

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203255Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: August 8, 2014

Reviewer: Carolyn L. Yancey, M.D., Senior Medical Officer, Division of Risk Management (DRISK)

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Subject: Evaluation to determine whether a REMS is necessary to ensure that the benefits of pasireotide long-acting release powder for injection outweigh the risks

Drug Name: SIGNIFOR® Long-Acting Release (pasireotide) for Injection

Therapeutic Class: Somatostatin Analog

Dosage and Form: Long-acting depot injection: 20, 40, and 60 mg, powder for suspension for (b) (4) intramuscular injection. Recommended initial dose is 40 mg by (b) (4) intramuscular (IM) injection once every 28 days.

Office of New Drugs: Division of Metabolism and Endocrinology Products

Application Type/Number: NDA 203-255 (b) (4)

Applicant: Novartis Pharmaceuticals Corporation (Novartis)

OSE RCM #: 2013-2665

1 INTRODUCTION

This Division of Risk Management (DRISK) review evaluates whether a risk evaluation and mitigation strategy (REMS) is needed for pasireotide (Signifor) proposed as a long-acting release (LAR) (b)(4) intramuscular (IM) injection for the treatment of adult patients with acromegaly (b)(4). This original New Drug Application (NDA) 203-255 was received by the Division of Metabolism and Endocrinology Products (DMEP) on November 15, 2013. This NDA includes a proposed risk management plan (RMP) that does not include a REMS.

2 BACKGROUND

Pasireotide, a second-generation somatostatin analog (SSA), is a peptide hormone known as somatotropin release-inhibiting factor. The inhibitory effect of somatostatin on growth hormone (GH) secretion underlies the rationale to develop a SSA to treat acromegaly. Pasireotide pharmacologic activity is by binding to four of the five (5) known somatostatin subtype receptors (SSTR), SSTR-1, SSTR-2, SSTR-3 and SSTR-5. Somatostatin receptors are strongly expressed in many solid tumors where hormones are excessively secreted, such as acromegaly, gastroenteropancreatic/neuroendocrine (GEP/NET) tumors and Cushing's disease.¹ The binding profile of pasireotide includes the potential to stimulate both SSTR-2 and SSTR-5 subtype receptors for inhibition of GH and insulin-like growth factor-1 (IGF-1) secretion.¹

Proposed Formulation and Dosage

The proposed, to-be-marketed formulation and strength for pasireotide is a long-acting depot injection: 20, 40, and 60 mg powder for suspension. The recommended initial dose is 40 mg, via (b)(4) IM injection, once every 28 days. Dose adjustment is based on biochemical response and tolerability.

The proposed labeling cites that pasireotide LAR injection should only be administered by a trained health professional and includes detailed Patient Information and Instructions for Use.

Acromegaly

Acromegaly is a rare, serious, and debilitating condition caused by chronic increased secretion of growth hormone (GH) secondary to a GH-secreting pituitary adenoma.² The basal GH secretion in patients with acromegaly is characterized by high levels with bursts of GH, in contrast to the healthy population who usually maintain low GH levels during the day that may range from undetectable to peak levels ≤ 15 $\mu\text{g/L}$ during sleep. The IGF-1, which mediates most of the growth-promoting actions of GH, is elevated with the log of the GH concentration.³ The diagnosis of acromegaly is confirmed by an increased

¹ NDA 203-255 Signifor LAR (pasireotide) Injection, Global Submit (GS), Module 1.16 Risk Management Plans (RMP), p10/138.

² Chanson P, Salenave S, Kamenicky P, et al (2009) Acromegaly. *Best Pract. Res Clin Endocrinol Metab*; 23: 555-74.

³ Chanson P, Salenave S (2008) Acromegaly. *Orphanet J Rare Dis*; 3:1-17.

serum GH concentration that is not suppressed following an oral glucose tolerance test (GTT) and by increased IGF-1 levels.⁴

Clinical signs and symptoms of acromegaly are secondary to the peripheral actions of GH and IGF-1, and the mass effect from the local tumor. Chronic excess GH and IGF-1 levels lead to progressive somatic disfigurement due to excessive skeletal growth (for example, frontal bossing, mandibular enlargement with prognathism, and widened spaces between the lower incisor teeth). The typical soft tissue enlargement seen with acromegaly includes widening of the hands and feet, increased shoe and glove size, ring tightening, coarse facial features with a large fleshy nose, and thickening of the skin, sometimes described as oily. Additional clinical findings include:

- Metabolic complications of increased blood glucose levels, hyper-insulinemia, diabetes, and dyslipidemia.
- Visual field defects and, in the case of a large tumor, hydrocephalus or focal epilepsy.
- Pan-hypopituitarism, hypertension, cardiac myopathy, colonic polyps, carpal tunnel syndrome, goiter, and respiratory complications (e.g. sleep apnea, upper airway obstruction) are known to occur with acromegaly.
- Symptoms may include headache, excessive sweating, arthralgia, paresthesia, and severe lethargy.^{2, 5, 6}
- In patients with adenomas, which co-secrete GH *and* prolactin, prolactin excess leads to infertility and gonadal and sexual dysfunction.
- In rare cases, tumors may co-secrete thyroid-stimulating hormone (TSH) leading to hyperthyroxinemia, or adrenocorticotrophic hormone (ACTH) excess leading to hypercortisolism.

As cited in the literature referenced in the NDA (see below footnotes), acromegaly affects 40 to 70 cases per million persons with an annual incidence of 3 to 4 new cases per million people.⁷ Due to the insidious onset, acromegaly is often diagnosed late, such as 4 to 10 years after the onset of signs and symptoms and later in life at approximately 40 years of age. The high prevalence of co-morbidities and complications at diagnosis show advanced disease suggesting that acromegaly is under-recognized and under-diagnosed.⁸

Armamentarium of Therapy for Acromegaly

Current medical treatment options for patients with acromegaly include somatostatin analogs (SSAs), GH antagonists, and dopamine agonists. The SSA's are the medical treatment of choice for acromegaly. Currently, there are only two FDA approved and marketed first-generation, SSAs for the treatment of acromegaly: octreotide (Sandostatin) and lanreotide (Somatuline).

⁴ Melmed S (2009) Acromegaly pathogenesis and treatment. J clin Invest; 119:3189-202

⁵ Kumar et al (2009) current therapy and drug pipeline for the treatment of patients with acromegaly. Adv Ther; 26:383-403.

