▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

**AUSTRALIAN PRODUCT INFORMATION – WINREVAIR® (Sotatercept)**

## 1 NAME OF THE MEDICINE

Sotatercept

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 45 mg single-use vial provides 55 mg of sotatercept and after reconstitution with 1.0 mL sterile water for injections, the resulting concentration is 50 mg/1.0 mL of sotatercept and the nominal deliverable volume is 0.9 mL.

Each 60 mg single-dose vial provides 72.5 mg of sotatercept and after reconstitution with 1.3 mL sterile water for injections, the resulting concentration is 50 mg/1.0 mL of sotatercept and the nominal deliverable volume is 1.2 mL.

For the full list of excipients, see Section 6.1 List of excipients.

## 3 PHARMACEUTICAL FORM

Sotatercept for injection is a sterile, preservative-free, white to off-white lyophilised powder available in 45 mg and 60 mg single-dose vials for subcutaneous (SC) administration after reconstitution.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

WINREVAIR is indicated for the treatment of adults with pulmonary arterial hypertension (PAH) in WHO Functional Class (FC) II or III, in combination with standard therapy.

Efficacy has been shown in idiopathic and heritable PAH, PAH associated with connective tissue disease, drug or toxin-induced PAH and PAH associated with congenital heart disease with repaired shunts.

### 4.2 DOSE AND METHOD OF ADMINISTRATION

WINREVAIR should only be initiated and monitored by a physician experienced in the diagnosis and treatment of PAH.

**Recommended Starting Dosage in Adults**

Obtain haemoglobin (Hgb) and platelet count prior to the first dose of WINREVAIR. Rapid increases in Hgb of more than 2 g/dL have been observed after initiating treatment. It is not recommended to initiate treatment if platelet count is <50,000/$mm^3$ (<50.0 x $10^9$/L). [See section 4.2 Dose and Method of Administration (Dosage Modifications in Adults Due to Haemoglobin Increase or Platelet Count)]

WINREVAIR is administered once every 3 weeks by subcutaneous (SC) injection according to patient weight. The starting dose of WINREVAIR is 0.3 mg/kg (see Table 1).

**Table 1: Injection Volume for Dose of 0.3 mg/kg**

| Patient Weight Range (kg)* | Injection Volume (mL) | Administration Pack | Vial |
|---|---|---|---|
| 30.0 – 40.8 | 0.2 | 45 mg pack (containing 1x 45mg vial) | 45 mg |
| 40.9 – 57.4 | 0.3 | | |
| 57.5 – 74.1 | 0.4 | | |
| 74.2 – 90.8 | 0.5 | | |
| 90.9 – 107.4 | 0.6 | | |
| 107.5 – 124.1 | 0.7 | | |
| 124.2 – 140.8 | 0.8 | | |
| 140.9 – 157.4 | 0.9 | | |
| 157.5 – 174.1 | 1.0 | 60 mg pack (containing 1x 60mg vial) | 60 mg |
| 174.2 – 180.0 | 1.1 | | |

**Recommended Target Dosage in Adults**

Three weeks after a single starting dose of 0.3 mg/kg, the dose should be escalated to the recommended target dose of 0.7 mg/kg after verifying acceptable Hgb and platelet count (see Section 4.2 Dosage Modification in Adults Due to Haemoglobin Increase or Platelet Count Decrease). Treatment should be continued at 0.7 mg/kg every 3 weeks unless dose adjustments are required.

The target dose of WINREVAIR is 0.7 mg/kg (see Table 2) administered every 3 weeks.

**Table 2: Injection Volume for Dose of 0.7 mg/kg**

| Patient Weight Range (kg)* | Injection Volume (mL) | Administration Pack | Vial |
|---|---|---|---|
| 30.0 – 31.7 | 0.4 | 45 mg pack (containing 1x 45mg vial) | 45 mg |
| 31.8 – 38.9 | 0.5 | | |
| 39.0 – 46.0 | 0.6 | | |
| 46.1 – 53.2 | 0.7 | | |
| 53.3 – 60.3 | 0.8 | | |
| 60.4 – 67.4 | 0.9 | | |
| 67.5 – 74.6 | 1.0 | 60 mg pack (containing 1x 60mg vial) | 60 mg |
| 74.7 – 81.7 | 1.1 | | |
| 81.8 – 88.9 | 1.2 | | |
| 89.0 – 96.0 | 1.3 | 90 mg pack (containing 2x 45 mg vial) | 2 x 45 mg |
| 96.1 – 103.2 | 1.4 | | |
| 103.3 – 110.3 | 1.5 | | |
| 110.4 – 117.4 | 1.6 | | |
| 117.5 – 124.6 | 1.7 | | |
| 124.7 – 131.7 | 1.8 | | |
| 131.8 – 138.9 | 1.9 | 120 mg pack (containing 2x 60 mg vial) | 2 x 60 mg |
| 139.0 – 146.0 | 2.0 | | |
| 146.1 – 153.2 | 2.1 | | |
| 153.3 – 160.3 | 2.2 | | |
| 160.4 – 167.4 | 2.3 | | |
| 167.5 and above | 2.4 | | |

Missed Dose or Overdose

If a dose of WINREVAIR is missed, administer as soon as possible. If the missed dose of WINREVAIR is not taken within 3 days of the scheduled date, adjust the schedule to maintain 3-week dosing intervals. In case of an overdose, monitor for erythrocytosis [see Section 4.9 Overdose]. In case of overdose when WINREVAIR is administered by patient or caregiver, retrain the patient or caregiver if appropriate or consider ongoing administration by a healthcare professional (see Section 4.9 Overdose).

