

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

 **WINREVAIR®**

Sotatercept for injection

45 mg for subcutaneous injection

60 mg for subcutaneous injection

C02KX6 Activin Signaling Inhibitor

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RECENT MAJOR LABEL CHANGES

Not applicable.

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

WINREVAIR® (sotatercept) is indicated:

- In combination with standard pulmonary arterial hypertension (PAH) therapy, for the treatment of adults with World Health Organization [WHO] Group 1 PAH and Functional Class (FC) II or III.

Efficacy has been shown in a PAH population including etiologies of idiopathic PAH, heritable PAH, PAH associated with connective tissue disease, drug- or toxin-induced PAH, or PAH associated with congenital heart disease with repaired shunts (see [14 CLINICAL TRIALS](#)).

1.1 Pediatrics

Pediatrics (less than 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of WINREVAIR® in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Clinical studies of WINREVAIR® did not include sufficient numbers of patients aged 75 and older to determine whether they respond differently from younger patients (see [7.1.4 Geriatrics](#) and [14 CLINICAL TRIALS](#)).

2 CONTRAINDICATIONS

Patients who are hypersensitive to sotatercept or to any ingredient in the formulation or component of the container. For a complete listing, see [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).

4 DOSAGE AND ADMINISTRATION

WINREVAIR® is intended for use under the guidance of a healthcare professional.

The **single-use vial (45 mg or 60 mg)** representation of WINREVAIR® is intended to be administered by a healthcare professional. Based on their weight a patient may require the use of two 45 mg vials or two 60 mg vials of lyophilized product.

The **single-use vials (45 mg or 60 mg) packaged in a kit** representation of WINREVAIR® is intended for administration by the patient or caregiver use under the guidance of a healthcare professional. Patients and caregivers may administer WINREVAIR® when considered appropriate and when they receive training and follow-up from the healthcare professional (HCP) in how to reconstitute, prepare, measure, and inject WINREVAIR®. Review the IFU with the patient or caregiver step-by-step. Provide training to the patient or caregiver regarding proper preparation and administration of WINREVAIR® and decide whether a patient or caregiver is capable of preparing and administering WINREVAIR® independently. Make sure the patient or caregiver can do the following correctly:

- reconstitute the medicine,
- measure the correct amount of medicine according to the patient's prescription,
- select and prepare a proper injection site, and

- inject the medicine subcutaneously.

If a patient's weight requires the use of two 45 mg vials or two 60 mg vials of lyophilized product, a 2-vial kit should be used instead of two individual 1-vial kits. A 2-vial kit includes instructions to combine the contents of two vials, which aids in measuring the proper dosage and eliminates the need for multiple injections (see [11 STORAGE, STABILITY and DISPOSAL](#)). The healthcare professional should 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 kit
- if the patient develops erythrocytosis (see [7 WARNINGS AND PRECAUTIONS](#) and [8 ADVERSE REACTIONS](#)).

4.1 Dosing Considerations

Considerations related to Hemoglobin or Platelet Count Prior to and During Treatment

Increases in Hgb to levels greater than 2 g/dL above the upper limit of normal (ULN) and decreases in platelet count $<50,000/\text{mm}^3$ ($<50.0 \times 10^9/\text{L}$) have been observed after initiating treatment.

Obtain hemoglobin (Hgb) and platelet count prior to the first dose of WINREVAIR® and after 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 **4.2 Recommended Dose and Dosage Adjustment/Dosage Modifications Due to Hemoglobin Increase or Platelet Count Decrease**). Do not initiate treatment if platelet count is $<50,000/\text{mm}^3$ ($<50.0 \times 10^9/\text{L}$) or if patient is experiencing a bleeding event.

Serious bleeding events and severe thrombocytopenia are more common with WINREVAIR® treatment in patients on prostacyclin therapy; exercise caution in initiating WINREVAIR® treatment in these patients (see [7 WARNINGS AND PRECAUTIONS](#) and [8 ADVERSE REACTIONS](#)).