⁶ Melmed S (2009) Acromegaly pathogenesis and treatment. J Clin Invest; 119:3189-202.

⁷ Holdaway IM and Rajasoorya C (1999) Epidemiology of acromegaly. Pituitary; 2:29-41.

⁸ Chanson P and Salenave S (2008) Acromegaly. Orphanet J Rare Dis; 3:1-17.

Octreotide and lanreotide act via the SST-2 receptor. According to the applicant and the Clinical Pharmacology Reviewers for this NDA (Sang Chung, Pharm.D. and Immo Zadezensky, Pharm.D.), octreotide and lanreotide have weak affinity for SST-3 and SST-5 receptors and no affinity for SST-1 and SST-4 receptors. Pasireotide, by comparison, has binding affinity that is 30 to 40 times higher for human SST-1 and SST-5 receptors, 5 times higher for human SST-3 receptor, and 2.5 times lower for human SST-2 receptor. Pasireotide binds with high affinity to four (4) of the 5 SST receptors.²

Signifor (pasireotide) LAR is currently not approved in any country. See the **Appendix**, to this review, **Table 1**, Class of Somatostatin Analog Products.

Risk Management Plans

As cited in the **Introduction** of this review, the applicant submitted a proposed RMP for pasireotide that includes a routine pharmacovigilance (PV) plan and does not include a proposed REMS. As of this review, the DMEP has not requested a consult from the Division of Pharmacovigilance (DPV) on the proposed RMP.

Generic Products for the Treatment of Acromegaly

The FDA is not aware of any abbreviated NDA (ANDA) submission for the treatment of acromegaly and/or of any patent challenges (though a patent challenge may occur at any time) for the two FDA approved drug products indicated for the treatment of acromegaly.

Concerns from the Division of Metabolism and Endocrine Products

- Increased risk of hyperglycemia-related events in the clinical trial experience with pasireotide LAR formulation compared with the active controls (octreotide and lanreotide).
- The DMEP proposes to keep the labeling for pasireotide LAR injection, if approved, as similar to the approved labeling for pasireotide solution for SC injection, indicated for the treatment of Cushing's disease. Currently, the DMEP does not plan to require a Medication Guide for pasireotide LAR, should this formulation be approved.

2.1 Regulatory History

The regulatory history specific to this NDA for pasireotide follows:

- December 14, 2012: Signifor (pasireotide) Solution for Injection (via SC injection) was approved by the FDA for the treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed. A Medication Guide is part of approved labeling of the Signifor Solution for Injection.⁹
- November 15, 2013: The applicant submitted the original NDA 203-255 for Signifor LAR Injection proposed for the treatment of patients with acromegaly.

2.2 Materials Reviewed

⁹ Signifor (pasireotide) Solution for SC Injection was approved on April 24, 2012 in the European Union for the treatment of Cushing's disease. Signifor (pasireotide) Solution was approved on December 14, 2012 for the same indication, Cushing's disease, in Switzerland.

- November 15, 2013: Original NDA 203-255 Signifor (pasireotide) LAR Injection, proposed for the treatment of patients with acromegaly (b) (4). This NDA includes a RMP (Module 1.16 Risk Management Plan).
- March 14, 2014: NDA 203-255 Signifor (pasireotide) LAR, 120-Day SUR of safety data collected up to cut-off date of June 3, 2013.¹⁰
- May 16, 2014: NDA 203-255 Signifor (pasireotide) LAR Mid-Cycle Review slides by Smita B. Abraham, M.D., Clinical Reviewer, DMEP.
- July 17, 2014: Interdisciplinary Review Team (IRT) for QT Studies Consultation: Thorough QT Study Review for Pasireotide LAR by Jiang Liu, Ph. D., Lian Ma, Ph. D., Qianyu Dang, Ph. D., and Michael Y. Li, Ph. D.

3 OVERVIEW OF THE CLINICAL DEVELOPMENT PROGRAM

The efficacy and safety of pasireotide LAR in acromegaly are derived from two pivotal, Phase (P) 3, randomized (R), studies comparing pasireotide LAR with active controls in a superiority design. Brief description of each study follows:

P3, Study C2305 is a multi-center, R, blinded (B), active control (AC), study of pasireotide LAR 40 mg (176 patients) versus (vs) octreotide LAR 20 mg (182 patients), every 28 days, in patients with acromegaly who have not been treated medically. Data includes:

- 12-month blinded, core phase
- \geq 13 months of treatment, extension (E) phase (74 patients continued pasireotide LAR; 46 patients continued octreotide LAR), including both patients who remained on the same treatment as in the core, and patients who crossed-over (81 patients crossed-over) to the other treatment in the extension phase because of inadequate response to the initial randomized treatment (pasireotide LAR or octreotide LAR). See the **Appendix**, to this review, **Figure 1**. Study 2305 Design.

P3, Study C2402 is a multicenter, R, parallel-group, 3-arm study of double-blind (DB), pasireotide LAR 40 mg and 60 mg, vs open label (OL) octreotide LAR 30 mg or lanreotide Autogel (ATG)¹¹ 120 mg in patients with inadequately controlled acromegaly. Study C2402 consists of a 24-week core phase and OLE phase with cut-off for each patient at Week (Wk) 24 (6 months).¹² Patients must have received \geq 6 months of treatment with the maximally indicated dose of octreotide LAR.

¹⁰ Safety data for the two Phase (P) 3 studies, C2305 and C2402; for the extensions of supportive P1 study C2110E1 with the cut-off date of July 31, 2013; and for the P2 Study B2201E with the cut-off date of July 4, 2013

¹¹ Lanreotide Autogel (ATG) 60 mg, 90 mg, and 120 mg is first-line treatment of acromegaly (ATG1 line) to further extend the duration of release of the active ingredient in this formulation.

¹² Patients had to have received at least 6 months of treatment with the maximally indicated dose of currently available SSAs, octreotide LAR 30 mg or lanreotide ATG 120 mg, and have inadequately controlled acromegaly defined as GH >2.5 $\mu\text{g/L}$ and IGF-1 $>1.3 \times \text{ULN}$ before randomization. Enrollment was stratified according to previous treatment (octreotide LAR or lanreotide ATG) and GH levels at Visit 1 (>2.5 $\mu\text{g/L}$ and ≤ 10 $\mu\text{g/L}$; and >10 $\mu\text{g/L}$)

Supportive efficacy and safety data with the pasireotide LAR and SC follow:

See the **Appendix**, to this review, **Table 2**. Clinical Studies in Patients with Acromegaly (that includes both the pivotal studies and supportive safety and efficacy studies).