## Dosage Adjustment

**Dosage Modifications in Adults Due to Haemoglobin Increase or Platelet Count Decrease**
Increases in Hgb to levels greater than 2 g/dL above the upper limit of normal (ULN) and decreases in platelet count <50,000/$mm^3$ (<50.0 x $10^9$/L) have been observed. 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. Consider assessment of benefit-risk for the individual patient in determining whether dose modification is appropriate [see Section 4.4 Special Warnings and Precautions for Use].

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

- Hgb increases >2.0 g/dL from the previous dose and is above ULN.
- Hgb increases >4.0 g/dL from baseline.
- Hgb increases >2.0 g/dL above ULN.
- Platelet count decreases to <50,000/$mm^3$ (<50.0 x $10^9$/L).

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

**Renal Impairment**
No dose adjustment of WINREVAIR is required based on renal impairment. Sotatercept has not been studied in PAH patients with severe renal impairment (eGFR <30 mL/min/1.73$m^2$) [see Section 4.4 Special Warnings and Precautions for Use and Section 5.2 Pharmacokinetic Properties].

**Hepatic Impairment**
WINREVAIR use has not been studied in patients with hepatic impairment (Child-Pugh Classification A to C). Hepatic impairment is not expected to influence sotatercept metabolism since sotatercept is metabolised via cellular catabolism [see Section 4.4 Special Warnings and Precautions for Use and Section 5.2 Pharmacokinetic Properties].

**Paediatric Patients**
Safety and efficacy of WINREVAIR have not been established in patients less than 18 years of age.

**Elderly Patients**
No dose adjustment of WINREVAIR is required based on age [see Section 4.4 Special Warnings and Precautions for Use].

## Method of Administration

**Administration Pack Presentation**
WINREVAIR is intended for use under the guidance of a health care professional. Patients and caregivers may administer WINREVAIR when considered appropriate and when they receive training and follow-up from the doctor in how to reconstitute, prepare, measure, and inject WINREVAIR.

Consider confirming at subsequent visits that the patient or caregiver can prepare and administer WINREVAIR correctly:

- if the dose changes or the patient requires a different administration pack
- if the patient develops erythrocytosis [see Section 4.4 Special Warnings and Precautions for Use].

Refer to the Instructions for Use (IFU) for detailed instructions on the proper preparation and administration of WINREVAIR.

Selecting the Appropriate Administration Pack
If a patient's weight requires the use of two 45 mg vials or two 60 mg vials of lyophilized product, a 2-vial administration pack should be used instead of two individual 1-vial administration packs. A 2-vial administration pack includes instructions to combine the contents of two vials, which aids in measuring the proper dosage and eliminates the need for multiple injections [see Section 6.5 Nature and Contents of Container].

Reconstitution Instructions

- Remove the administration pack from the refrigerator and wait 15 minutes to allow the prefilled syringe(s) and drug product to come to room temperature prior to preparation.
- Check the vial to ensure the product is not expired. The powder should be white to off-white and may look like a whole or fragmented cake.
- Remove the lid from the vial containing the WINREVAIR lyophilized powder and swab the rubber stopper with an alcohol wipe.
- Attach the vial adapter to the vial.
- Visually inspect the pre-filled syringe for any damage or leaks and the sterile water inside to ensure there are no visible particles.
- Snap off the cap of the pre-filled syringe and attach the syringe to the vial adapter.
- Inject all of the sterile water from the attached syringe into the vial containing the lyophilized powder. This will provide a final concentration of 50 mg/mL.
- Gently swirl the vial to reconstitute the drug product. DO NOT shake or vigorously agitate.
- Allow the vial to stand for up to 3 minutes to allow bubbles to disappear.
- Visually inspect the reconstituted solution. When properly mixed, WINREVAIR should be clear to opalescent and colorless to slightly brownish-yellow and does not have clumps or powder.
- Unscrew the syringe from the vial adapter and discard the emptied syringe into a sharps container.
- If prescribed a 2-vial presentation, repeat the steps within this section to prepare the second vial.
- Use the reconstituted solution as soon as possible, but no later than 4 hours after reconstitution.

Syringe Preparation

- Swab the vial adapter with an alcohol wipe.
- Remove dosing syringe from packaging and attach the syringe to the vial adapter.
- Turn the syringe and vial upside-down and withdraw the appropriate volume for injection, based on the patient's weight.
    - If the dose amount requires the use of two vials, withdraw the entire contents of the first vial and slowly transfer full contents into the second vial.
    - Turn the syringe and vial upside-down and withdraw the required amount of drug product.
- If necessary, push plunger in to remove excess drug product or air from the syringe.
- Remove the syringe from the vial and attach the needle.

Administration Instructions

WINREVAIR is for subcutaneous injection.

- Select the injection site on the abdomen (at least 2 inches away from navel), upper thigh, or upper arm, and swab with an alcohol wipe. Select a new site for each injection that is not scarred, tender, or bruised.
    - For administration by the patient or caregiver, use only the abdomen and upper thigh (see IFU).
- Perform subcutaneous injection.
- Discard the emptied syringe into a sharps container. Do not reuse the syringe.

## 4.3 CONTRAINDICATIONS

WINREVAIR is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**Erythrocytosis**

Hgb increases have been observed in patients during treatment with WINREVAIR. Severe erythrocytosis (high haemoglobin) 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 [see Section 4.2 Dose and Method of Administration and Section 4.8 Adverse Effects (Undesirable Effects)].

**Severe Thrombocytopenia**

Decreased platelet count has been observed in some patients taking WINREVAIR and severe thrombocytopenia (platelet count <50,000/$mm^3$ (<50.0 x $10^9$/L)) has been observed. Thrombocytopenia

occurred more frequently in patients also receiving prostacyclin infusion.

Do not initiate treatment if platelet count is <50,000/mm3 (<50 x 109/L) [see Section 4.2 Dose and Method of Administration].

