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RESEARCH**

APPLICATION NUMBER:

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**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 Management Options Review Addendum

Date: 11/27/2012

Reviewer(s): Amarilys Vega, M.D., M.P.H, Medical Officer
Division of Risk Management (DRISK)

Team Leader: Cynthia LaCivita, Pharm.D., Team Leader
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Drug Name(s): Pasireotide (Signifor[®])

Therapeutic Class: Somatostatin analog

Dosage and Route: 0.3 mg, 0.6 mg, or 0.9 mg, subcutaneous (s.c.) injection

Application Type/Number: 200677

Submission Number: 0001, 0004, 0010, 0017

Applicant/sponsor: Novartis

OSE RCM #: 2012-588

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION

This review is an addendum to DRISK's review dated October 16, 2012 with the objective of documenting DRISK's recommendations for the management of the risks associated to pasireotide (Signifor®). Novartis is seeking approval of pasireotide for the treatment of patients with Cushing's disease who require medical therapeutic intervention.

2 ADVISORY COMMITTEE RECOMMENDATIONS

On November 7, 2012, FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted unanimously (10:0) in favor of approval of pasireotide for the treatment of Cushing's Disease. Panel members expressed concern about pasireotide-induced hyperglycemia and the potential of hepatotoxicity and recommended close monitoring of blood glucose, HbA1c, and transaminases for all patients treated with pasireotide. In addition, committee members expressed their support for the conduct of a clinical study proposed by the sponsor to determine the effectiveness of intense management of pasireotide-induced hyperglycemia and for an observational study to evaluate these risks further.

3 PROPOSED POST MARKETING REQUIREMENTS

The following PMRs will be developed and implemented by the sponsor to expand our understanding of pasireotide's safety profile and the management of pasireotide-induced hyperglycemia.

- Clinical study – to evaluate the management of pasireotide-induced hyperglycemia.
- Observational cohort study – to assess serious cases (i.e., treatment in emergency department, hospitalization, or death) of hyperglycemia, liver-related adverse events, deaths, (b) (4) and events potentially related to QT prolongation), atypical infections, and adrenal insufficiency.
- Enhanced pharmacovigilance – to monitor reports of serious (treatment in emergency department, hospitalization, or death) hyperglycemia, acute liver injury, and adrenal insufficiency in patients with Cushing's disease treated with pasireotide for a period of (b) (4) from the date of approval to collect data that will be analyzed to better define these risks.

4 DRISK CONCLUSIONS AND RECOMMENDATIONS

There is an unmet medical need for the treatment of Cushing's Disease and the clinical development program showed pasireotide is effective in the treatment of this disease. The Division of Metabolism and Endocrinology Products (DMEP) determined that the benefits of pasireotide for the treatment of Cushing's Disease exceed the risks associated with its use, including the risk of hyperglycemia/diabetes and the potential risk of liver injury.

The risk management plan initially proposed by the sponsor consisted of labeling and routine pharmacovigilance. DRISK does not recommend a Risk Evaluation and Mitigation Strategy (REMS) for the management of the risks associated with pasireotide for the following reasons: (1) Cushing's disease is primarily managed by healthcare providers familiar with the treatment of this disease; and (2) the general adverse event profile of pasireotide is similar to that of other drugs in the class (i.e., octreotide and lanreotide) which are managed through labeling and routine pharmacovigilance, with the notable exception of the drug-induced hyperglycemia and the potential risk of liver injury. The risk of hyperglycemia and elevation of transaminases will be addressed in the Warnings and Precautions section of the label along

with the risks for hypocortisolism and deficiency of pituitary hormones¹, cardiovascular-related events², gallbladder abnormalities², and drug-drug interaction with cyclosporine.³ Pasireotide is contraindicated in patients with severe hepatic impairment (Child Pugh C).⁴

DRISK concurs with DMEP that the management of the risks associated with treatment of pasireotide, including the risks of hyperglycemia and potential liver injury, can be managed at this time through labeling and postmarketing requirements (PMRs) developed to further assess the risks. If new safety information becomes available, the proposed risk management options may need to be reassessed.