Study Population and Demographics

In Study 2305, a total of 358 medically naïve patients were randomized: 176 patients in the pasireotide LAR 40 mg group and 182 patients in the octreotide LAR 20 mg group. Baseline demographics were balanced between treatment arms and the target population mean age is 45.5 years, with an equal proportion of men and women, 60% of patients were Caucasian, and the median time since diagnosis of acromegaly was 6 months. Less than half, (42.2%) of all patients, had prior pituitary surgery. Distribution of diabetic status at baseline was slightly higher in the octreotide LAR group (36.7%) vs the pasireotide LAR group (29.8%). In Study 2305, the majority of patients who crossed over to pasireotide LAR 40 mg were either diabetic or pre-diabetic (86.4%) while all patients (100%) who switched to octreotide LAR 20 mg were diabetic or pre-diabetic.

In Study 2402, a total of 191 inadequately controlled patients with acromegaly were randomized: 63 patients in the pasireotide LAR 40 mg group, 62 patients in the pasireotide LAR 60 mg group, and 66 patients in the active-control group. Demographics were balanced across the 3 treatment groups with the exception of a slight imbalance in diabetic status: pasireotide LAR 40 mg group (71.4%), pasireotide LAR 60 mg group (59.7%), and active control group (69.7%) were diabetic.

Efficacy Results - Study C2305: GH and IGF-1 Response at Month 12

The efficacy of pasireotide LAR was superior to that of octreotide LAR in medically naïve patients. Study C2305 achieved the primary efficacy endpoint: the proportion of responders (that is, patients with GH < 2.5 µg/L and normalized IGF-1 at the end of the 12-month blinded, core phase) was 31.3% (pasireotide LAR) and 19.2% (octreotide LAR). The odds ratio is (95% CI) of 1.942 (1.190, 3.168) in favor of pasireotide LAR ($p = 0.007$).¹³

The proportion of patients with a full-response (FR), including patients with IGF-1 below the lower limits of normal in the response definition at month 12 was higher in the pasireotide LAR arm (35.8%) than in the octreotide LAR arm (20.9%). The median duration of first response (for patients who achieved response) was twice as long in the pasireotide LAR arm (51.6 wks) than in the octreotide LAR arm (24.1 wks).

The majority of patients responding to pasireotide LAR achieved biochemical control with the 40 mg dose. A small proportion of patients, not achieving biochemical control with the 40 mg dose, had a dose increase to 60 mg and achieved biochemical control.⁹

During the conduct of Study C2305, two (2) sites were closed for critical Good Clinical Practices (GCP) violations. The applicant claims that additional sensitivity analyses were conducted for efficacy and safety in which a total of 22 patients were excluded; however,

¹³ NDA 203-255 Signifor (pasireotide) LAR, Global Submit (GS), Module 2.7.3, Clinical Efficacy, p 8/96

according to the applicant, the main analyses results were not affected by these GCP violations.¹⁴

Efficacy Results - Study 2402: Inadequately Controlled Patients

The primary objective was to compare the proportion of patients achieving biochemical control (GH < 2.5 µg/L and normalization of sex- and age- adjusted IGF-1) with pasireotide LAR 40 mg or pasireotide LAR 60 mg vs continued treatment with active control at Wk 24. Study C2402 achieved the primary objective for both pasireotide LAR doses: response rate (95% CI) at Wk 24 was 15.4% (7.63, 26.48) for pasireotide LAR 40 mg, 20% (11.0, 31.77) for pasireotide LAR 60 mg, and zero (0) in the active control arm. Both pasireotide LAR 40 mg (p = 0.0006) and pasireotide LAR 60 mg (p<0.0001) were found to be statistically significantly superior to the active control.¹⁵

Key Secondary Efficacy Results

In Study C2305 and C2402, pasireotide LAR is superior to octreotide LAR in normalizing IGF-1 levels. These results were discussed and concurred with by the Clinical Reviewer for this NDA, Smita Abraham, MD.

3.1 Clinical Safety

The clinical safety profile for pasireotide LAR is based on safety data collected from 491 patients with acromegaly exposed to pasireotide, of which 419 patients were treated with the pasireotide LAR formulation and 72 patients were treated with the SC formulation. Pooled safety data for patients treated with pasireotide LAR from Studies C2305 (after crossover) and C2402 (core) that were not adequately controlled on their previous SSA treatment are also included.

Supportive safety data is from Study C2110 (and extension Study C2110E/1) conducted with pasireotide LAR, and Study B2103 and B2201 (and extension Study B2201E/3) conducted with pasireotide SC formulation.

Exposure:

Medically Naïve Patients

- The mean duration of exposure (days) was 527.2 days [Standard Deviation (SD) 334.34] to pasireotide LAR (n=178 patients, medically naïve, Study C2305, up-to-crossover) and 414.6 days (190.01 SD) to octreotide LAR (n=180 patients).
- The median (min-max) number of injections was 13.0 (1.0 - 48.0) for pasireotide LAR and 13.0 (1.0-34.0) for octreotide LAR.
- After crossover in Study C2305, the mean duration of exposure was longer for pasireotide LAR (449.8 days) than for octreotide LAR (341.7 days).

Inadequately Controlled Patients

- The mean duration of exposure (Wks) to pasireotide LAR 40 mg (n=63 patients) was 23.67 Wks (2.461 SD), pasireotide LAR 60 mg (n=62 patients) was 23.28 Wks (3.471 SD), and active control (n=66 patients) was 24.45 Wks (2.581 SD).

¹⁴ NDA 203-255 Signifor (pasireotide) LAR, GS, Module 2.5, Clinical Overview, p14/77

¹⁵ NDA 203-255 Signifor (pasireotide) LAR, GS, Module 2.7.3, Clinical Efficacy, p 20/96

- The median (min-max) number of injections was 6 (3-6), 6 (1-6), and 6 (2-8), pasireotide LAR 40 mg, pasireotide LAR 60 mg, and active control, respectively.

