syringe):
Carmellose sodium
Mannitol (E421)
Poloxamer 188
Water for injections

Please see the Summary of Product Characteristics.