Sotatercept (WINREVAIR)
National Drug Monograph
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VA Pharmacy Benefits Management Services and VA National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information[1]

Description/Mechanism of Action

- Sotatercept-csrk is a novel, first in class recombinant activin receptor type IIA-Fc inhibitor. By inhibiting binding of activin-A and other TGF-β superfamily ligands, sotatercept improves the balance between pro-proliferative and anti-proliferative signaling to modulate vascular proliferation.

Indication(s) Under Review in This Document

- Sotatercept is indicated for the treatment of adults with pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group 1 to increase exercise capacity, improve WHO functional class, and reduce the risk of clinical worsening events.

Dosage Form(s) Under Review

- Sotatercept is available as a lyophilized powder for injection in single-use vials (45 mg and 60 mg). The product is packaged in 1- or 2- vial kits containing the syringe(s), safety needle(s), sterile water for injection in prefilled syringe(s), vial adapter(s), and alcohol pads. The product is stored in the refrigerator until ready for use.
- The starting dose of sotatercept is 0.3 mg/kg by subcutaneous (SC) injection once every 3 weeks. The target dose is 0.7 mg/kg SC once every 3 weeks.

Clinical Evidence Summary

Efficacy Considerations

- Efficacy for FDA approval of sotatercept was based mainly on results from one multinational, randomized, placebo-controlled, industry sponsored, 24-week, phase 3 trial (STELLAR) that evaluated patients with confirmed PAH on stable background therapy.[2,3] Patients were randomized (1:1) to receive sotatercept or placebo subcutaneously every 21 days. Sotatercept was initially dosed at 0.3 mg/kg and then escalated to a target dose of 0.7 mg/kg. Dosing modifications were made if patients met predefined thresholds for alterations in hemoglobin, platelet count, or severity of talengiectasia. The primary endpoint was the change from baseline to week 24 in the 6-minute walk distance (6MWD). A phase 2 study (PULSAR) provided additional supportive data.

- Key inclusion and exclusion: Included patients had Group 1 PAH that was idiopathic, heritable, drug-induced, connective tissue disease-associated, or after shunt correction. Other Group 1 subtypes were excluded (PAH associated with HIV, portal-pulmonary disease, schistosomiasis, or veno-occlusive disease). Patients were symptomatic (WHO functional class II or III) and on stable doses of PAH background therapy for at least 90 days. Notable exclusion criteria were platelet count <50,000/mm^3 and hepatic aminotransferase levels >3 times the upper limit of normal.

- Baseline/Disposition: The mean age of the study population was 48 years, and the majority of patients were women (79%). PAH subtypes were predominantly idiopathic (59%) and heritable (18%), and connective-tissue disease (15%). Ninety percent of patients were White, and 2% were Black. One-third of patients were from North America. Of the total 323 randomized patients, 95% completed the 24-week trial. Nearly all patients received the target dose of 0.7 mg/kg, and 89% of patients had no dose reductions or delays. Additional baseline characteristics are included in Table 1.

Table 1: Selected baseline characteristics from STELLAR[3]

Characteristic	Total N=323
Median time from diagnosis	8.8 yrs
WHO Functional Class II	49%
PAH Group 1 subtype	
Idiopathic	59%
Heritable	18%
Connective-tissue disease associated	15%
Drug or toxin induced	3%
Associated with corrected congenital shunts	5%
WHO Functional Class III	51%
Background PAH therapy	
Monotherapy	4%
Double therapy	35%
Triple therapy	61%
Prostacyclin infusion therapy	40%
Mean 6MWD	401 meters

- Results: Patients who received sotatercept experienced a greater improvement in 6MWD from baseline compared to patients in the placebo group. Secondary endpoints tested in hierarchical order were also improved including clinical, functional, and supportive laboratory (pulmonary vascular resistance [PVR], N-terminal pro-B-type natriuretic peptide [NT-pro-BNP]) endpoints. Two of three components of a PAH-specific quality of life measurement (PAH-SYMPACT) showed small statistically significant improvements with sotatercept vs. placebo; however, the clinical significance is unknown.