Monitor platelet count before each dose for the first 5 doses, or longer if values are unstable and periodically thereafter to determine whether dose adjustments are required [see Section 4.2 Dose and Method of Administration and Section 4.8 Adverse Effects (Undesirable Effects)].

**Serious Bleeding**
In clinical studies, serious bleeding events (e.g., gastrointestinal, intracranial hemorrhage) were reported in 4% of patients taking WINREVAIR and 1% of patients taking placebo. Patients with serious bleeding events were more likely to be on prostacyclin background therapy and/or antithrombotic agents, or have low platelet counts. Advise patients about signs and symptoms of blood loss. Evaluate and treat bleeding accordingly. Do not administer WINREVAIR if the patient is experiencing a serious bleeding event [see Section 4.8 Adverse Effects (Undesirable Effects)].

**Embryofetal Toxicity**
Based on findings in animal reproduction studies, WINREVAIR may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with WINREVAIR and for at least 4 months after the final dose [see Section 4.6 Fertility, Pregnancy and Lactation].

**Impaired Fertility**
Based on findings in animals, WINREVAIR may impair female and male fertility. Advise patients on the potential effects on fertility [see Section 4.6 Fertility, Pregnancy and Lactation].

**Use in Renal Impairment**
No dose adjustment of WINREVAIR is required based on renal impairment. Sotatercept has not been studied in PAH patients with severe renal impairment (eGFR <30 mL/min/1.73m$^2$) [see Section 4.2. Dose and Method of Administration and Section 5.2 Pharmacokinetic Properties].

**Use in Hepatic Impairment**
WINREVAIR use has not been studied in patients with hepatic impairment (Child-Pugh Classification A to C). Hepatic impairment is not expected to influence sotatercept metabolism since sotatercept is metabolised via cellular catabolism [see Section 4.2. Dose and Method of Administration and Section 5.2 Pharmacokinetic Properties].

**Use in the Elderly**
No dose adjustment of WINREVAIR is required based on age. A total of 81 patients ≥65 years of age participated in clinical studies for PAH, of which 52 (16%) were treated with WINREVAIR.

No overall differences in efficacy of WINREVAIR have been observed between the <65-year-old and ≥65-year-old subgroups.

With the exception of bleeding events (a collective group of adverse events of clinical interest), there were no differences in safety between the <65-year-old and ≥65-year-old subgroups. Bleeding events occurred more commonly in the older WINREVAIR subgroup; however, there was no notable imbalance between age subgroups for any specific bleeding event.

**Paediatric Use**
Safety and efficacy of WINREVAIR have not been established in patients less than 18 years of age.

**Effects on laboratory tests**
Not applicable.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No other interaction studies have been performed.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Effects on Fertility

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential before starting treatment.

Contraception

*Females*

Females of reproductive potential should use effective contraception during treatment with WINREVAIR and for at least 4 months after the last dose if treatment is discontinued [see Use in Pregnancy].

Infertility

Based on findings in animals, sotatercept may impair female and male fertility.

Reproduction

In a fertility and early embryonic development study in female rats, sotatercept was administered SC once weekly at doses of 5, 15, and 50 mg/kg beginning 2 weeks prior to mating and through gestation day 7. At doses ≥ 15 mg/kg (≥ 9-fold the MRHD, based on estimated AUC), pregnancy rates were decreased and there were increases in pre-implantation and post-implantation loss and reductions in live litter size. Increased oestrous cycle duration occurred at 50 mg/kg only (21-fold the MRHD, based on estimated AUC).

In a fertility study in male rats, sotatercept was administered SC once weekly at doses of 0.3, 3, and 30 mg/kg for 13 weeks (beginning 10 weeks prior to mating). A subset of animals was examined after a 13-week recovery period. At ≥ 0.3 mg/kg (0.5-fold the MRHD, based on estimated AUC) there were non-reversible histologic changes in the efferent ducts, testes, and epididymides. Reversible decreases in functional fertility endpoints occurred at 30 mg/kg (20-fold the MRHD, based on estimated AUC).

### Use in Pregnancy - Category D

Risk Summary

There are no available data on WINREVAIR use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. However, based on animal embryofetal toxicity studies, WINREVAIR may cause post-implantation loss or fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus.

Animal Data

In embryo-fetal developmental toxicity studies, pregnant animals were dosed subcutaneously with sotatercept during the period of organogenesis. Sotatercept was administered to rats on gestation days 6 and 13 at doses of 5, 15, or 50 mg/kg and to rabbits on gestation days 7 and 14 at doses of 0.5, 1.5, or 5 mg/kg. Effects in both species included lower numbers of live fetuses and fetal body weights, delays in ossification, and increases in resorptions and post-implantation losses. In rats and rabbits, these effects were observed at exposures (based on area under the curve (AUC)) approximately 4-fold and 0.6-fold the maximum recommended human dose (MRHD), respectively. In rats only, skeletal variations (increased number of supernumerary ribs and changes in the number of thoracic or lumbar vertebrae) occurred at an exposure 15-fold the human exposure at the MRHD.

In a pre- and postnatal development study in rats, sotatercept was administered subcutaneously at doses of 1.5 and 5 mg/kg on gestation days 6 and 13, or at dosages of 1.5, 5, or 10 mg/kg during lactation on days 1, 8, and 15. There were no adverse effects in first filial generation (F1) pups from dams dosed during gestation at estimated exposures up to 2-fold the MRHD. In F1 pups from dams dosed during lactation, lower pup weight and delays in sexual maturation were seen at estimated exposures (based on AUC) ≥ 2-fold the MRHD.

