IOWA | Health and Human Services

PDL DRUG REVIEW

Proprietary Name: Winrevair®
Common Name: sotatercept-csrk for injection
PDL Category: Pulmonary Anti-Hypertensives

Comparable Products	Preferred Drug List Status
Ambrisentan	Preferred with Conditions
Sildenafil	Preferred with Conditions

Pharmacology/Usage: Sotatercept-csrk, the active ingredient of Winrevair®, is a homodimeric recombinant fusion protein consisting of the extracellular domain of the human activin receptor type IIA (ActRIIA) linked to the human IgG1 Fc domain. Sotatercept-csrk, a recombinant activin receptor type IIA-Fc (ActRIIA-Fc) fusion protein, is an activin signaling inhibitor that binds to activin A and other TGF-β superfamily ligands. As a result, sotatercept-csrk improves the balance between the pro-proliferative and anti-proliferative signaling to modulate vascular proliferation. In animal models of PAH, a sotatercept-csrk analog reduced inflammation and inhibited proliferation of endothelial and smooth muscle cells in diseased vasculature. These cellular changes were associated with thinner vessel walls, partial reversal of right ventricular remodeling, and improved hemodynamics.

Indication: For the treatment of adults with pulmonary arterial hypertension (PAH, World Health Organization [WHO] Group 1) to increase exercise capacity, improve WHO functional class (FC), and reduce the risk of clinical worsening events.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings in animal reproduction studies, Winrevair® may cause fetal harm when administered to a pregnant woman. There are risks to the mother and fetus associated with pulmonary arterial hypertension in pregnancy. There are no available data on use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Advise pregnant women of the potential risk to a fetus. Pregnancy testing is recommended for females of reproductive potential before starting treatment. Advise females of reproductive potential to use effective contraception during treatment and for at least 4 months after the final dose if treatment is discontinued. Note that based on findings in animals, Winrevair® may impair female and male fertility. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Lyophilized cake or powder appearance in a single-dose vial for Injection: 45mg and 60mg.

Remove the injection kit from the refrigerator and wait 15 minutes to allow the prefilled syringe(s) and drug product to come to room temperature prior to preparation.

Recommended Dosage: Obtain hemoglobin (Hgb) and platelet count prior to the first dose of Winrevair®. Do not start treatment if platelet count is <50,000/mm^3 (<50 x 10^9/L).

Winrevair® is intended for use under the guidance of a healthcare professional. Patients and caregivers may administer Winrevair® when considered appropriate and whey they receive training and follow-up from the healthcare provider on how to reconstitute, prepare, measure, and inject Winrevair®. It is for subcutaneous (SC) injection. Select the injection site on the abdomen (at least 2 inches away from the navel), upper thigh, or upper arm. For administration by the patient or caregiver, use only the abdomen and upper thigh.

Winrevair® is administered once every 3 weeks by SC injection per patient body weight. The starting dose is 0.3mg/kg. Refer to the prescribing information for information on calculating the injection volume based on patient's weight for the starting dose. Injection volume should be rounded to the nearest 0.1ml.

After verifying acceptable Hgb and platelet count, increase to the target dose of 0.7mg/kg. Continue treatment at 0.7mg/kg every 3 weeks unless dosage adjustments are required. Refer to the prescribing information for information on calculating the injection volume. Injection volume should be rounded to the nearest 0.1ml.

If a dose of Winrevair® is missed, administer as soon as possible. If the missed dose is not administered within 3 days of the scheduled date, adjust the schedule to maintain 3-week dosing intervals. In case of an overdose, monitor for erythrocytosis.

Check Hgb and platelet count before each dose for the first 5 doses, or longer if values are unstable. Thereafter, monitor Hgb and platelet count periodically.

Delay treatment for at least 3 weeks if any of the following occur:

- Hgb increases >2.0g/dL from the previous dose and is above upper limit of normal (ULN).
- Hgb increases >4.0g/dL from baseline.
- Hgb increases >2.0g/dL above ULN.
- Platelet count decreases to <50,000/mm^3 (<50 X 10^9/L).

Recheck Hgb and platelet count before restarting treatment. For treatment delays lasting >9 weeks, restart treatment at 0.3mg/kg, and escalate to 0.7mg/kg after verifying acceptable Hgb and platelet count.

Drug Interactions: There are no drug interactions listed with this product.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Winrevair®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included headache (7%), epistaxis (20.2%), rash (12.1%), telangiectasia (12.2%), diarrhea (5.3%), dizziness (8.5%), and erythema (10.4%). Shifts in Hgb from normal to above normal levels occurred (39%), as well as shifts in platelet count from normal to below normal (9%).