Discontinuations

- In Study C2305, 297 patients (83%) completed the 12-month core phase. The proportion of patients who discontinued prior to month 12 was higher in the pasireotide LAR group (19.9%) than in the octreotide LAR group (14.3%). The most frequent reasons for discontinuation were AEs (pasireotide LAR: 8.0%; octreotide LAR: 3.3%) and protocol deviation (pasireotide LAR: 4.0%; octreotide LAR: 4.4%). Hyperglycemia or diabetes mellitus is the most frequent reason for discontinuation in Study C2305.

Discontinuation rates (month 12/core phase and month 26/extension phase) were higher in the pasireotide LAR (31.1%) group than in the octreotide LAR (21.7%) group. According to the applicant, the difference was mainly due to a higher incidence of consent withdrawal in patients treated with pasireotide LAR (12.2%) vs patients treated with octreotide LAR (4.3%). Most patients who withdrew consent elected to undergo pituitary surgery.

- In Study C2402, discontinuation rates in pasireotide LAR groups were higher (9% in 40 mg group and 12% in 60 mg group) than in the active control group (4%), mainly due to hyperglycemia or diabetes mellitus with pasireotide LAR treatment: 2 patients and 4 patients, 40 mg and 60 mg group, respectively.

Adverse Events:

Medically Naïve Patients (Study 2305)

The AEs \geq 5% in the pasireotide LAR group were mostly related to glucose metabolism: hyperglycemia, diabetes mellitus, blood glucose increased, and type 2 diabetes mellitus. The AEs that were less frequent in the pasireotide LAR group than the octreotide LAR group were mostly related to GI disorders: diarrhea (39.9% vs 45%), cholelithiasis (32.6% vs 39.4%), abdominal pain (18.5% vs 24.4%), nausea (15.2% vs 22.8%), and constipation (5.6% vs 10.6%).¹⁵

The most common Grade 3 to 4 AEs in the pasireotide LAR group were: hyperglycemia (9%), diarrhea (0.6%), and Gallbladder (GB)/Biliary events (1.7%).

The most common Grade 3 - 4 AEs in the octreotide LAR group were: hyperglycemia (1.7%), diarrhea (0.2%), and GB/Biliary events (1.1%). These data are confirmed with the Clinical Reviewer, Smita Abraham, MD, DMEP, and are the same data presented at the Mid-Cycle Meeting.

Inadequately Controlled Patients (Study C2402)

In Study C2402, Metabolism and Nutrition disorders was the most frequent SOC in all 3 treatment groups AEs. The three most common AEs in the pasireotide LAR, 40 mg and 60 mg groups, respectively, were hyperglycemia (33.3% and 30.6%) and diabetes mellitus (20.6% and 25.8%), followed by diarrhea (15.9% and 19.4%). In the active control group, the most common AEs were: hyperglycemia and cholelithiasis (13.6% each), and diabetes mellitus (7.6% each).

In Study C2305 (after crossover), events were similar to those reported in Study C2402. The most frequent AEs were: hyperglycemia (57.3%), diarrhea (39.3%) and GB/biliary events (30.9%) in the pasireotide LAR group vs hyperglycemia (21.7%), diarrhea (45%) and GB/Biliary (38.9%) in the octreotide LAR group.

Deaths

There were a total of four (4) deaths reported in Study C2305 during treatment (within 56 days of the last LAR injection). There were no deaths reported during the core treatment phase of Study C2402; no deaths were reported in P1 trials B2201, B2201E, and C2110. See **Appendix, Section C, Table 3**, Deaths due to Grade 5 events in Pasireotide LAR Clinical Development Program in Acromegaly.

Adverse Events of Special Interest

The applicant reports that AEs of special interest occurred with $\geq 5\%$ difference and with a higher incidence in the pasireotide LAR group were all hyperglycemia-related (57.3% vs 21.7%, octreotide LAR). Diarrhea-related, GB/Biliary-related, and nausea-related AEs occurred with higher frequency in the octreotide LAR group (data confirmed with the Clinical Reviewer, Smita Abraham, MD, DMEP). The data up-to-crossover and after crossover are comparable. In the after crossover phase, there was an increased frequency of rhabdomyolysis-related events, (15.8% with octreotide LAR vs 8.6% with pasireotide LAR), and pancreatitis (10.5% with octreotide LAR vs 3.7% pasireotide LAR).

Additional events of special interest follow:

- **Alopecia:** The Class of SSA products is known to cause alopecia. In Study C2305, alopecia is reported as 18% and 19.4% of patients in the pasireotide LAR group and octreotide LAR group, respectively. In Study C2402, alopecia is reported as 1.6% and 6.5%, pasireotide 40 mg and 60 mg, respectively; no alopecia was reported in the active control group. This later outcome may be due to the finding that all patients in Study C2402 had prior SSA exposure to with development of alopecia, prior to study entry.
- **Glucose Metabolism:** Hyperglycemia-related AEs¹⁶ [includes the Preferred-Terms from Meddra] was the only category more frequent ($\geq 5\%$) in the pasireotide group (63.5%) vs 25.0% in the octreotide group. Hyperglycemia events tended to occur during the first 3 months of pasireotide LAR treatment (0 to 3 months: 47.8%; 3 to 6 months: 20%; 6 to 12 months: 18.5%; > 12 months: 24.3%). The trend was less apparent with octreotide LAR treatment: (0 to 3 months: 12.8%; 3 to 6 months: 7.6%; 6 to 12 months: 11.3%; > 12 months: 10%). Hyperglycemia-related AEs appeared to be reversible after stopping pasireotide LAR. The incidence of hyperglycemia is slightly higher in patients previously exposed to SSA therapy.

Hemoglobin A1c (HbA1c) levels followed fasting plasma glucose (FPG) levels and mean HgA1c values increased by 0.90% between baseline and month 3 in the

¹⁶ Hyperglycemia-related AEs refers to a collection of Preferred Terms (PT) from the Medical Dictionary for Regulatory Activities (MedDRA). See NDA 203-255, Signifor (pasireotide) LAR, GS, Module 2.7 Clinical Summary, Subsection 2.7.4, Section 2. Adverse Events, 2.1.1 Standardization of terms and use of dictionaries, Table 2-1. MedDRA versions

pasireotide LAR group, then, gradually decreased up to Month 12 and beyond for patients in the extension study.