Table 2: Selected efficacy results from STELLAR[3]

Endpoint (at week 24)	Sotatercept N=163	Placebo N=160
Primary Endpoint		
Median change in 6MWD from baseline (m)	34.4	1.0
Hodges-Lehmann location shift from placebo estimate (m)†	40.8	-
Secondary Endpoints		
Multicomponent improvement* (%)	38.9	10.1
WHO functional class improvement from baseline (%)	29.4	13.8
Clinical worsening or death (%)	5.5	26.2

P <0.05 for all comparisons
†Median of all paired differences
*Improvement in 1) 6MWD increase of ≥30m; 2) NT-proBNP reduction of ≥30% or <300 pg/mL; and 3) WHO functional class or maintenance of class II

- Phase 2 study: The double-blind PULSAR trial evaluated two doses of sotatercept (0.3 mg/kg and 0.7 mg/kg) and placebo in a PAH population on stable background therapy (n=106) for 24 weeks.[4] Results showed that both doses of sotatercept reduced PVR. Extension study supports continued effect of sotatercept for up to 24 months.[5]

Safety Considerations

Safety Results from Clinical Trials: Safety data for FDA approval was obtained from the phase 3 placebo-controlled STELLAR trial and the phase 2 placebo-controlled PULSAR study. The median duration of treatment in STELLAR was 313 days in the sotatercept group and 273 days in the placebo group. Additional data from a cumulative database provided supportive information.

- **Boxed warnings:** none
- **Contraindications:** none
- **Other warnings:**
  - Erythrocytosis
  - Thrombocytopenia
  - Serious bleeding
  - Embryo-fetal toxicity
  - Impaired fertility
- **Adverse reactions**
  - **Serious adverse events:** 14.1% SOT vs. 22.5% PBO
  - **Deaths:** 1.2% SOT vs. 4.4% PBO
  - **Discontinuation due to adverse events:** 1.8% SOT vs. 6.2% PBO

- **Other adverse events of interest**
  - ***Increased bleed risk:*** Sotatercept was associated with increased bleeding compared to placebo in STELLAR. Excess bleeding was seen primarily as epistaxis and gingival bleeding and occurred irrespective of concomitant use of prostacyclin or antithrombotic therapy. Serious bleeding was reported in more patients receiving sotatercept vs. placebo in STELLAR (4% vs. 1%). Patients with serious bleeds were more likely to be receiving prostacyclin therapy, antithrombotics, or had a low platelet count.

  - ***Thrombocytopenia:*** Sotatercept was associated with an increased risk of thrombocytopenia vs. placebo. Platelet counts dropped below normal in 25% of sotatercept and 16% of placebo treated patients. Platelet counts less than 50,000/m^3 were seen in 3% of patients on sotatercept; all of those patients were receiving epoprostenol.

  - ***Erythrocytosis:*** Increased hemoglobin >2g/dL above upper limit of normal (ULN) occurred in 15% of sotatercept patients. Severe erythrocytosis may increase the risk of thromboembolic events or hyperviscosity syndrome.

Table 3. Adverse reactions from STELLAR occurring in >10% of sotatercept patients

Adverse reaction	Sotatercept (N=163)	Placebo (N=160)
Headache	24.5	17.5
Epistaxis	22.1	1.9
Rash	20.2	8.1
Telangiectasia	16.6	4.4
Diarrhea	15.3	10.0
Dizziness	14.7	6.2
Erythema	13.5	3.1

Other Considerations

- **Monitoring and dosing adjustments for increased hemoglobin or decreased platelets:**
  - Check hemoglobin and platelet counts prior to each dose for the first 5 doses (or longer if values are unstable).
  - Delay treatment for at least 3 weeks if any of the following occur:
    - Hemoglobin increased >2.0 g/dL from previous dose and is above ULN
    - Hemoglobin increased >4.0 g/dL from baseline
    - Hemoglobin increased >2.0 g/dL above ULN
    - Platelet count decreased to <50,000/mm^3