### Use in Lactation

Risk Summary

There are no data on the presence of sotatercept in human milk, the effects on the breastfed infant, or the effects on milk production. In a rat pre/postnatal study, lower weights and delayed sexual maturation were seen in breast-fed pups following maternal exposure to sotatercept. Since it is not known if sotatercept is excreted in human breast milk, breastfeeding is not recommended during treatment with sotatercept and for 4 months after the final dose.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of this medicine on a person's ability to drive and use machines were performed as part of its registration.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

**Clinical Trials Experience**
The following data reflect exposure to WINREVAIR in the pivotal STELLAR trial. Patients (n=323) were randomised in a 1:1 ratio to receive WINREVAIR or placebo in combination with background standard of care (SOC) therapies. Patients received a starting dose of 0.3 mg/kg via SC injection and the dose was increased to the target dose of 0.7 mg/kg once every 3 weeks for 24 weeks. After completing the primary 24-week treatment phase, patients continued into a long-term double-blind (LTDB) treatment period, maintaining their current therapy, until all patients completed the primary treatment period. The median durations of treatment were similar between the placebo and WINREVAIR groups (229.5 days vs 252.0 days, respectively) [see Section 5.1 Pharmacodynamic Properties – Clinical Trials].

Adverse events occurring in STELLAR by the time all patients completed the primary 24-week period of the study are summarised in Table 3.

**Table 3: Treatment-Emergent Adverse Events Experienced by ≥5% in One or More Treatment Groups Term Week 24 Results (DBPC)***

| Adverse Event | Placebo N=160 n(%) | WINREVAIR N=163 n(%) |
|---|---|---|
| Headache | 24 (15.0) | 33 (20.2) |
| COVID-19 | 21 (13.1) | 24 (14.7) |
| Nausea | 18 (11.3) | 16 (9.8) |
| Diarrhea | 12 (7.5) | 20 (12.3) |
| Fatigue | 12 (7.5) | 17 (10.4) |
| Epistaxis | 3 (1.9) | 20 (12.3) |
| Telangiectasia | 5 (3.1) | 17 (10.4) |
| Injection site pain | 10 (6.3) | 11 (6.7) |
| Dizziness | 3 (1.9) | 17 (10.4) |
| Thrombocytopenia† | 4 (2.5) | 10 (6.1) |
| Dyspnoea | 14 (8.8) | 4 (2.5) |
| Oedema peripheral | 10 (6.3) | 8 (4.9) |
| Nasopharyngitis | 9 (5.6) | 7 (4.3) |
| Hypokalaemia | 5 (3.1) | 9 (5.5) |
| Rash | 4 (2.5) | 9 (5.5) |
| Flushing | 3 (1.9) | 9 (5.5) |
| Increased Haemoglobin‡ | 0 (0.0) | 9 (5.5) |

N = number of subjects in the treatment group. n = number of subjects in the category.
* Double-blind placebo-controlled period.
† Composites of preferred terms: Thrombocytopenia and Platelet Count increased.
‡ Composites of preferred terms: Haemoglobin increased and Polycythaemia.

**Description of Selected Adverse Reactions from STELLAR (DBPC+LTDB)**

Increased Haemoglobin
The majority of events of increased Hgb (Hgb increased, polycythemia) were non-serious, mild, and reversible, and were not associated with discontinuation of therapy. Moderate elevations in Hgb (>2 g/dL above ULN) occurred in 12.3% of patients taking WINREVAIR. No severe elevations (≥4 g/dL above ULN) were observed. Increases in Hgb were manageable by dose delays, dose reductions, or both.

Thrombocytopenia
The majority of events of thrombocytopenia (thrombocytopenia and platelet count decreased) were non-serious, mild, reversible, and have not been associated with discontinuation of therapy. Severe reduction

in platelet count <50,000/mm$^3$ (<50.0 x 10$^9$/L) occurred in 1.8% of patients taking WINREVAIR.

Telangiectasia
Events of telangiectasia were non-serious and did not progress in severity over time. In all patients exposed to WINREVAIR, the median time to onset was 47.1 weeks. Discontinuations of therapy due to telangiectasia were 1% in the WINREVAIR group vs 0% in the placebo group. No episodes of serious bleeding have been associated with telangiectasia.

Increased Blood Pressure
Events of increased blood pressure (hypertension, blood pressure diastolic increased, blood pressure increased) were nonserious and no severe events were reported. In patients taking WINREVAIR, mean systolic blood pressure increased from baseline by 2.2 mmHg and diastolic blood pressure increased by 4.9 mmHg at 24 weeks. In patients taking placebo, the change from baseline in mean systolic blood pressure was -1.6 mmHg and -0.6 mmHg change in diastolic blood pressure.

Treatment Discontinuation
The overall incidence of treatment discontinuations due to an adverse reaction was 4% in the WINREVAIR group and 7% in the placebo group. There were no specific adverse reactions causing treatment discontinuations that occurred with a frequency greater than 1% and more often in the WINREVAIR group.

Long-term Safety Data
Long-term safety data are available from pooled phase 2 and phase 3 clinical studies (n=431). The median duration of exposure was 657 days. The safety profile was generally similar to that observed in the pivotal STELLAR study.

In SOTERIA, an ongoing open-label study of the long-term safety and efficacy of WINREVAIR, right-to-left intrapulmonary shunting has been reported in 2 participants (<0.5%) who developed worsening hypoxemia despite improved PAH haemodynamics.

**Immunogenicity**
The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the study described below with the incidence of anti-drug antibodies in other studies, including those of WINREVAIR or of other sotatercept products.

During the 24-week treatment period in the pivotal study (STELLAR), 44/163 (27%) of sotatercept-treated patients developed anti-sotatercept antibodies. Among these 44 patients, 12 (27%) tested positive for neutralising antibodies against sotatercept. Anti-sotatercept antibodies generally had low titers with a median titer of 30 (range <20 to 640).