4.2 Recommended Dose and Dosage Adjustment

WINREVAIR® is administered once every 3 weeks by subcutaneous (SC) injection according to patient weight.

Recommended Starting Dosage

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)	Single Dose Vial	Single Dose Vial packaged in a Kit
30.0 – 40.8	0.2	45 mg	45 mg kit (containing 1 x 45 mg vial)
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	60 mg kit (containing 1 x 60 mg vial)
174.2 – 180.0	1.1		

Recommended Target Dosage

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

Obtain and review hemoglobin (Hgb) and platelet count prior to increasing to the target dose. Continue treatment at 0.7 mg/kg every 3 weeks unless dosage adjustments are required (see **Dosage Modifications Due to Hemoglobin Increase or Platelet Count Decrease**, below).

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

Patient Weight Range (kg)	Injection Volume (mL)	Single Dose Vial(s)	Single Dose Vial(s) packaged in a Kit
30.0 – 31.7	0.4	45 mg	45 mg kit (containing 1 x 45 mg vial)
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	60 mg kit (containing 1 x 60 mg vial)
74.7 – 81.7	1.1		
81.8 – 88.9	1.2		
89.0 – 96.0	1.3	2 x 45 mg	90 mg kit (containing 2 x 45 mg vials)
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	2 x 60 mg	120 mg kit (containing 2 x 60 mg vials)
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		

Dosage Modifications Due to Hemoglobin Increase or Platelet Count Decrease

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/mm³ (<50.0 x 10⁹/L).

Continue to delay treatment until Hgb stabilizes and platelets are ≥50,000/mm³. For treatment delays lasting >9 weeks, restart treatment at the starting dose of 0.3 mg/kg. For treatment delays lasting >9 weeks, restart treatment at 0.3 mg/kg.

Dosing for Special Populations

Pediatric Patients: Health Canada has not authorized an indication for pediatric use.

Geriatric Patients: No dose adjustment of WINREVAIR® is required based on age (see [7.1.4 Geriatrics](#) and [10 CLINICAL PHARMACOLOGY](#)).

Renal Impairment: No dose adjustment of WINREVAIR® is required based on renal impairment.

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 metabolized via cellular catabolism (see [10 CLINICAL PHARMACOLOGY](#)).

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

4.3 Instructions for Preparation and Administration for KIT

WINREVAIR® is intended for use under the guidance of a healthcare professional. Patients and caregivers may administer WINREVAIR® when considered appropriate and when they receive training and follow-up from the healthcare professional 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 kit
- if the patient develops erythrocytosis (see [7 WARNINGS AND PRECAUTIONS](#))

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

Selecting the Appropriate Product Kit

If a patient's weight requires the use of two 45 mg vials or two 60 mg vials of lyophilized product, a 2-vial kit should be used instead of two individual 1-vial kits. A 2-vial kit includes instructions to combine the contents of two vials, which aids in measuring the proper dosage and eliminates the need for multiple injections (see [11 STORAGE, STABILITY and DISPOSAL](#)).

Reconstitution Instructions

- 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.
- 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

<u>Strength</u>	<u>Volume of Sterile Water for Injection to be Added to Vial</u>	<u>Approximate Available Volume</u>	<u>Concentration per mL</u>
<u>45 mg/vial</u>	<u>1.0 mL</u>	<u>0.9 mL</u>	<u>50 mg/mL</u>
<u>60 mg/vial</u>	<u>1.3 mL</u>	<u>1.2 mL</u>	<u>50 mg/mL</u>

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.

4.4 Preparation and Administration for VIAL

WINREVAIR® lyophilized powder should be prepared and administered by a healthcare professional. Step-by-step preparation and administration instructions are provided below.

Reconstitution Instructions

- Remove the vial(s) from the refrigerator and wait 15 minutes to allow the 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.
- Reconstitute the content of the vial with sterile water:
 - For each vial of WINREVAIR® 45 mg, inject 1.0 mL of sterile water
 - For each vial of WINREVAIR® 60 mg, inject 1.3 mL of sterile waterThis 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.
- 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.