¹ Consistent with pasireotide's mechanism of action.

² Also observed in octreotide and lanreotide.

³ Pasireotide product label draft, November 21, 2012.

⁴ Child Pugh class, based on Child-Pugh scores, is used as a classification of chronic liver disease.

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**Department of Health and Human Services
Public Health Service
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Risk Management Options Review

Date: 10/16/2012

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Division of Risk Management (DRISK)

Team Leader: Cynthia LaCivita, Pharm.D., Team Leader
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1 INTRODUCTION

This review documents DRISK’s evaluation of the proposed Risk Management Plan (RMP) for pasireotide (Signifor®). Novartis is seeking approval of pasireotide for the treatment of patients with Cushing’s disease who require medical therapeutic intervention.

On January 19, 2012, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorization for Signifor, 0.3 mg, 0.6 mg, 0.9 mg, solution for injection, for the treatment of Cushing’s disease.

1.1 BACKGROUND

*Cushing’s disease.*¹ Cushing's syndrome, is considered a rare disease (incidence of 1-2/100,000 population per year), results from chronic exposure to excess glucocorticoids of any etiology and could be adrenocorticotrophic hormone (ACTH)-dependent (e.g., pituitary corticotrope adenoma, ectopic secretion of ACTH by nonpituitary tumor), ACTH-independent (e.g., adrenocortical adenoma, adrenocortical carcinoma, nodular adrenal hyperplasia), or iatrogenic (e.g., administration of exogenous glucocorticoids to treat various inflammatory conditions). The term Cushing's disease refers to Cushing's syndrome caused by a pituitary corticotrope adenoma. Cushing's disease is more common among women, but before puberty, it is more common in boys. Signs and symptoms of Cushing’s Syndrome include the following:

• acne	• edema	• irritability
• amenorrhea	• emotional lability	• osteopenia
• atherosclerosis	• eosinopenia	• osteoporosis
• broad and purple stretch marks	• hypercoagulation with increased risk of deep vein thrombosis and pulmonary embolism	• proximal myopathy
• central obesity	• facial plethora	• rounded face
• cognitive defects	• fat pad on back of neck ("buffalo hump")	• susceptibility to infections
• decreased libido	• glucose intolerance/diabetes	• thin and brittle skin
• decreased linear growth in children	• hirsutism	• weakness
• depression	• hypertension	• weight gain
• dyslipidemia	• hypokalemia	
• easy bruising	• increased white blood cell count	

¹ Arlt W. (2012). Chapter 342. Disorders of the Adrenal Cortex. In D.L. Longo, A.S. Fauci, D.L. Kasper, S.L. Hauser, J.L. Jameson, J. Loscalzo (Eds), *Harrison's Principles of Internal Medicine*, 18e. Retrieved September 4, 2012 from <http://www.accessmedicine.com/content.aspx?aID=9140931>.

The treatment of choice for Cushing's disease is selective removal of the pituitary corticotrope tumor. In February 2012, Korlym (mifepristone) a cortisol receptor blocker, was approved for the indication of controlling hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery. Currently there is no other approved marketed drug therapy for the treatment of patients with Cushing's Disease.

Pasireotide. Pasireotide is a somatostatin analog. Somatostatin, a peptide hormone (also known as somatotropin release-inhibiting factor or hormone) produced in the brain and digestive system, is an inhibitory hormone with action on the anterior pituitary and the gastrointestinal system. Somatostatin receptors are expressed in many hormone-secreting solid tumors such as in pituitary corticotrope adenomas that result in Cushing's disease. Pasireotide binds to four of the five known somatostatin receptors (SSTR) (i.e. sst1, sst2, sst3, and sst5) inhibiting the release of ACTH which results in decreased adrenal corticosteroid production. The proposed pasireotide dosing regime consists of 0.9 mg by subcutaneous injection twice a day. It is supplied as a solution in a single-dose, 1 mL ampule containing pasireotide in 0.3 mg/mL, 0.6 mg/mL, or 0.9 mg/mL strengths for subcutaneous injection. The sponsor estimates that between 2010-2015, the target patient population in the US to receive treatment with pasireotide is approximately 7,200 – 7,500.