- **Patients of reproductive potential**
  - *Fetal harm:* Based on the mechanism of action and on findings from animal reproduction studies, sotatercept may cause fetal harm during pregnancy. Patients of childbearing

potential should be advised of the potential risk to the fetus and to use effective contraception during treatment and for at least 4 months after stopping sotatercept.
    - *Fertility impairment:* Based on findings in animals, sotatercept may impair fertility (female and male). Patients should be advised of potential effects on fertility.

- **Geriatric use:** There was no difference in efficacy of sotatercept noted between the subgroups of patients < 65 years and ≥65 years of age. There were more bleeding events in the older vs. younger sotatercept subgroups. Insufficient numbers of patients aged 75 years and older were included in clinical trials to evaluate efficacy and safety.

Other Therapeutic Options
Sotatercept is a first in class agent used as add-on therapy; there are no alternative treatments.

Projected Place in Therapy

- Group 1 PAH is a rare, progressive, and serious disease characterized by elevation in PVR that ultimately leads to right ventricular heart failure and death.
- Prevalence of PAH is estimated to be 48-55 cases per million.[6]
- Life expectancy of patients with PAH has improved with the availability of PAH directed therapies (from 2.8 years to more than 5 years), but morbidity and mortality remain high.[7,8]
- PAH-specific therapies include endothelin-receptor antagonists, phosphodiesterase-5 inhibitors, prostacyclin analogs, guanylate cyclase stimulators, and prostacyclin receptor agonists. These agents act mainly by promoting vasodilation or relaxation and reducing proliferation of smooth muscle cells.
- Sotatercept is a first in class activin signaling inhibitor that regulates signaling pathways for inflammation, cell proliferation, apoptosis, and tissue homeostasis.
- Sotatercept is administered as a weight-based subcutaneous injection once every 3 weeks, which may be less burdensome than some other therapies. Sotatercept requires laboratory monitoring of platelets and hemoglobin.
- There is moderate quality evidence that sotatercept improves hemodynamics, exercise capacity and functional class, and delays clinical worsening in patients already on background PAH therapy. The improvement in 6MWD of 41 meters with sotatercept exceeds a minimal clinically important difference of about 33 meters.[9] Extension study suggests maintenance of effect, and more study is underway.
- Patients enrolled in STELLAR were young and predominantly white females with idiopathic, heritable, or connective tissue disease associated PAH and had functional class II or III symptoms. Results may not be generalizable to other PAH subtypes or patient populations. Per subgroup analysis in STELLAR, the benefit of PAH in connective-tissue disease associated PAH on 6MWD was less clear than the benefit in idiopathic and heritable PAH.
- Sotatercept use is associated with epistaxis, thrombocytopenia, telangiectasia, serious bleeding, embryofetal toxicity, and possibly impaired infertility. Few patients discontinued treatment due to adverse effects.
- Long term safety, durability, and use in other PAH subtypes and sicker patients are unknown at this time.

- The institute for clinical and economic review (ICER) of sotatercept concluded that there is moderate certainty of a small to substantial net health benefit, with a high certainty of at least a small net health benefit.
- Ongoing areas of study for sotatercept include in patients with a recent PAH diagnosis (HYPERION; NCT04811092), extension study from controlled trials (SOTARIA; NCT04796337) pulmonary hypertension associated with left heart disease (CADENCE; NCT 04945460), and rescue therapy in severe PAH (ZENITH NCT04896008).

References

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Prepared July 2024. Contact person: Lisa Longo, Pharm.D., BCPS, National PBM Clinical Pharmacy Program Manager, Formulary management, VA Pharmacy Benefits Management Services (12PBM)