- **Gallbladder and Biliary System:** GB/biliary system AEs are a known AE associated with the class of SSAs. GB/biliary AEs occurred more commonly with octreotide LAR treated patients (16.7%) vs pasireotide LAR 60 mg treatment (14.5%) and pasireotide LAR 40 mg treatment (12.7%).
- **Liver Safety Events:** Liver AEs in the medically naïve patients following pasireotide LAR treatment occurred during the first 3 months of treatment in 14 patients (7.9%), between 3 to 6 months in 5 patients (3%), 6 to 12 months in 6 patients (3.8%), and after 12 months in 7 patients (6.3%). In the inadequately controlled patients, 4 patients had AEs related to liver safety: 2 patients in the pasireotide LAR 40 mg group (ALT increased, liver chemistry test abnormal), 1 patient in the pasireotide LAR 60 mg group (ALT and GGT increased) and 1 patient in the active control (AST and GGT increased).¹⁷ Most cases were mild and events resolved without sequelae.
- **Bradycardia/QT Prolongation:** The AEs of bradycardia ($\geq 5\%$) were: pasireotide LAR (15.2%) and octreotide LAR (13.3%). There was no Grade 3 to 4 bradycardia event with pasireotide LAR vs 0.6% with octreotide LAR.

The QT prolongation AEs were reported with pasireotide LAR (6.7%) vs octreotide LAR (5.6%). Grade 3 to 4 AEs were reported with pasireotide LAR (1.1%) vs octreotide LAR (0.6%). QT-prolongation events were low and no increase in the incidence or severity of QT related AEs observed in the extension phases. To-date, there are no cases of torsade de pointes reported in the pasireotide clinical trials.

The TQT-IRT Consult (dated July 17, 2014) reports that pasireotide SC is shown to have significant QTc prolongation effect detected with doses of 0.6 mg and 1.95 mg twice-a-day, respectively. Although the QT prolongation is dose-related, there is a time lag (~ 2 hours) between the peak in pasireotide concentration and peak QT effect. With the LAR formulation, the C_{max} following the highest therapeutic LAR dose is similar to that of the 0.6 mg bid therapeutic dose in the TQT study. The TQT-IRT expects that the QT effect of the LAR formulation is likely to be covered by those observed with the SC solution. The applicant completed concentration-QT analyses in Study C2305 and C2402 using the LAR formulation in patients with acromegaly. No significant QT effect was observed.¹⁸

The TQT-IRT and the applicant recommend caution with pasireotide LAR exposure in patients with hepatic impairment because the area under the curve (AUC) increased by 60% to 70%, and C_{max} is increased by 67% and 69%, respectively, relative to the active control group. Proposed labeling recommends avoiding pasireotide LAR in severe hepatic impaired patients with acromegaly.

¹⁷ ALT - alanine transaminase; AST - aspartate transaminase; GGT - gamma-glutamyl transpeptidase.

¹⁸ See TQT-IRT Consult Review (dated July 17, 2014) in DARRTS. Authors of this consult review are cited in Section 2.2 Materials Reviewed, of this review.

There were no significant differences in the rates of high and low systolic or diastolic blood pressure between pasireotide LAR and octreotide LAR in the core phase of Study C2305 or C2402.

- **Weight Changes:** A decrease in weight $\geq 10\%$ was observed in 5.1% vs 4.4% of patients treated with pasireotide LAR vs octreotide LAR. The weight decrease following pasireotide LAR treatment may be due to decreases in IGF-1 levels.
- **Pituitary Hormone Function:** In Study C2305, 88.8% of patients had normal thyroid-stimulating hormone (TSH) levels at study entry. The frequency between hypothyroidism-related AEs was similar between pasireotide LAR (13 patients; 7.3%) and octreotide LAR (11 patients; 6.1%). The most frequent pituitary function AE was hypothyroidism (6 patients in each treatment group).

In Study C2402, 74.6%, 83.9% and 75.8% of patients in the pasireotide LAR 40 mg, 60 mg, and active control groups, respectively, had normal TSH at study entry. Among these patients 6.4%, 1.9% and 14% of patients had a TSH value that was below normal limits during the study. No hypothyroid-related AEs were reported in Study C2402.

- **Hypocortisolism:** In Study 2305, hypocortisolism was reported in 7 patients (with 8 events of decreased cortisol/adrenal insufficiency). Two of these 7 patients had a history of adrenal insufficiency prior to enrolling in Study C2305. Among the remaining 5 patients, 4 events of hypocortisolism occurred in the core phase (2.2%) and 1 event in the extension phase. In study C2402, 1 patient was reported with hypocortisolism. There were 5 cases of decreased cortisol/adrenal insufficiency reported in the octreotide LAR group, 1 case was reported as an SAE.

120-Day Safety Update Report

The safety profile of pasireotide LAR in patients with acromegaly remains unchanged compared with the observed AEs reported in the original NDA. In the 120-Day SUR, cholelithiasis increased with increased exposure, not an unexpected trend with SSAs. In Study C2402, GB/biliary-related AEs increased by slightly more than 5% in patients randomized to the pasireotide LAR treatment group.

One additional death occurred in a 26-year old male, pasireotide LAR 40 mg treatment group, in Study 2402. His fatality on Day 410 was attributed to sudden death (see the **Appendix**, to this review, **Table 3** for brief details of this case).

4 DISCUSSION

The class of somatostatin analogs, SSAs, is the current medical treatment of choice for patients with acromegaly. The two commercially available, first-generation SSAs, octreotide and lanreotide, have weak affinity across the 5 SST receptors compared with the proposed pasireotide LAR with have high affinity for 4 of the 5- SST receptors.

The proposed pasireotide LAR formulation achieved superiority to octreotide LAR in medically naïve patients based on the proportion of responders (GH < 2.5 $\mu\text{g/L}$ and normalized IGF-1 at 12-months) and in patients inadequately controlled on previous SSA therapy. Reduction of GH and IGF-1 levels occur within the first 3 months of treatment and appear to be sustained as demonstrated in the extension phases of the clinical trials.

The proposed administration schedule for pasireotide LAR, every 28 days, is the same administration schedule approved for octreotide LAR and lanreotide LAR.