There were no identified clinical effects of anti-sotatercept antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of sotatercept over the treatment duration of 24 weeks.

**Post-marketing experience**
The following adverse reaction has been reported during post-approval use of WINREVAIR. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Cardiac disorders:* pericardial effusion

**Reporting suspected adverse effects**
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

## 4.9 OVERDOSE

In healthy volunteers, WINREVAIR dosed at 1 mg/kg resulted in increases in Hgb associated with hypertension; both improved with phlebotomy. In the event of overdose, monitor closely for increases in

Hgb and blood pressure, and provide supportive care as appropriate. WINREVAIR is not dialysable during haemodialysis.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

**Mechanism of action**
Sotatercept, a recombinant activin receptor type IIA-Fc (ActRIIA-Fc) fusion protein, is an activin signalling inhibitor that binds to activin A and other TGF- β superfamily ligands. As a result, sotatercept improves the balance between the pro-proliferative (ActRIIA/Smad2/3-mediated) and anti-proliferative (BMPRII/Smad1/5/8-mediated) signalling to modulate vascular proliferation. In rodent-models of PAH, a sotatercept-csrk analogue reduced inflammation and inhibited proliferation of endothelial and smooth muscle cells in diseased vasculature. These cellular changes were associated with thinner vessel walls, reversal of right ventricular remodelling, and improved haemodynamics.

**Pharmacodynamics**
A Phase 2 clinical study assessed pulmonary vascular resistance (PVR) in patients with PAH after 24 weeks of treatment with sotatercept. The decrease from baseline in PVR was significantly greater in the sotatercept 0.7 mg/kg and 0.3 mg/kg groups compared with the placebo group. The placebo-adjusted least squares (LS) mean difference from baseline was -269.4 dynes*sec/cm$^5$ (95% CI: -365.8, -173.0) for the sotatercept 0.7 mg/kg group and -151.1 dynes*sec/cm$^5$ (95% CI: -249.6, -52.6) for the sotatercept 0.3 mg/kg group. In STELLAR, the decrease from baseline in PVR was also significantly greater in the sotatercept 0.7 mg/kg group compared with the placebo group.

**Clinical Trials**

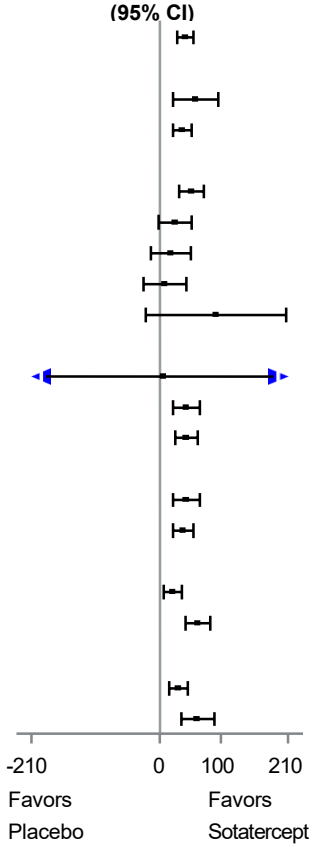
**Pulmonary Arterial Hypertension Adult Subjects**
The efficacy of WINREVAIR was evaluated in adult patients with PAH in the STELLAR trial. STELLAR was a global, double-blind, placebo-controlled, multicenter, parallel-group clinical trial in which 323 patients with PAH (WHO Group 1 FC II or III) were randomised 1:1 to WINREVAIR (target dose 0.7 mg/kg) (n=163) or placebo (n=160) administered subcutaneously once every 3 weeks.

The demographic and baseline clinical characteristics were generally comparable between the WINREVAIR and placebo groups. Participants in this study were adults with a median age of 48.0 years (range: 18 to 82 years); median weight 68 kg (range: 38.0 to 141.3 kg); 89.2% of participants were White, and 79.3% were not Hispanic or Latino; and 79.3% were female. The most common PAH etiologies were idiopathic PAH (58.5%), heritable PAH (18.3%), and PAH associated with connective tissue diseases (CTD) (14.9%). The mean time since PAH diagnosis to screening was 8.76 years. Most participants were receiving either triple (61.3%) or double (34.7%) background PAH therapy, and more than one-third (39.9%) were receiving prostacyclin infusions. The proportions of participants in WHO FC II (48.6%) and WHO FC III (51.4%) were similar in both groups. The STELLAR trial excluded patients diagnosed with human immunodeficiency virus (HIV)-associated PAH, PAH associated with portal hypertension, schistosomiasis-associated PAH, and pulmonary veno occlusive disease.

The primary efficacy endpoint was the change from baseline at Week 24 in 6-Minute Walk Distance (6MWD). In the WINREVAIR treatment group, the median of the placebo-adjusted change in 6MWD from baseline at Week 24 was 40.8 meters (95% CI: 27.5, 54.1; p <0.001). The median of the placebo-adjusted changes in 6MWD at Week 24 were also evaluated in subgroups (see Figure 1).