Other Somatostatin Analogs. Octreotide (Sandostatin[®]) and lanreotide (Somatuline[®] Depot) are other FDA approved somatostatin analogs.

Octreotide was approved by FDA in 1988 and is indicated for the treatment of acromegaly (reduce growth hormone and somatomedin C levels), carcinoid tumors (reduce symptoms), and vasoactive intestinal peptide tumors (reduce symptoms) and has a warning for increased incidence of gallstone or biliary sludge formation. In addition, product label includes precautions for potential hypoglycemia, hyperglycemia, suppression of thyroid stimulating hormone secretion, cardiac conduction abnormalities (e.g., bradycardia, QT prolongation), and increased potential for pregnancy (normalization of growth hormone and somatomedin C may restore fertility). Octreotide is pregnancy category B.

Lanreotide was approved by the FDA in 2007 and is indicated for the long-term treatment of acromegalic patients (reduce growth hormone and somatomedin C levels) who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option. The product label includes warning for gallstones, hypo- and/or hyperglycemia, bradycardia, hypertension, and decrease in thyroid function. Lanreotide is pregnancy category C.

A side-by-side comparison of octreotide, lanreotide, and pasireotide is included in the Appendix.

1.2 REGULATORY HISTORY

Following are pertinent milestones in the regulatory history of pasireotide:

- **2003:** Pasireotide clinical development program for symptoms of metastatic carcinoid tumors (b) (4) acromegaly, and Cushing's disease (IND 68,635) with the s.c. injection.
- **2006:** Pasireotide clinical development program for symptoms of metastatic carcinoid tumors (b) (4) acromegaly, and Cushing's disease (b) (4) with the LAR i.m. formulation.
- **June 13, 2011:** Initial submission of NDA 200677 for treatment of Cushing's disease in patients for whom medical therapy is appropriate.
- **August 19, 2011:** Withdrawal of NDA 200677. No explanation provided by sponsor.
- **September 2011 to January 2012:** Multiple communications between FDA and Novartis regarding liver-related safety concerns with pasireotide.
- **February 17, 2012:** Re-submission of NDA 20677.
- **May 18, 2012:** Updates of efficacy and safety were submitted on May 18, 2012 to report data from ongoing and extension studies.
- **July 2, 2012:** Mid-cycle review.

Important upcoming dates:

- **October 22, 2012:** Wrap-up meeting
- **November 7, 2012:** Advisory Committee meeting
- **December 17, 2012:** PDUFA goal date

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Pasireotide, Risk Management Plan, Novartis, January 27, 2012.
- Pasireotide, proposed label, Novartis, July 17, 2012.
- Pasireotide, Clinical overview, Novartis, January 27, 2012.
- Pasireotide, Introduction, Novartis, January 27, 2012.
- Pasireotide, Clinical efficacy and safety summaries, Novartis, January 27, 2012 and updates submitted on May 18, 2012.
- Pasireotide, FDA, DMEP background document for the Advisory Committee meeting scheduled for November 2012.

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

The clinical development program for pasireotide focused on Cushing's disease, acromegaly, and gastroenteropancreatic neuroendocrine tumors. The two formulations of pasireotide studied include an immediate release formulation for subcutaneous (s.c.) injection and a long-acting release (LAR) formulation for intramuscular injection. Only the subcutaneous injection has been studied in the treatment of Cushing's disease.