Administration Instructions

Withdraw the appropriate dose of WINREVAIR® from one or two vials, depending on the volume to inject.

- 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. For each injection, select a new site that is not scarred, tender, or bruised.
- Perform subcutaneous injection.
- Discard the emptied syringe into a sharps container. Do not reuse the syringe.

4.5 Missed Dose

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.

For the Kit presentation only: In case of an underdose, consider retraining the patient or caregiver on proper administration as appropriate.

5 OVERDOSAGE

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 erythrocytosis, increases in Hgb and blood pressure, and provide supportive care as appropriate. WINREVAIR® is not dialyzable during hemodialysis.

For the Kit presentation only: In case of an overdose, consider retraining the patient or caregiver on proper administration as appropriate.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3: Dosage Forms, Strengths, Composition and Packaging

Route of Administration / Dosage Form	Strength/Composition	Non-medicinal Ingredients (in alphabetical order)
Subcutaneous (SC) lyophilized powder	45 mg/vial* After reconstitution with 1.0 mL Sterile Water for Injection, the resulting concentration is 50 mg/mL of sotatercept and the nominal deliverable volume is 0.9 mL	citric acid monohydrate polysorbate 80 sucrose tri-sodium citrate dihydrate
	60 mg/vial* After reconstitution with 1.3 mL Sterile Water for Injection, the resulting concentration is 50 mg/mL of sotatercept and the nominal deliverable volume is 1.2 mL.	
*white to off-white lyophilized powder in a single-use vial for reconstitution		

WINREVAIR® (sotatercept) for injection is supplied in:

- single-use vial (45 mg or 60 mg)
- single-use vial (45 mg or 60 mg) packaged in a kit. The kit contains the following components (see Table 4 for quantities):
 - 3 mL dosing syringe for administration
 - safety needle for injection
 - vial adapter(s)
 - pre-filled syringe of sterile water for injection, necessary to reconstitute the lyophilized powder in the dose vial
 - alcohol wipes

Table 4: WINREVAIR® Kit Contents

WINREVAIR®	Vial	3 mL dosing syringe	Safety needle	Vial Adapter	Alcohol Wipe	Pre-filled syringe of Sterile Water for injection
45 mg kit	1 x 45 mg	1	1	1	4	1 x 1.0 mL
60 mg kit	1 x 60 mg	1	1	1	4	1 x 1.3 mL
90 mg kit	2 x 45 mg	1	1	2	8	2 x 1.0 mL
120 mg kit	2 x 60 mg	1	1	2	8	2 x 1.3 mL

7 WARNINGS AND PRECAUTIONS

Hematologic

Erythrocytosis: Hemoglobin (Hgb) increases have been observed in patients during treatment with WINREVAIR®. Severe erythrocytosis may increase the risk of thromboembolic events or hyperviscosity syndrome. In clinical studies, moderate elevations in Hgb (>2 g/L above ULN) occurred in 15% of patients taking WINREVAIR®. Monitor Hgb before each dose for at least the first 5 doses, or longer if values are unstable and periodically thereafter to determine if dose adjustments are required (see [4. DOSAGE AND ADMINISTRATION](#), [8. ADVERSE REACTIONS](#)).

Severe Thrombocytopenia: Decreased platelet count has been observed in some patients taking WINREVAIR®. In clinical studies, severe thrombocytopenia (platelet count <50,000/mm³ (<50.0 x 10⁹/L)) occurred in 3% of patients taking WINREVAIR®. Thrombocytopenia occurred more frequently in patients also receiving prostacyclin infusion.

WINREVAIR® should not be initiated in patients with platelet count <50,000/mm³ (<50.0 x 10⁹/L). 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 [4. DOSAGE AND ADMINISTRATION](#)).

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 [4. DOSAGE AND ADMINISTRATION](#), [8. ADVERSE REACTIONS](#)).

Reproductive Health: Female and Male Potential

Pregnancy Testing

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

Contraception

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 [7.1 Special Populations](#), [16. NON-CLINICAL TOXICOLOGY](#)).