The safety profile of the pasireotide LAR formulation is consistent with the class of SSAs with the exception of a higher degree and frequency of hyperglycemia events compared with the active controls, octreotide LAR and lanreotide LAR. The risks for the two FDA approved products (octreotide LAR and lanreotide depot injection) for the treatment of acromegaly are communicated via labeling and routine pharmacovigilance. As of this review, neither of these two products for acromegaly has a REMS.

The most important serious safety risks reported with the pasireotide LAR formulation are: hyperglycemia and diabetes, cholelithiasis and GB related events, bradycardia and QT prolongation, liver test elevations, deficiency of pituitary hormones, and hypocortisolism.

- Based on the clinical trials in this NDA, hyperglycemia-related events appear to be a greater risk in patients with uncontrolled diabetes mellitus prior to pasireotide LAR exposure. If pasireotide LAR should be approved, early and close monitoring of serum glucose is recommended in the first three-months of therapy and, periodically, particularly, in patients at-risk for elevated serum glucose levels.
- Cholelithiasis is a known AE associated with exposure to SSAs and is consistent with the reported AEs in these clinical trials.
- The risk of bradycardia is reported with use of pasireotide LAR (15.2%) compared with octreotide LAR (13.3%); however, there were no Grade 3 to 4 bradycardia events reported with exposure to pasireotide LAR. If this formulation is approved, patients with cardiac disease and/or risk factors for bradycardia, high-grade heart-block, or concomitant use of drugs associated with bradycardia will need to be carefully monitored with pasireotide exposure.

QT prolongation is considered a class effect of SSAs. There was no significant QT effect observed in the clinical trials with pasireotide LAR in acromegaly. The TQT-IRT reviewers and the applicant recommend that proposed labeling include text to avoid pasireotide LAR in patients with severe hepatic impairment and recommend use of a lower starting dose in patients with moderately impaired hepatic function with the option to up-titrate based on clinical response.

- Liver test elevations with pasireotide LAR were mild and transient and no cases of Hy's law were reported in the clinical trial safety data. Hepatic safety with pasireotide is not a new risk as cited in labeling for Signifor (pasireotide) Solution, Warnings and Precautions section, recommending that liver tests be evaluated prior to and during pasireotide treatment.
- The risk of pituitary hormone abnormalities is known to occur with the class of SSAs. The risk of hypothyroidism-related AEs was similar between pasireotide LAR and octreotide LAR and not unexpected with pasireotide LAR therapy. There was no major difference between pasireotide LAR and the active controls regarding ACTH and cortisol reduction. The DMEP acknowledges that it is unclear if there is a direct cause-and-effect relationship between pasireotide LAR and development of adrenal insufficiency. Given that the mechanism of action of pasireotide is through pituitary

somatostatin receptors known to lower ACTH levels, adrenal insufficiency must be considered a serious safety risk with use of the proposed pasireotide LAR formulation.

As cited in the **Introduction** of this review, the applicant submitted a RMP for pasireotide LAR proposed for the treatment of adult patients with acromegaly (b) (4)

The DMEP did not require the applicant to submit a proposed REMS for pasireotide LAR in this NDA. The applicant proposes to manage the reported serious risks with pasireotide LAR with routine pharmacovigilance and labeling that includes Patient Information and Instructions for Use. The proposed pasireotide LAR labeling, Warnings and Precautions section, includes the 6 key serious risks observed in the clinical trials with use of pasireotide LAR and is consistent with the Warnings and Precautions section of Signifor (pasireotide) Solution for SC injection approved for the treatment of Cushing's disease.

The rationale for the conclusion that a REMS is not required for pasireotide LAR follows:

- The NME, Signifor (pasireotide diaspertate) Solution for SC injection, was approved December 14, 2012 under NDA 200-677 without a REMS for the treatment of Cushing's disease. Labeling for Signifor Solution includes Patient Counseling Information with the same 6 serious risks that are proposed in labeling for pasireotide LAR injection. A Medication Guide is not part of the approved labeling for Signifor Solution. No new safety signals have been reported with Signifor Solution via routine postmarketing pharmacovigilance (confirmed with the Ramon Dragos, MD, Team Leader for this NDA in the DMEP).
- The reported safety profile of pasireotide LAR is comparable to pasireotide SC formulation. However, pasireotide LAR demonstrated increased reporting of hyperglycemia-related events compared with the active control, octreotide LAR, in the clinical development program for acromegaly. This risk management of hyperglycemia will be communicated to prescribers via labeling, if this formulation should be approved.
- According to the Clinical Reviewer in DMEP, the risk of serious liver events is less with pasireotide LAR vs pasireotide SC formulation and the incidence of nausea is significantly less with pasireotide LAR compared with pasireotide SC solution. The proposed order of serious risks in the proposed pasireotide LAR labeling lists hyperglycemia and diabetes first, followed by the serious risks of bradycardia and QT prolongation, liver test elevations, cholelithiasis, deficiency of pituitary hormones, and hypocortisolism.
- The target providers for the proposed pasireotide LAR are most likely the same providers as for pasireotide solution, in particular, endocrinologists and/or internal medicine and family practice/general practice physicians. Physicians who prescribe pasireotide solution for SC injection are familiar with the known serious risks associated with SSAs and, as cited above, the same key serious risks are reported with pasireotide LAR in this NDA.

5 CONCLUSION

The DRISK and the DMEP concur that the benefit risk profile of the proposed pasireotide LAR formulation for the treatment of patients with acromegaly ^{(b) (4)} is acceptable and, based on the reported data, a REMS is not necessary, at this time, to ensure that the benefits outweigh the risks. The DMEP should consult the DRISK if additional safety information is identified that warrants re-evaluation of the risk management measures for pasireotide LAR Injection.