**Figure 1: Change from Baseline in 6-Minute Walk Distance (meters) at Week 24 in Subgroups**

| Subgroup | Placebo (N=160) n | Sotatercept (N=163) n | Sotatercept vs. Placebo HL* Location Shift (95% CI) | Sotatercept vs. Placebo HL* Location Shift (ASE) (95% CI) |
|---|---|---|---|---|
| Overall | 160 | 163 | | 40.8 (6.79) (27.53, 54.14) |
| Sex | | | | |
| Male | 33 | 34 | | 58.5 (19.46) (20.34, 96.61) |
| Female | 127 | 129 | | 37.2 (7.50) (22.47, 51.87) |
| PAH Diagnostic Group | | | | |
| iPAH [idiopathic PAH] | 106 | 83 | | 51.3 (9.74) (32.17, 70.35) |
| hPAH [heritable PAH] | 24 | 35 | | 25.6 (13.76) (-1.34, 52.61) |
| Drug/Toxin-induced PAH | 4 | 7 | | 18.4 (16.78) (-14.51, 51.25) |
| Connective Tissue Disease | 19 | 29 | | 8.7 (17.96) (-26.55, 43.86) |
| CHD with s/p Shunt Repair | 7 | 9 | | 92.4 (58.60) (-22.49, 207.26) |
| Background therapy at baseline | | | | |
| Monotherapy | 4 | 9 | | 6.3 (534.33) (-564.54, 1530.01) |
| Double | 56 | 56 | | 43.2 (11.32) (21.03, 65.42) |
| Triple | 100 | 98 | | 43.5 (8.65) (26.51, 60.44) |
| Prostacyclin infusion therapy at baseline | | | | |
| Yes | 64 | 65 | | 43.1 (10.45) (22.61, 63.59) |
| No | 96 | 98 | | 38.6 (8.88) (21.20, 56.00) |
| WHO Functional Class | | | | |
| II | 78 | 79 | | 21.7 (7.68) (6.63, 36.72) |
| III | 82 | 84 | | 61.7 (10.64) (40.90, 82.59) |
| Baseline PVR | | | | |
| <=800 (dynes*sec/cm^5) | 108 | 108 | | 30.8 (7.77) (15.54, 45.98) |
| >800 (dynes*sec/cm^5) | 52 | 55 | | 61.6 (13.48) (35.23, 88.06) |




CHD = Congenital heart disease

* Hodges-Lehmann location shift from placebo estimate (median of all paired differences). ASE = asymptotic standard error. Change from baseline in 6MWD at Week 24 for subjects who died was assigned a value of to -2000 meters to receive the worst rank. Change from baseline in 6MWD at Week 24 for subjects who have missing data due to a non-fatal clinical worsening event was imputed to -1000 meters to receive the next worst-rank.

Clinical improvement was a pre-defined endpoint measured by the proportion of patients achieving all three of the following criteria at Week 24 relative to baseline: improvement in 6MWD (increase ≥30 m), improvement in N-terminal pro-B-type natriuretic peptide (NT-proBNP) (decrease in NT-proBNP ≥30% or maintenance/achievement of NT-proBNP level <300 ng/L), and improvement in WHO FC or maintenance of WHO FC II. Disease progression was measured by the time to death or first occurrence of a clinical worsening event. Clinical worsening events and death were captured until the last patient completed the week 24 visit (data up to the data cutoff; median duration of exposure 33.6 weeks).

WINREVAIR-treated patients experienced statistically significant clinical improvement, improvement in WHO FC, and delayed disease progression, including reduced risk of death and hospitalisation versus placebo-treated patients (see Table 4, Table 5, and Figure 2).

**Table 4: Secondary Efficacy Results of STELLAR**

| Endpoint | Placebo (N=160) | WINREVAIR (N=163) | 95% CI | p-value |
|---|---|---|---|---|
| **Proportion of Patients Achieving Multicomponent Improvement* (MCI) from Baseline at Week 24, n (%)** | 16 (10.1) | 63 (38.9)† | N/A | <.001‡ |

| Endpoint | Placebo (N=160) | WINREVAIR (N=163) | 95% CI | p-value |
|---|---|---|---|---|
| **Change from Baseline PVR at Week 24 (ASE) (dynes*sec/cm^5)** | N/A | -234.6 (27.5)[§] | (-288.4, -180.8) | <.001[¶] |
| **Change from Baseline NT-proBNP Levels at Week 24 (ASE) (pg/mL)** | N/A | -441.6 (67.3)[#] | (-573.5, -309.6) | <.001[¶] |
| **Proportion of Patients who Improve FC Class from Baseline at Week 24, n (%)** | 22 (13.8) | 48 (29.4)[†] | N/A | <.001[‡] |
| **Time to Death or the First Occurrence of a Worsening Event[Þ], n (%)** | 42 (26.3) | 9 (5.5) | 0.163 (0.076, 0.347)[ß] | <.001[à] |
| **Proportion of Patients who Maintained or Achieved a Low Risk Score[è] at Week 24 vs. Baseline, n (%)** | 29 (18.2) | 64 (39.5) | N/A | <.001[‡] |
| **Change from Baseline in the Physical Impacts Domain Score of PAH-SYMPACT®[ð] at Week 24 (ASE)** | N/A | -0.26 (0.115)[ø] | (-0.490, -0.040) | 0.010[¶] |
| **Change from Baseline in the Cardiopulmonary Symptoms Domain Score of PAH-SYMPACT®[ð] at Week 24 (ASE)** | N/A | -0.13 (0.062)[ø] | (-0.256, -0.014) | 0.028[¶] |
| **Change from baseline in the Cognitive/Emotional Impacts Domain Score of PAH-SYMPACT®[ð] at Week 24 (ASE)** | N/A | -0.16 (0.123)[ø] | (-0.399, 0.084) | 0.156[¶] |

ASE= asymptotic standard error.

Note: Wherever stratified randomisation factors were used, the stratified randomisation factors were baseline WHO FC (Class II or III) and background PAH therapy (mono/double or triple therapy).

* A patient satisfies the MCI if all of the following occur at Week 24 relative to baseline: Improvement in 6MWD (increase ≥30 m), improvement in NT-proBNP (decrease ≥30% or maintenance/achievement of NT-proBNP <300 pg/mL), and improvement in WHO FC or maintenance of WHO FC II.

† A missing result at Week 24 not due to COVID-19 was considered a non-responder. Subjects who missed assessments due to COVID-19 were removed from the denominator.

‡ Comparison with placebo uses Cochran-Mantel-Haenszel (CMH) method stratified by randomisation factors.