- **Fertility**

Based on findings in animals, WINREVAIR® may impair female and male fertility. Advise patients on the potential effects on fertility (see [7.1 Special Populations](#), [16. NON-CLINICAL TOXICOLOGY](#)).

- **Teratogenic Risk**

Embryo-Fetal Toxicity

Based on findings in animal reproduction studies, WINREVAIR® may cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving

WINREVAIR® and for at least 4 months after the final dose if treatment is discontinued. Advise females to contact their HCP if they become pregnant or if pregnancy is suspected during treatment with WINREVAIR® (see [7.1 Special Populations](#), [16. NON-CLINICAL TOXICOLOGY](#)).

7.1 Special Populations

7.1.1 Pregnant Women

WINREVAIR® should not be used immediately before or during pregnancy. 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.

There are no available data on WINREVAIR® use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Based on developmental toxicity observed in animal embryo-fetal toxicity studies (increases in post-implantation loss, reduction in fetal body weights, and delays in ossification) WINREVAIR may cause developmental toxicity when administered to a pregnant woman. (see [16. NON-CLINICAL TOXICOLOGY](#)).

Report exposure during pregnancy to Merck Canada Medical Information Center at 1-800-567-2594.

7.1.2 Breast-feeding

There are no data on the presence of sotatercept in human milk, the effects on the breastfed infant, or the effects on milk production. Since it is not known if sotatercept is excreted in breast milk, advise females not to breastfeed during treatment with WINREVAIR® and for 4 months after the final dose if treatment is discontinued.

7.1.3 Pediatrics

Pediatrics (less than 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

A total of 52 patients ≥65 years of age were treated with WINREVAIR® in clinical studies for PAH.

Bleeding events occurred more commonly in the older WINREVAIR® subgroup (see [14. CLINICAL TRIALS](#)).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Increased Hemoglobin (see [4. DOSAGE AND ADMINISTRATION](#), [7. WARNINGS AND PRECAUTIONS](#)).
- Severe Thrombocytopenia (see [4. DOSAGE AND ADMINISTRATION](#), [7. WARNINGS AND PRECAUTIONS](#)).

- Embryo-Fetal Toxicity (see [7. WARNINGS AND PRECAUTIONS](#)).
- Impaired Fertility (see [7. WARNINGS AND PRECAUTIONS](#)).

The safety of WINREVAIR® was evaluated in the pivotal trial STELLAR, a long-term placebo-controlled trial of 323 patients with PAH who were already on standard PAH therapies. After completing the primary 24-week treatment phase, patients continued into a long-term double-blind treatment period, maintaining their current therapy, until all patients completed the primary treatment period. The median duration of treatment with sotatercept at the time of data cut-off for analyses was 252 days (see [14. CLINICAL TRIALS](#)). The overall incidence of treatment discontinuations due to an adverse reaction was 4% in the sotatercept group and 7% in the placebo group. Serious adverse events occurred in 22.1% of WINREVAIR®-treated patients and 27.5% in the placebo group; the serious events were deemed to be treatment-related for 1.8% of WINREVAIR®-treated patients and 1.3% in the placebo group. The most frequently reported adverse events occurring more frequently than placebo were headache (20%), COVID-19 (15%), upper respiratory tract infections (13%), diarrhoea (12%), and epistaxis (12%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use (see [14. CLINICAL TRIALS](#)).