APPENDIX

See **Table 1.** Class of Somatostatin Analog Products (on the next page)

Class of Somatostatin Analog Products			
Product	SIGNIFOR LAR	Sandostatim LAR Inject	Somatuline Depot Injection
Est. Name/ Route Adm.	Pasireotide/ $\text{\textcircled{S}}$ IM Inject.	Octreotide Acetate/ Deep SC/IV Inject	Lanreotide Acetate/ Deep SC Inject
NDA/ Approval Date	203-255 / Pre-Approval Rev.	019-667 / 25-Nov-98	022-074 / 30-Aug-07
NME	No (New Dosage Form)	No (New Dosage Form)	Yes
Indication	1) Tx of pts w/acromegaly $\text{\textcircled{S}}$ $\text{\textcircled{S}}$ $\text{\textcircled{S}}$ $\text{\textcircled{S}}$	1) For tx in pts who have responded to tolerated Sandostatim SC Inject. For: a) Acromegaly b) Severe diarrhea/flushing episodes assoc. w/metastatic carcinoid tumors; c) Profuse watery diarrhea assoc. w/ VIP-secreting tumors.	1) For long-term tx of acromegalic pts who have had inadequate response to or cannot be tx w/ surgery and/or radiotherapy.
Boxed Warning	None Proposed	None	None
Warnings & Precautions	Hyperglycemia and Diabetes: Intensive glucose monitoring is recommended and may require initiation or adjustment of anti-diabetes treatment; Bradycardia & QT Prolong Use w/caution in at-risk pts, ECG testing prior to dosing and on treatment; Liver Test Elevations: Evaluate liver tests prior to/during tx. Cholelithiasis: Pts should be monitored periodically.	Gallbladder Abnormalities may occur - monitor periodically; Glucose Metabolism: Hypoglycemia or hyperglycemia may occur. Glucose monitoring is rec. and anti-diabetic tx may need adjustment; Thyroid Function: Hypothyroidism may occur - monitor periodically; Cardiac Function: Bradycardia, arrhythmia or conduction abnormal. may occur. Use w/caution in at-risk pt.	Cholelithiasis & Gallbladder Sludge; Hyperglycemia & Hypoglycemia; Thyroid Function Abnormalities; Cardiovascular Abnormalities; Sinus bradycardia; Hypertension Drug Interactions; Monitoring Laboratory Tests.
Contraindications	None Proposed	None	None
PPI	Proposed PI (reads as MG)	Yes, PI (minimal information)	Yes, PI (reads as MG)
Instructions for Use	Proposed IFU	None	None
Medication Guide	None Proposed	None	None
REMS	None Proposed	None	None
Abbreviations: ECG-Electrocardiogram; Eval-evaluate; IFU-Instructions for Use; IM-Intramuscular; Inject-Injection; IV-Intravenous; LAR-long-acting release; NDA-new drug application; NME-new molecular entity; MG-Medication Guide; Pts-patients; PI-Patient Instructions; PPI-Patient Prescribing Information; REMS-Risk Evaluation and Mitigation Strategy; Rev-review; SC-Subcutaneous; Tx-Treatment; VIP-Vasoactive Intestinal Peptide; w-with.			

- **Sandostatin Long-Acting Release (LAR) Depot** (octreotide acetate injectable suspension) is available as a microsphere formulation administered by ^{(b) (4)} intra-gluteal injection every 4 weeks (for 3 months).
- **Somatuline Depot (lanreotide) Injection** is available in a microsphere formulation sustained-release (SR) and a saturated aqueous solution [Autogel (ATG)] administered every 4 weeks (for 3 months). The recommended initial injection frequency is every 2 weeks for the SR formulation and every 4 weeks for the ATG formulation.¹⁹

Figure 1. Study Design of Study 2305 Incorporating Amendment 4

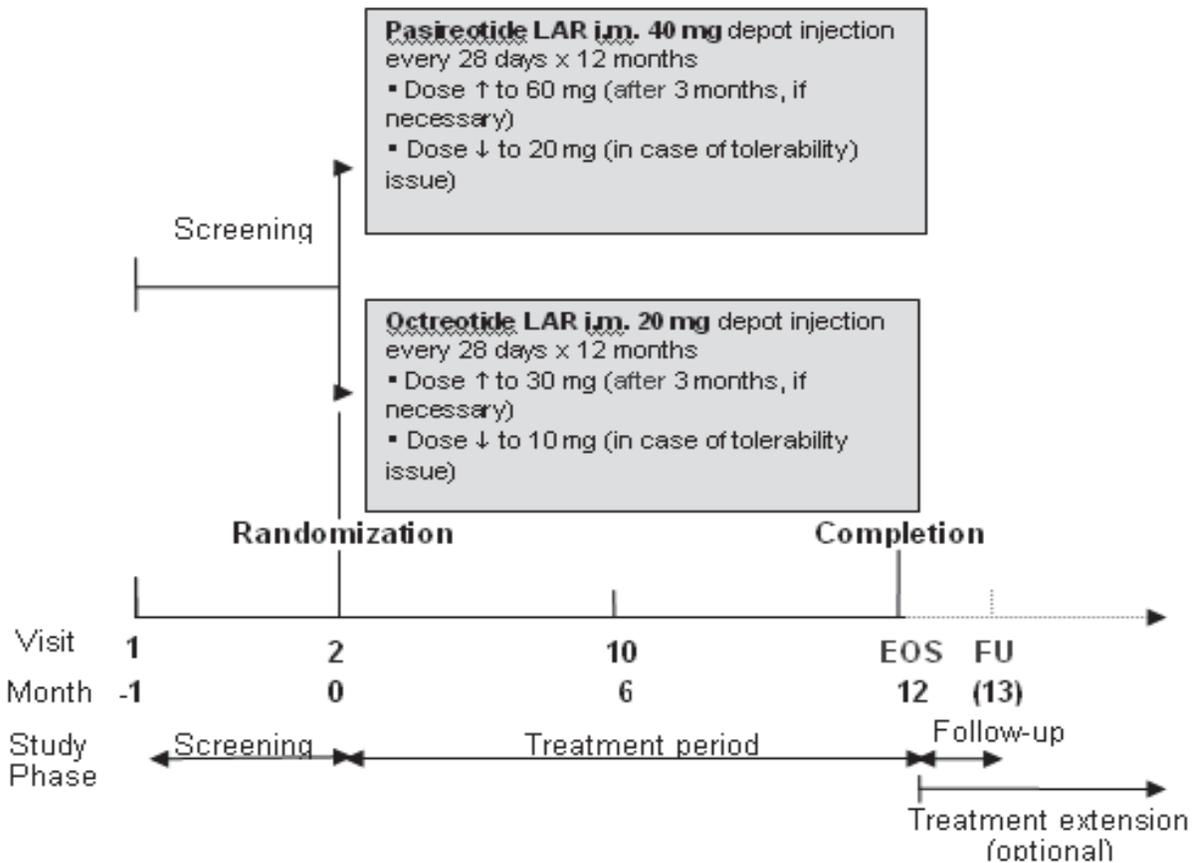


Figure is from the draft Clinical Review of NDA 203-255 Signifor (pasireotide) by Smita Abraham, MD, DMEP, and is modified from NDA 203-255, Signifor (pasireotide) in GS, Module 2.5 Clinical Overview, Sub-Section 4.2.1 Study Design, p 26 of 77.