§ Hodges-Lehmann location shift from placebo estimate (median of all paired differences). Change from baseline in PVR at Week 24 for subjects who died was assigned as 20000 to receive the worst rank. Change from baseline in PVR at Week 24 for subjects who had missing data due to a non-fatal clinical worsening event was imputed as 15000 to receive the next-worst rank.

¶ Wilcoxon p-value refers to p-value from the aligned rank-stratified Wilcoxon test with randomisation factors as strata.

# Hodges-Lehmann location shift from placebo estimate (median of all paired differences). Change from baseline in NT-proBNP at Week 24 for subjects who died was assigned as 200000 to receive the worst rank. Change from baseline in NT-proBNP at Week 24 for subjects who had missing data due to a non-fatal clinical worsening event was imputed as 150000 to receive the next-worst rank.

Þ Time to death or the first occurrence of any of the following clinical worsening events: a) worsening-related listing for lung and/or heart transplant, b) need to initiate rescue therapy with an approved background PAH therapy or the need to increase the dose of infusion prostacyclin by 10% or more, c) need for atrial septostomy, d) hospitalisation for worsening of PAH (≥24 hours), e) deterioration of PAH defined by both of the following events occurring at any time (even if they began at different times) as compared to their baseline values: worsened WHO FC and decrease in 6MWD by ≥15% confirmed by 2 tests at least 4 hours apart but no more than 1 week.

ß The hazard ratio (WINREVAIR/ placebo) was derived from a Cox proportional hazard model with treatment group as the covariate stratified by the randomisation factors.

à Log-rank test comparison with placebo stratified by the randomisation factors.

è Utilising French Risk score calculator

ð Pulmonary Arterial Hypertension-Symptoms and Impact

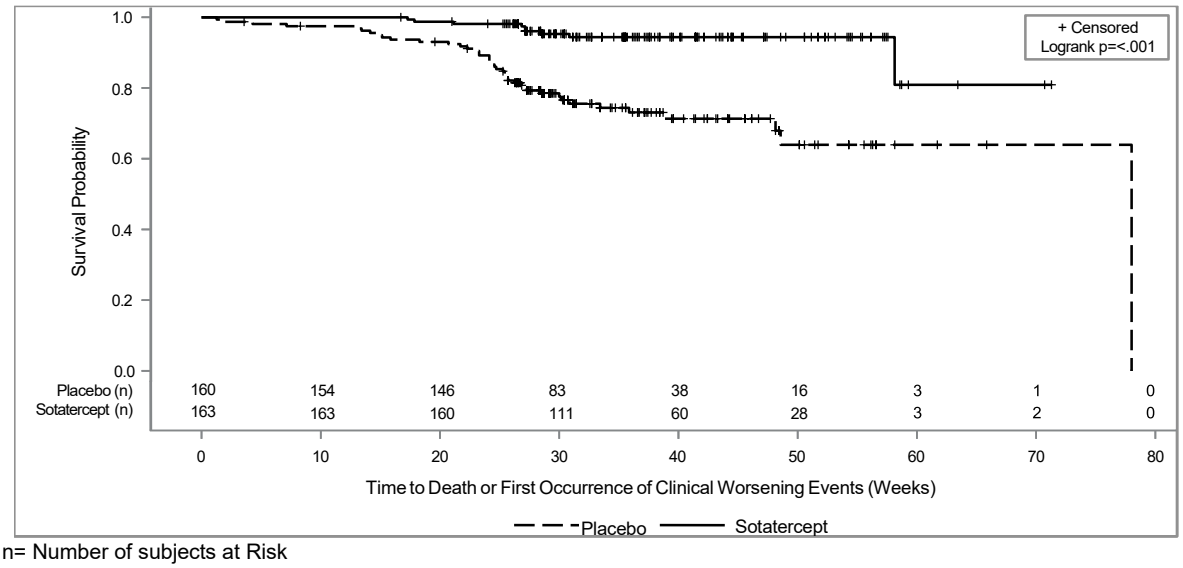
ø Hodges-Lehmann location shift from placebo estimate (median of all paired differences). Change from baseline in SYMPACT scores at Week 24 for subjects who died was assigned as 200 to receive the worst rank. Change from baseline in SYMPACT scores at Week 24 for subjects who had missing data due to a non-fatal clinical worsening event was imputed as 150 to receive the next-worst rank.

**Table 5: Death or Clinical Worsening Events**

| | Placebo (N=160) | WINREVAIR (N=163) |
|---|---|---|
| Total number of subjects who experienced death or at least one clinical worsening event, n (%) | 42 (26.3) | 9 (5.5) |
| Assessment of death or first occurrence of clinical worsening events*, n (%) | | |
| Death | 6 (3.8) | 2 (1.2) |
| Worsening-related listing for lung and/or heart transplant | 1 (0.6) | 1 (0.6) |
| Need to initiate rescue therapy with an approved PAH therapy or the need to increase the dose of infusion prostacyclin by 10% or more | 17 (10.6) | 2 (1.2) |
| Need for atrial septostomy | 0 (0.0) | 0 (0.0) |
| PAH-specific hospitalisation (≥24 hours) | 7 (4.4) | 0 (0.0) |
| Deterioration of PAH† | 15 (9.4) | 4 (2.5) |

* A subject can have more than one assessment recorded for their first event of clinical worsening. There were 3 placebo subjects and 0 sotatercept subjects who had more than one assessment recorded for their first event of clinical worsening.
† Deterioration of PAH therapy is defined by both of the following events occurring at any time, even if they began at different times, as compared to their baseline values: (a) Worsened WHO functional class (II to III, III to IV, II to IV, etc.); and (b) Decrease in 6MWD by ≥15% (confirmed by two 6MWTs at least 4 hours apart but no more than one week).
N = number of subjects in FAS population; n = number of subjects in the category. Percentages are calculated as (n/N)*100.