The efficacy of pasireotide in the treatment of Cushing's disease was based on data from pivotal Study B2305, a randomized, multi-center, double-blind Phase III study that evaluated efficacy and safety of 2 doses of pasireotide s.c. (600 µg b.i.d. and 900 µg b.i.d.) in 162 patients with Cushing's disease. The pivotal trial did not include a control arm; in many cases the frequency of adverse events were derived from the comparison of baseline laboratory values to values obtained while on drug treatment. The primary efficacy endpoint was the proportion of patients who achieved levels of mean urinary-free cortisol (mUFC) \leq upper limit of normal (ULN) after 6 months of treatment with pasireotide and no dose increase (relative to the randomized dose) prior to month 6. Secondary endpoints included: (1) effect on plasma ACTH and serum cortisol; (2) the effect on clinical signs and symptoms of Cushing's disease; (3) the effect on tumor volume by magnetic resonance imaging; and (4) the effect of pasireotide treatment on the quality of life (QoL).

The sponsor's safety information was obtained from the pivotal trial Study B2305, Phase 1 and 2 studies, as well as in several safety studies. Safety analyses included monitoring of adverse events (AEs) and serious adverse events (SAEs), laboratory parameters, electrocardiograms (ECGs), and gallbladder ultrasounds.

Updates of efficacy and safety were submitted on May 18, 2012 to report data from ongoing and extension studies. The updated safety data comes from 232 patients (202 patients with Cushing's and 30 patients with acromegaly) exposed to pasireotide.

3.2 KEY EFFICACY AND SAFETY FINDINGS REPORTED BY THE SPONSOR

The pivotal study demonstrated that treatment with pasireotide resulted in a decrease in the mean UFC, ACTH, and serum cortisol (biochemical measures of disease activity) within the first month of treatment in both dose arms and in improvements in the signs and symptoms associated with Cushing's disease. Efficacy data reported in the May 18, 2012 update showed that the improvements in the biochemical measures of disease activity were sustained during the extension period for patients who remained in the study.

Safety Concerns and Risk Management Plan Proposed by the Sponsor

The most frequently reported adverse events (AEs) ($\geq 20\%$) were diarrhea, nausea, hyperglycemia, cholelithiasis, abdominal pain, and diabetes mellitus. These adverse events were predominantly low grade and generally manageable with dose

adjustments/interruptions, concomitant medications, non-drug therapies, or dietary interventions.

The sponsor reported the most commonly observed AEs of special interest in the 600 µg b.i.d. and 900 µg b.i.d. groups were hyperglycemia-related AEs (75.6% and 73.8%, respectively), diarrhea-related AEs (61% and 57.5%, respectively), nausea-related AEs (50% and 57.5%, respectively), and gallbladder-biliary-related AEs (36.6% and 36.3%, respectively).² Hyperglycemia, diabetes mellitus, and type 2 diabetes mellitus were commonly reported as grade 3-4 adverse events. Following is a list of adverse events reported by the sponsor as “identified” or “potential” risks associated with the use of pasireotide and their proposed risk management approach.

Identified risks

- **Hypocortisolism/Cortisol withdrawal:** risk management through routine pharmacovigilance, targeted follow-up of all SAE reports using a targeted checklist, and labeling (Warnings and Precautions).
- **Hyperglycemia:** risk management through routine pharmacovigilance, targeted follow-up of all SAE reports using a targeted checklist, and labeling (Warnings and Precautions).
- **Bradycardia:** risk management through routine pharmacovigilance and labeling (Warnings and Precautions).
- **QTc interval prolongation:** risk management through routine pharmacovigilance, targeted follow-up of all SAE reports using a targeted checklist, and labeling (Warnings and Precautions).
- **Cholelithiasis:** risk management through routine pharmacovigilance and labeling (Warnings and Precautions).
- **Hematological abnormalities:** risk management through routine pharmacovigilance and labeling.
- **Liver enzymes increased:** risk management through routine pharmacovigilance and labeling (Warnings and Precautions, Contraindications).
- **Injection site reactions:** risk management through routine pharmacovigilance and labeling.
- **Gastrointestinal disorders:** risk management through routine pharmacovigilance and labeling.

