PDL NEW DRUG REVIEW

Proprietary Name: Signifor®
Common Name: pasireotide
PDL Category: Somatostatic Agents

Comparable Products	Preferred Drug List Status
Korlym	Non-Preferred

Summary

Indications and Usage: Treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative. This is a pregnancy category C medication. The safety and efficacy of use in children under the age of 18 have not been established.

Drug Interactions: Additive effects on the prolongation of the QT interval may be seen if pasireotide is given concomitantly with anti-arrhythmic medications or other drugs that are known to prolong the QT interval; therefore, it is recommended to use this combination with caution. The relative bioavailability of cyclosporine may be reduced if given concomitantly with pasireotide, and thus dose adjustment of cyclosporine may be needed. The concomitant use of pasireotide with bromocriptine may result in increased blood levels of bromocriptine, thus reductions in the dose of bromocriptine may be needed. As there have been reports of bradycardia with Signifor® treatment, dose adjustments of beta-blockers, calcium channel blockers, or correction of electrolyte disturbances may be needed.

Dosage Forms: Injection: 0.3mg/ml, 0.6mg/ml, and 0.9mg/ml in a single-dose 1ml glass ampule

Recommended Dosage: 0.3 to 0.9mg SC BID, and titrate based on response and tolerability. For those with moderate hepatic impairment, the recommended initial dose is 0.3mg BID, up to a maximum of 0.6mg BID. With treatment, all should be assessed for response and treatment should continue as long as a benefit is seen. Temporarily reduce the dose of Signifor® if adverse events arise, with a reduction of 0.3mg decrements per injection.

Dosage adjustment is not required in those with renal impairment, or in those with mild hepatic impairment. Dose adjustment is required in those with moderate hepatic impairment, and use is not recommended in those with severe hepatic impairment.

Prior to starting treatment, it is recommended that certain baseline tests be performed. They include: fasting plasma glucose, hemoglobin A1c, and liver tests. As QT prolongation is associated with Signifor® treatment, baseline electrocardiogram should be performed. Lastly, a baseline gallbladder ultrasound should be performed.

Common Adverse Drug Reactions: *Placebo data was not available to compare with Signifor®. Thus, the % provided for each adverse event below was that reported with Signifor 0.6mg BID at an incidence ≥10%.* The most common adverse events reported with Signifor® include diarrhea (59%), nausea (46%), hyperglycemia (38%), cholelithiasis (30%), headache 28%), abdominal pain (23%), fatigue (15%), DM (16%), injection site reactions (17%), nasopharyngitis (12%), alopecia (12%), asthenia (16%), elevated glycosylated hemoglobin (12%), increased alanine aminotransferase (13%), peripheral edema (11%), decreased appetite (9%), hypercholesterolemia (9%), dizziness (10%), DM type 2 (12%), influenza (11%), myalgia (12), and sinus bradycardia (10%).

As cholelithiasis has been reported with Signifor® use, it is recommended that a baseline gallbladder ultrasound be performed, as well as at 6-12 month intervals. As abnormal liver enzyme levels have been reported with Signifor® treatment, it is recommended that a baseline liver test be performed, as well as 1-2 weeks after starting treatment, monthly for 3 months, and then every 6 months thereafter. Inhibition of pituitary hormones other than ACTH may occur with Signifor® use; therefore, it is recommended that pituitary function (eg TSH/free T_4, GH/IGF-1) be assessed prior to starting treatment and periodically thereafter as clinically appropriate.

Signifor® treatment may cause suppression of adrenocorticotropic hormone (ACTH) secretion, which may potentially lead to hypocortisolism. Those using Signifor® treatment should be monitored and educated on the signs and symptoms of hypocortisolism, and if it occurs then temporary dose reduction or interruption of treatment should be considered.

There have been reports of elevations in blood glucose levels in those being treated with Signifor®. It is recommended that glycemic status be assessed prior to the initiation of Signifor®. Self-monitoring of blood glucose should be performed every week for the first 2-3 months of treatment, and periodically thereafter as needed. If hyperglycemia occurs, it is recommended to start or adjust anti-diabetic treatment.

As discussed, Signifor® treatment is associated with QT prolongation, and this was reported when used at therapeutic doses. It is thus recommended that Signifor® be used with caution in those at risk of developing QT prolongation, including those with congenital long QT prolongation, those with uncontrolled or significant cardiac disease, those on anti-arrhythmic therapy or other medications known to cause QT prolongation, and those with hypokalemia and/or hypomagnesemia.

Contraindications: There are no contraindications listed in the prescribing information.

Manufacturer: Novartis Pharmaceuticals Corp.

Analysis: Pasireotide, the active ingredient of Signifor®, is a cyclohexapeptide somatostatin analog. It binds to somatostatin receptors (ssts), which results in inhibition of ACTH secretion. This leads to decreased cortisol secretion. Pasireotide binds with high affinity to the somatostatin receptors.

One multicenter, randomized, 6-month trial (N=162) was performed to assess the safety and efficacy when used as treatment for those with Cushing's disease with persistent or recurrent disease despite pituitary surgery or for whom surgery was not indicated or was refused. Adults were randomized to receive either Signifor® 0.6mg BID or 0.9mg BID. The primary outcome was the amount who achieved normalization of mean 24-hour urine free cortisol (UFC) levels at the end of treatment. Results suggested that at the end of month 6, 15% (N=12/82) of the 0.6mg group were responders and 26% (N=21/80) of the 0.9mg group were responders. 34% of the 0.6mg group and 41% of the 0.9mg group had a mean UFC (mUFC) ≤upper normal limit (UNL) or ≥50% reduction from baseline. The mean % change in UFC from baseline was -22% with the 0.6mg group and -42% with the 0.9mg group.

Signifor® is the first medicine to gain FDA approval that targets the underlying mechanism of Cushing's disease. It is recommended that Signifor® remain non-preferred and require prior authorization to verify clinical diagnosis.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☐ **Preferred with Conditions**

References

[1] Signifor [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2012.