Winrevair® may increase hemoglobin. Severe erythrocytosis may increase the risk of thromboembolic events or hyperviscosity syndrome. Monitor Hgb before each dose for the first 5 doses, or longer if values are unstable, and periodically thereafter, to determine if dose adjustments are required.

Winrevair® may decrease platelet count. Severe thrombocytopenia may increase the risk of bleeding. Thrombocytopenia occurred more frequently in patients also receiving prostacyclin infusion. Do not start treatment if platelet count is <50,000/mm^3. Monitor platelets before each dose for the first 5 doses, or longer if values are unstable, and periodically thereafter to determine whether dose adjustments are required.

In clinical studies, serious bleeding was reported in 4% of patients taking Winrevair® and 1% of patients taking placebo. Patients with serious bleeding were more likely to be on prostacyclin background therapy and/or anti-thrombotic agents or have low platelet counts. Advise patients about signs and symptoms of blood loss. Do not administer Winrevair® if the patient is experiencing serious bleeding.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Merck

Analysis: The efficacy of Winrevair® was assessed in adult patients with PAH in the STELLAR study, a global, multicenter, double-blind, placebo-controlled, parallel-group clinical trial. The trial included patients

(N=323) with PAH (WHO Group 1 FC II or III) who were randomized to Winrevair® (target dose 0.7mg/kg) or placebo administered SC once every 3 weeks.

Included patients were mostly female (79%) with a median age of 48 years (range 18 to 82 years), and a median body weight of 68kg. In addition, 89% were white. The most common PAH etiologies were idiopathic PAH (59%), heritable PAH (18%), and PAH associated with connective tissue diseases (CTD; 15%). The mean time from PAH diagnosis to screening was 8.8 years, and most patients were receiving either three (61%) or two (35%) background drugs for PAH, while 40% were receiving prostacyclin infusions. Patients had a WHO FC II (49%) or III (51%) at baseline.

The primary efficacy endpoint was the change from baseline at week 24 in the 6-minute walk distance (6MWD). Results suggested that in the Winrevair® group, the placebo-adjusted median increase in 6MWD was 41 meters ($p<0.001$).

Change from baseline in 6MWD at week 24 for subjects who died was imputed to -2000 meters to receive the worst rank. Change from baseline in 6MWD at week 24 for subjects who had missing data due to a non-fatal clinical worsening event was imputed to -1000 meters to receive the next-worst rank.

Treatment with Winrevair® led to an improvement from baseline by at least 1 WHO FC at week 24 in 29% of patients compared to 14% of patients treated with placebo ($p<0.001$).

Treatment with Winrevair® resulted in an 84% reduction in the occurrence of death from any cause or PAH clinical worsening events compared to placebo. These outcomes were captured until the last patient completed the week 24 visit. Results are presented in the table below, which was adapted from the prescribing information.

	Placebo (N=160)	Winrevair® (N=163)	Hazard Ratio
Number of subjects who experienced death or ≥1 clinical worsening event	42 (26.3%)	9 (5.5%)	0.16; p<0.001
NNT	5		
Assessment of clinical worsening events			
Death	7 (4.4%)	2 (1.2%)	
Worsening-related listing for lung and/or heart transplant	2 (1.3%)	1 (0.6%)	
Need to initiate rescue therapy with an approved PAH therapy or the need to ↑ dose of infusion prostacyclin by 10% or more	17 (10.6%)	2 (1.2%)	
Need for atrial septostomy	0 (0%)	0 (0%)	
PAH-specific hospitalization (≥24 hours)	8 (5%)	0 (0%)	
Deterioration of PAH	15 (9.4%)	4 (2.5%)	

Place in Therapy: Winrevair® is an activin signaling inhibitor indicated for the treatment of adults with pulmonary arterial hypertension (PAH; WHO Group 1) to increase exercise capacity, improve WHO functional class (FC) and reduce the risk of clinical worsening events. The efficacy of Winrevair® was

assessed in a double-blind, placebo-controlled study that included patients with PAH (WHO Group 1 FC II or III) who were randomized to either Winrevair® or placebo. The primary endpoint was the change from baseline at week 24 in 6MWD. In the Winrevair® group, the placebo-adjusted median increase in in 6MWD was 41 meters ($p<0.001$). The number of subjects who experienced death or at least one clinical worsening event was significantly less in the Winrevair® group as compared with placebo ($p<0.001$; NNT 5). Winrevair® is a first-in-class treatment for PAH WHO Group 1.

Summary

There is some evidence at this time to suggest that Winrevair® plus background therapy is more effective than background therapy alone for the primary endpoint of improved exercise capacity; however, there is no evidence at this time to support that Winrevair® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Winrevair® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Winrevair® [package insert]. Rahway, NJ: Merck Sharpe & Dohme LLC; 2024.