² Clinical Safety Update report, Novartis, May 18, 2012. Adverse events of special interest included AEs where pasireotide may influence a common mechanism of action responsible for triggering them or AEs which are similar in nature. AEs of special interest were divided into three categories: included the following: known somatostatin analogues class effects (QT-prolongation, bradycardia, hyperglycemia, cholelithiasis, hematological abnormalities, abnormal liver functions, injection site reactions, pancreatitis, hypothyroidism and growth hormone deficiency), Cushing’s disease-related risks (adrenal hypocortisolism/cortisol withdrawal syndrome), and risks which were observed mainly in pre-clinical studies (coagulation abnormalities, hypotension, hypocalcaemia, and gastrointestinal erosions/bleedings).

Potential risks

The sponsor plans to manage the following potential risks with pasireotide through routine pharmacovigilance and/or labeling. Potential risks include: decrease in growth hormone (GH)/ insulin-like growth factor-1 (IGF-I), hypothyroidism, pancreatitis, coagulation abnormalities, hypotension, hypocalcemia, gastrointestinal erosions/bleedings, potential interactions with cyclosporine, drugs metabolized by CYP3A4, bromocriptine, antiarrhythmic medicines and antidiabetics (resulting in increased concentrations of pasireotide), off-label use in children and other indications, allergic reactions/immunogenicity and tumor expansion.

There were no new or unexpected safety findings reported in the safety update submitted on May 18, 2012.

3.3 KEY EFFICACY AND SAFETY FINDINGS REPORTED BY DMEP REVIEW TEAM³

Regarding the efficacy, the review team from the Division of Metabolism and Endocrinology Products (DMEP) concluded that the 900 µg dose was shown to meet the primary efficacy criterion having a response rate of 26% and a lower bound of the two-sided 95% CI of 17% which exceeded the pre-specified 15% criterion, however the 600 µg dose did not meet the primary efficacy criterion. The response observed with the 900 µg bid dose regimen was only slightly better than that observed with the 600 µg bid dose regimen, and the review team believes that the additional benefit was modest clinically and statistically non-significant. Of interest, drug-related serious adverse events were almost doubled in the 900 µg b.i.d. group (15.0%) vs. the 600 µg b.i.d. group (8.5%); which included adverse events predominantly related to diabetes and hyperglycemia.

The review team only used the data from the Phase 3 pivotal trial 2305, which was in the indicated population, for their safety analysis. Of special concern are the serious risks of elevation in serum glucose, increases in HbA1c levels, and the clinical significance of increases in transaminases observed in clinical trials.⁴

Elevations in serum glucose – A goal of treating Cushing’s disease is to improve the clinical signs and symptoms of hypercortisolemia. Diabetes is a known complication of hypercortisolemia and although treatment with pasireotide reduced cortisol levels, it also impaired insulin secretion resulting in sustained increases serum glucose and HbA1c from baseline. The frequency of adverse events associated with disturbances in glucose metabolism included; hyperglycemia (40.1%), diabetes mellitus (17.9%), increased glycosylated hemoglobin (11.1%), and type 2 diabetes mellitus (9.3%).

Increases in HbA1c - HbA1c levels increased during treatment relative to baseline occurred early during pasireotide treatment and continued throughout the duration of the trial. The increase in HbA1c is concerning because a goal of treating Cushing’s disease is to improve the clinical signs and symptoms related to hypercortisolemia, specifically glucose impairment/diabetes and its long-term complications. HbA1c increased in the

³ Pasireotide, FDA, DMEP background document for the Advisory Committee meeting scheduled for November 2012.

⁴ Naomi Lowy, M.D., Clinical Review Pasireotide/SOM230 (Signifor), Mid-Cycle Review Meeting, July 2, 2012.

diabetes range in both dose groups and did not return to baseline values, the increase was approximately 1.5% mean absolute change. The change in HbA1c was greater with pasireotide than what has been observed with other approved somatostatin analogs.