Table 2. Pasireotide Clinical Studies in Patients with Acromegaly

Study	Study Design	Safety Data Set	Treatment Duration	Dosing Regimen
C2305	P3, B, AC, R study to access efficacy, safety, OL, PK, PK/PD relationship	Core & Ext up to crossover (CO): Pasireotide LAR: 178 pts Octreotide LAR: 180 pts	12 Months (Core) 14 Months (Ext.)	Pasireotide LAR q 28d: 40 mg Octreotide LAR q 28d: 20 mg
		Extension p CO: Pasireotide LAR: 81 pts Octreotide LAR: 38 pts	13 months	
C2402	P3, DB, 40 mg or 60 mg pasireotide LAR vs OL octreotide LAR or lanreotide ATG to assess efficacy and safety	Core Pasireotide LAR 40 mg: 63 pts Pasireotide LAR 60 mg: 62 pts.	24 Weeks	Pasireotide LAR q 28d: 40 mg Pasireotide LAR q 28d: 60 mg Octreotide LAR q 28d: 30 mg Lanreotide ATG q 28d: 120 mg
C2110	P1, OL, R study assessing PK, safety, and tolerability profiles of 3 doses of pasireotide LAR	35 pts	3 Months	Pasireotide LAR q 28d: 20, 40, or 60 mg
C2120E	OL, Ext Study C2110 to assess long-term safety, PK/PD profiles	29 pts	Dependent on clinical benefit	Pasireotide LAR q 28d: 20 mg, 40 mg, or 60 mg; Dose adjustment permitted
B2201	P2, OL, R, CO study in pts w/acromegaly of multiple doses of pasireotide and octreotide SC	60 pts	Octreotide SC for 28d followed by pasireotide 200 µg, 400 µg, or 600 µg bid for 28 d in Period 1; pts progressed to remaining pasireotide SC doses in Period 2, and 3.	Octreotide SC: 100 µg tid Pasireotide SC: 200 µg bid, 400 µg bid, and 600 µg bid
B2201E	OL ext of B2201	30 pts	17 d; 3 SD inject.	Pasireotide SC: 200 µg bid, 400 µg bid, and 600 µg bid
B2103	P2, DB, R, CO	12 pts		Octreotide SC: 100 µg SD Pasireotide SC: 100 µg, 250 µg SD
Abbreviations: CO-crossover; Tx-treatment, SD-single-dose;				

Table 3.

Deaths in Pasireotide LAR Clinical Development Program for Treatment of Acromegaly

Study Drug Treatment Group	Summary Description
<p>Core Phase, Study C2305: Octreotide LAR 20 mg switched to ↓ Pasireotide LAR 40 mg</p>	<p>74-year old male, Caucasian, with acromegaly. First dose 20 mg octreotide LAR on (b) (6). Non-responder at 12 months; switched to 40 mg pasireotide LAR on (b) (6) (Day 377). Last dose of 40 mg pasireotide LAR on (b) (6) (Day 908). Patient death on (b) (6) (Day 931) causally attributed to aortic aneurysm rupture.</p>
<p>Core Phase, Study C2305: Octreotide LAR 20 mg increased to ↓ Octreotide LAR 30 mg</p>	<p>58-year old female, Caucasian, with acromegaly, diagnosed June 2002. Pituitary surgery (b) (6). First dose 20 mg octreotide LAR (b) (6) baseline ECG with ventricular premature complexes evaluated as normal. Switched to 30 mg octreotide LAR due to lack of efficacy with octreotide LAR 20 mg dose. Cardiac hypertrophy (Grade 1) noted November 2008. (b) (6) she was hospitalized due to myocardial infarction (MI); she died on the same day. Death (Day 256) causally attributed to the MI/cardiac hypertrophy.</p>
<p>Extension Phase, Study C2305 Octreotide LAR 20 mg</p>	<p>33-year old female, Caucasian, with acromegaly. First study drug on (b) (6); completed core phase on (b) (6). Study drug stopped on January 7, 2011. Day 411 (b) (6), she had diarrhea (Grade 3) and septic shock (Grade 4). A convulsion was reported on Day 415 (b) (6) and she was hospitalized with sepsis (urinary track infection, hypotension, tachycardia, tachypnea, stupor, and abdominal pain). Day 417 (b) (6), she was diagnosed with acute renal failure. Patient died on (b) (6) with diarrhea, septic shock, renal failure acute, lung infiltration, cardiac arrest, and multi-organ failure. Death (day 421) causally attributed to septic shock.</p>
<p>Extension Phase, Study C2305 Pasireotide LAR 40 mg Increased to ↓ Pasireotide LAR 60 mg</p>	<p>45-year old male, race cited as “other”, with acromegaly. First study drug, 40 mg pasireotide LAR, on (b) (6); dose increased to 60 mg due to lack of efficacy. The patient completed the core phase and entered the extension phase on day 337 (b) (6). On Day 352 (b) (6), patient noted with major depression (Grade 4) associated with persecution after a constraint situation at work. No action taken with study drug. Patient committed suicide by setting himself on fire with gasoline on Day 361 (b) (6). Death (Day 361) attributed to major depression ongoing at time of death.</p>
120-Day SUR	
<p>Extension Phase, Study 2402 Pasireotide LAR 40 mg</p>	<p>26-year old male, had active medical conditions of hypopituitarism, diabetes insipidus and adrenal insufficiency. Autopsy revealed features of sudden death with hyperemia and pulmonary edema, cholelithiasis. The brain showed marked signs of edema, hyperemia and edema of the meninges.</p>

See NDA 203-255 pasireotide, GS, Module 2.7.4, Subsection 2.1.6 Serious AEs, page 61 of 153; and 120-Day SUR, Module 2.7., Table 2-11, page 34 of 65.

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/s/

CAROLYN L YANCEY

08/08/2014

REMS Review, NDA 203-255 SIGNIFOR (pasireotide) Long Acting Release for Injection in adult patients with acromegaly

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08/08/2014

Concur