Table 5: Treatment-emergent adverse events (TEAEs) occurring in ≥5% of Sotatercept-treated patients and more frequently than in Placebo-treated patients during the 24-week double-blind placebo-controlled period of the STELLAR study

Treatment-Emergent Adverse Events (Preferred Term)	Sotatercept n = 163 n (%)	Placebo n = 160 n (%)
Blood and lymphatic system disorders		
Thrombocytopenia	8 (5%)	3 (2%)
Gastrointestinal disorders		
Diarrhoea	20 (12%)	12 (7.5%)
General disorders and administration site conditions		
Fatigue	17 (10%)	12 (7.5%)
Injection site reactions ^a	17 (10%)	10 (6%)
Infections and infestations		
COVID-19	24 (15%)	21 (13%)
Upper respiratory tract infections ^b	21 (13%)	16 (10%)

Treatment-Emergent Adverse Events (Preferred Term)	Sotatercept n = 163 n (%)	Placebo n = 160 n (%)
Metabolism and nutrition disorders		
Hypokalemia	9 (5.5%)	5 (3%)
Nervous System Disorders		
Headache	33 (20%)	24 (15%)
Dizziness	17 (10%)	3 (2%)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	20 (12%)	3 (2%)
Skin and subcutaneous tissue disorders		
Telangiectasia	17 (10%)	5 (3%)
Rash	9 (5.5%)	4 (2.5%)
Vascular disorders		
Flushing	9 (5.5%)	3 (2%)

^a: As a MedDRA HLT which includes the following MedDRA preferred terms: injection site bruising, injection site erythema, injection site inflammation, injection site irritation, injection site pain, injection site pruritus, injection site rash, injection site swelling, injection site warmth

^b: As a MedDRA HLT which includes the following MedDRA preferred terms: nasopharyngitis, pharyngitis, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection.

Description of Selected Adverse Reactions: STELLAR double-blind placebo-controlled and long-term double-blind periods

Increased haemoglobin

Increases in Hgb (Hgb increased, polycythaemia) were reported in 6.1% of patients taking sotatercept and in no patients taking placebo.. Moderate elevations in Hgb (>2g/dL above ULN) occurred in 12.3% of patients taking sotatercept. No severe elevations (≥4g/dL above ULN) were observed. Increases in Hgb were manageable by dose delays (10%), dose reductions (6%), or both (5%) (see [4. DOSAGE AND ADMINISTRATION](#), [7. WARNINGS AND PRECAUTIONS](#)).

Thrombocytopenia

Thrombocytopenia (thrombocytopenia and platelet count decreased) was reported in 8.6% of patients taking sotatercept and 3.1% of patients taking placebo. . Severe reduction in platelet count <50,000/mm³ (<50.0 x 10⁹/L) occurred in 1.8% of patients taking sotatercept.. Events of thrombocytopenia were manageable by dose delays (2%), dose reductions (2%), or both (2%) (see [4. DOSAGE AND ADMINISTRATION](#), [7. WARNINGS AND PRECAUTIONS](#)).

Telangiectasia

Telangiectasia was observed in 14.1% of patients taking sotatercept and 3.8% of patients taking placebo. In all patients exposed to sotatercept, who experienced telangiectasia, the median time to onset was 47.1 weeks. Discontinuations of treatment due to telangiectasia were 1% in the sotatercept group versus 0% in the placebo group. No episodes of serious bleeding associated with telangiectasia were observed in the clinical trial.

Increased blood pressure

Increased blood pressure (hypertension, blood pressure diastolic increased, blood pressure increased) was reported in 4.3% of patients taking sotatercept and 0.6% of patients taking placebo. In patients taking sotatercept, 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 mean systolic blood pressure decreased from baseline by 1.6 mmHg and diastolic blood pressure decreased by 0.6 mmHg at 24 weeks.

8.3 Less Common Clinical Trial Adverse Reactions

Treatment-related adverse events reported in < 5% patients by system organ class (SOC) are shown below:

Blood and lymphatic system disorders: iron deficiency anaemia, polycythaemia

Cardiac disorders: atrial flutter, atrial fibrillation, bradycardia, cardiopulmonary failure, supraventricular tachycardia

Ear and labyrinth disorders: excessive cerumen production, otorrhea

Eye disorders: cataract, eczema of the eyelid, erythema of eyelid, eye inflammation, eye irritation, eye pruritus, eye swelling, ocular hyperaemia, periorbital swelling, refraction disorder, swelling of eyelid, vision blurred, visual impairment

