PATIENT FOLLOW-UP DURING SANDOSTATIN® LAR® (OCTREOTIDE) THERAPY

DOSING ADJUSTMENTS FOR A PATIENT WITH ACROMEGALY WHO HAS NOT REACHED BIOCHEMICAL CONTROL

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 6-12.**
Consider the following patient

MEET PAUL

51-YEAR-OLD MAN BEING TREATED FOR HIS ACROMEGALY WITH SANDOSTATIN® LAR®

Current Condition:

Paul has received 3 injections of Sandostatin® LAR®. His GH and IGF-1 levels have decreased but are not controlled.

Current Treatment:

Sandostatin® LAR® 20 mg every 4 weeks

GH Level:

4.0 ng/mL

IGF-1 Level:

350 ng/mL

Symptoms:

A decrease in symptoms, including headaches, joint pain, and sweating.

Physician Recommendation:

Increase dose to Sandostatin® LAR® 30 mg every 4 weeks

Important Notes:

Paul is upset to learn his dose of Sandostatin® LAR® will need to be increased. He is concerned treatment isn’t working.

During medical therapy for acromegaly, biochemical control includes GH <2.5 NG/ML and IGF-1 normalized for age.

*In most patients, Sandostatin® LAR® markedly reduces the clinical symptoms of the disease, such as headache, perspiration, paresthesia, fatigue, osteoarthralgia, and carpal tunnel syndrome.

†Please see important dosing information on page 4.
WHAT SHOULD THE PATIENT KNOW?

Patients like Paul, who require dose escalations, should be reassured that dose increases are not a sign of failure. They only mean the current dose is not achieving the desired results expected since treatment initiation.

Sandostatin® LAR® is not a one-size-dose-fits-all treatment, and you can help ease patient concerns by letting them know1,4:

- Dose increases of Sandostatin® LAR® are not uncommon, and in fact are a normal part of treatment in many patients

- It can take some patients several months, even with dose changes, to reach biochemical control

Even though Paul has not reached his goal levels of GH and IGF-1, he can be reminded of other ways to tell if Sandostatin® LAR® is working1:

1. Biochemical testing. Even though Paul has not reached biochemical control, his GH and IGF-1 levels have decreased with treatment

2. Symptom control.* Paul has seen improvement in his symptoms since treatment initiation

*In most patients, Sandostatin® LAR® markedly reduces the clinical symptoms of the disease, such as headache, perspiration, paresthesia, fatigue, osteoarthralgia, and carpal tunnel syndrome.1
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

Upon completion of 3 months of treatment with Sandostatin® LAR®, patients should be assessed for biochemical (GH and IGF-1) and symptom control.

For a patient like Paul, who has not achieved biochemical control, the physician may consider:

- A dose increase to 30 mg of Sandostatin® LAR® every 4 weeks

Note: After 3 months of the 30-mg dose, the patient should be reassessed for biochemical and symptom control. The dose may be increased to 40 mg every 4 weeks for patients who have not reached treatment goals.

HELPING PATIENTS COPE WITH ACROMEGALY

Writing down feelings may relieve stress and help patients discover triggers to their bad days, such as symptoms that may make them react emotionally.

ENCOURAGE PATIENTS TO KEEP A JOURNAL OR NOTE UPDATES ON A CALENDAR.

A journal can also serve as a memory aid for patients at future doctor appointments. A detailed and accurate recollection of symptoms and side effects can help the doctor identify and address any disease or treatment-related concerns.

*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

Below are topics to discuss with your patients at follow-up visits for Sandostatin® LAR® treatment:

<table>
<thead>
<tr>
<th>Reason</th>
<th>Details</th>
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</thead>
<tbody>
<tr>
<td>Reasons for Sandostatin® LAR® dose changes</td>
<td>1</td>
</tr>
<tr>
<td>Identification of treatment response</td>
<td>1</td>
</tr>
<tr>
<td>– Decrease in GH and IGF-1 levels</td>
<td></td>
</tr>
<tr>
<td>– Decrease in symptoms</td>
<td></td>
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<tr>
<td>Biochemical control</td>
<td>1</td>
</tr>
<tr>
<td>– Patient’s goal GH and IGF-1 levels</td>
<td></td>
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<tr>
<td>Factors that may influence biochemical test results</td>
<td>5:</td>
</tr>
<tr>
<td>– Sleep, exercise, stress levels, food intake, and blood sugar level</td>
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<tr>
<td>Importance of continued monitoring and adherence to therapy</td>
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</tr>
<tr>
<td>Current symptoms</td>
<td>1</td>
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<tr>
<td>– Frequency, severity, and management</td>
<td></td>
</tr>
<tr>
<td>Treatment side effects</td>
<td></td>
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<td>Current medication list</td>
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</table>
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>
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</thead>
<tbody>
<tr>
<td></td>
<td>Common: Dyspepsia, vomiting, abdominal bloating, steatorrhea, loose stools, discoloration of feces.</td>
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<tr>
<td>Nervous system disorders</td>
<td>Very common: Headache.</td>
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<td></td>
<td>Common: Dizziness.</td>
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<tr>
<td>Endocrine disorders</td>
<td>Common: Hypothyroidism, thyroid disorder (e.g., decreased TSH, decreased total T4, and decreased free T4).</td>
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<tr>
<td>Hepatobiliary disorders</td>
<td>Very common: Cholelithiasis.</td>
</tr>
<tr>
<td></td>
<td>Common: Cholecystitis, biliary sludge, hyperbilirubinemia.</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Very common: Hyperglycemia.</td>
</tr>
<tr>
<td></td>
<td>Common: Hypoglycemia, impaired glucose tolerance, anorexia.</td>
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<tr>
<td></td>
<td>Uncommon: Dehydration.</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very common: Injection site reactions.</td>
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<tr>
<td></td>
<td>Common: Asthenia.</td>
</tr>
<tr>
<td>Investigations</td>
<td>Common: Elevated transaminase levels.</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common: Pruritus, rash, alopecia.</td>
</tr>
<tr>
<td>Respiratory disorders</td>
<td>Common: Dyspnea.</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Common: Bradycardia.</td>
</tr>
<tr>
<td></td>
<td>Uncommon: Tachycardia.</td>
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</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>Description of selected adverse reactions</th>
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<tbody>
<tr>
<td>Gallbladder and related reactions</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>Hypersensitivity and anaphylactic reactions</td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>
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.