**Figure 2: Time to Death or First Occurrence of Clinical Worsening Events Kaplan-Meier Plot**




n= Number of subjects at Risk

## 5.2 PHARMACOKINETIC PROPERTIES

In patients with PAH, the geometric mean (%CV) steady-state AUC and steady-state peak concentration ($C_{max}$) at the dose of 0.7 mg/kg Q3W were 171.3 mcg×d/mL (34.2%) and 9.7 mcg/mL (30%CV), respectively. Sotatercept AUC and $C_{max}$ increase proportionally with dose. Steady state is achieved after approximately 15 weeks upon multiple Q3W dosing. The accumulation ratio of sotatercept AUC was approximately 2.2.

### Absorption

The SC formulation has an absolute bioavailability of approximately 66%. The maximum sotatercept

concentration is achieved at a median time to peak drug concentration ($T_{max}$) of approximately 7 days (range from 2 to 8 days) after multiple (0.1 mg/kg every 4 weeks) SC doses in post-menopausal women.

**Distribution**
The central volume of distribution (%CV) of sotatercept is approximately 3.6 L (24.7%). The peripheral volume of distribution (%CV) is approximately 1.7 L (73.3%).

**Metabolism**
Sotatercept is catabolised by general protein degradation processes.

**Elimination**
Sotatercept clearance is approximately 0.18 L/day. The geometric mean terminal half-life (%CV) is approximately 21 days (33.8%).

**Specific Populations**

**Age, Sex, and Race**
No clinically significant differences in sotatercept pharmacokinetics (PK) were observed based on age (18 to 81 years of age), sex, or race.

**Body Weight**
The clearance (CL) and central volume of distribution (Vc) of sotatercept increased with increasing body weight. The recommended weight-based dosing regimen results in consistent sotatercept exposures regardless of body weight.

**Renal Impairment**
Sotatercept PK was comparable in PAH patients with mild to moderate renal impairment (eGFR ranging from 30 to 89 mL/min/1.73m$^2$) to those with normal renal function (eGFR ≥90 mL/min/1.73m$^2$). Additionally, sotatercept PK is comparable between non-PAH end-stage kidney disease (ESKD) patients and patients with normal renal function. WINREVAIR is not dialysable during haemodialysis. No dose adjustment is recommended for renally impaired patients. Sotatercept has not been studied in PAH patients with severe renal impairment (eGFR <30 mL/min/1.73m$^2$).

**Hepatic Impairment**
Hepatic impairment (determined by Child-Pugh Classification) is not expected to influence sotatercept metabolism since sotatercept is metabolised via cellular catabolism. Sotatercept has not been studied in PAH patients with hepatic impairment (Child-Pugh Classification A to C).

## 5.3 PRECLINICAL SAFETY DATA

**Genotoxicity**
No data available. As a high molecular weight protein, sotatercept is not expected to interact directly with DNA or other chromosomal material.

**Carcinogenicity**
No data available.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

45 mg single-use vial: citric acid monohydrate (0.48 mg), polysorbate 80 (0.22 mg), sucrose (88 mg), and sodium citrate dihydrate (2.56 mg).

60 mg single-use vial: citric acid monohydrate (0.64 mg), polysorbate 80 (0.29 mg), sucrose (116 mg), and sodium citrate dihydrate (3.37 mg).

The product does not contain antimicrobial preservative.

## 6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in Section 4.2 Dose and Method of Administration.

## 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store vials refrigerated at 2°C to 8°C in original carton to protect from light. Do not freeze.

Use the reconstituted solution as soon as possible, but no later than 4 hours after reconstitution.

## 6.5 NATURE AND CONTENTS OF CONTAINER

WINREVAIR is a sterile, preservative-free, white to off-white lyophilised powder for injection available in 45 mg and 60 mg single-use vials.

The product is for single use in one patient only. Discard any residue.

WINREVAIR supplied in the following packaging configurations:

WINREVAIR 45 mg – carton containing 1 or 2 vials.
WINREVAIR 60 mg – carton containing 1 or 2 vials.

WINREVAIR 45 mg administration pack contains:

- 1 or 2 vials of powder for injection, 1 or 2 pre-filled syringes of sterile Water for Injections (1.0 mL each), 1 or 2 vial adaptors, 1 syringe for injection (3.0 mL), 1 needle, 4 or 8 alcohol wipes.

WINREVAIR 60 mg administration pack contains:

- 1 or 2 vials of powder for injection, 1 or 2 pre-filled syringes of sterile Water for Injections (1.3 mL each), 1 or 2 vial adaptors, 1 syringe for injection (3.0 mL), 1 needle, 4 or 8 alcohol wipes.

Not all presentations may be supplied.
None of the components contain natural rubber latex.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

## 6.7 PHYSICOCHEMICAL PROPERTIES

### Chemical structure

Sotatercept is a recombinant human homodimeric fusion protein consisting of the extracellular domain of the human activin receptor type IIA (ActRIIA) linked to the human IgG1 Fc domain. The molecular weight based on the amino acid sequence of sotatercept is approximately 78 kDa as a homodimer.

### CAS number

1001080-50-7

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

## 8 SPONSOR

**Merck Sharp & Dohme (Australia) Pty Limited**
Level 1, Building A,
26 Talavera Road
Macquarie Park NSW 2113
http://www.msd-australia.com.au
Tel: 1800 818 553

## 9 DATE OF FIRST APPROVAL

8 November 2024

## 10 DATE OF REVISION

16 January 2026

### Summary table of changes

| Section changed | Summary of new information |
|---|---|
| 4.8 | Addition of pericardial effusion to the Post-marketing Experience section. |

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