Liver - Clinical use of pasireotide was associated with elevations of alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >3X upper limit of normal (ULN) in 5% of patients enrolled in Study 2305. Four cases of AST/ALT increases >2xULN accompanied by an increase in total serum bilirubin occurred in healthy volunteers and in one patient treated with pasireotide for compassionate use.

4 DISCUSSION

The efficacy and safety of pasireotide for the treatment of patients with Cushing's disease is the subject of discussion at an upcoming Advisory Committee meeting in November 2012. The Advisory Committee will weigh on the available evidence in support of the efficacy and safety of pasireotide. Regarding safety, the panel will address questions about the potential risk for liver toxicity (i.e., need for routine monitoring and for additional safety data), dysglycemia, and the marked increases in HbA1c from baseline (i.e., if the patient's baseline glycemic profile should be considered with regard to choosing pasireotide in the management of Cushing's disease, dose selection, and/or duration of use).

There is an unmet medical need for the treatment of Cushing's disease and the clinical development program showed pasireotide is effective in the treatment of this disease. Until the risk:benefit profile of pasireotide is established, an appropriate risk management strategy cannot be determined. Therefore, DRISK defers comment on the sponsor's proposed Risk Management Plan at this time.

5 CONCLUSION AND RECOMMENDATIONS

DRISK defers recommendations for the management of the risks associated with the use of pasireotide until after the Advisory Committee meeting and until DMEP completes their risk:benefit assessment of pasireotide for the treatment of patients with Cushing's disease.

Appendix 1. A side-by-side Comparison of Pasireotide, Octreotide, and Lanreotide

	Pasireotide (proposed by the sponsor)	Octreotide	Lanreotide
Trade Name:	Signifor	Sandostatin	Somatuline Depot
NDA:	200677	019667	022074
Sponsor:	Novartis	Novartis, multiple ANDAs	Ipsen Pharma
FDA Approval:	Pending	1988	2007
Class:	Somatostatin Analog	Somatostatin Analog	Somatostatin Analog
Indication:	Cushing's disease	Acromegaly, carcinoid tumors, Vasoactive Intestinal Peptide Tumors	Acromegaly
Risk Management	Labeling (Patient Labeling)	Labeling	Labeling (Patient Labeling)
Labeling			
o Box Warning	None	None	None
o Warning & Precautions	(b) (4)	<ul style="list-style-type: none"> o Gallbladder abnormalities: may occur. Monitor periodically. o Glucose Metabolism: hypoglycemia or hyperglycemia may occur. Glucose monitoring is recommended and antidiabetic treatment may need adjustment. o Cardiac Function: bradycardia, arrhythmia or conduction abnormalities may occur. Use with caution in at-risk patients. o Thyroid Function: hypothyroidism may occur. Monitor thyroid levels periodically. o Nutrition: may alter absorption of dietary fats. o Monitoring Laboratory Tests: laboratory tests may be helpful as biochemical markers in determining and following patient response depend on the specific tumor. o Drug Interactions: concomitant administration of octreotide injection with cyclosporine may decrease blood levels of cyclosporine. 	<ul style="list-style-type: none"> o Gallbladder: Gallstones may occur; consider periodic monitoring. o Glucose Metabolism: Hypo- and/or hyperglycemia may occur. Glucose monitoring is recommended and anti-diabetic treatment adjusted accordingly. o Cardiac Function: Decrease in heart rate may occur. Use with caution in at-risk patients. o Thyroid Function: slight decreases in thyroid function have been seen during treatment. Thyroid function tests are recommended where clinically indicated. o Monitoring Laboratory Tests: Serum GH and IGF-1 levels are useful markers of the disease and the effectiveness of treatment. o Drug Interactions: may reduce the intestinal absorption of concomitant drugs: may decrease the relative bioavailability of cyclosporine.
o Pregnancy Category	C	B	C

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