Gastrointestinal disorders: abdominal discomfort, abdominal distension, abdominal pain, bowel movement irregularity, chapped lips, dental caries, dry mouth, feces discoloured, gastritis, gastrointestinal disorder, gastrointestinal hemorrhage, gingival bleeding, inguinal hernia, pancreatitis, melaena

General disorders and administration site conditions: application site haematoma, application site pain, catheter site erythema, chest discomfort, chills, feeling hot, mucosal dryness, non cardiac chest pain, pyrexia, swelling face, thirst

Immune system disorders: sarcoidosis

Infections and infestations: carbuncle, catheter site infection, cellulitis, clostridium difficile infection, conjunctivitis, device related infection, fungal infection, furuncle, gastroenteritis, gastrointestinal bacterial overgrowth, gastrointestinal infection, gastrointestinal viral infection, gingivitis, herpes zoster, influenza, injection site abscess, injection site infection, lower respiratory tract infection, ophthalmic herpes simplex, oral candidiasis, otitis media, pneumonia influenza, post-viral fatigue syndrome, pulpitis dental, pyelonephritis, sialoadenitis, tooth infection, urinary tract infection, vascular device infection

Injury, poisoning and procedural complications: arthropod bite, cartilage injury, epicondylitis, fall, nasal injury, post procedural hematoma, spinal compression fracture, thoracic vertebral fracture, vaccination complication

Investigations: blood cholesterol increased, blood cholinesterase increased, blood pressure diastolic increased, blood pressure increased, computerised tomogram thorax abnormal, c-reactive protein increased, eosinophil count increased, hemoglobin increased, lipase increased, mean cell volume increased, platelet count decreased

Metabolism and nutrition disorders: decreased appetite, dyslipidemia, gout, hypercalcemia, hypertriglyceridemia, hypovolemia, hypomagnesemia, increased appetite

Musculoskeletal and connective tissue disorders: arthralgia, back pain, bursitis, coccydynia, groin pain, jaw disorder, joint swelling, musculoskeletal pain, myositis, osteoporosis, pain in extremity, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, tenosynovitis

Neoplasms benign, malignant and unspecified (including cysts and polyps): haemangioma, leukoerythroblastosis

Nervous System disorders: cerebral hematoma, facial paralysis, hypoesthesia, lethargy, migraine, nerve compression, restless leg syndrome, sciatica, somnolence, sinus headache, tunnel vision

Psychiatric disorders: abnormal dreams, enuresis, initial insomnia, insomnia, pica

Renal and urinary disorders: nephritis, renal impairment

Reproductive system and breast disorders: amenorrhoea, breast mass, dysmenorrhoea, menstruation delayed, vaginal haematoma, vaginal haemorrhage, vaginal lesion, vulvovaginal dryness

Respiratory, thoracic and mediastinal disorders: bronchial hyperactivity, dry throat, haemoptysis, hyperventilation, lung opacity, nasal congestion, nasal obstruction, obstructive airways disorder, pleuritic pain, pulmonary artery aneurysm, pulmonary embolism, pulmonary mass, rhinitis hypertrophic, rhinorrhoea, sinus congestion, vasomotor rhinitis, wheezing

Skin and subcutaneous tissue disorders: alopecia, acne, cold sweat, dermatitis, dermatitis contact, dry skin, lichen sclerosus, macule, onycholysis, palmar erythema, pruritus, rash erythematous, rash macular, rash maculo-papular, skin disorder, skin lesion, skin mass, skin ulcer

Vascular disorders: angiopathy, claudication of jaw muscles, hematoma, hot flush, hypertension, orthostatic hypotension, superficial vein thrombosis

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

See [7 WARNINGS AND PRECAUTIONS](#) and [8.2 Clinical Trial Adverse Reactions](#) for information on increases in hemoglobin and erythrocytes and decreases in platelets with sotatercept treatment. See [4.1 Dosing Considerations](#) for recommendations related to monitoring of hemoglobin and platelets with sotatercept treatment.

8.5 Post-Market Adverse Reactions

- Not applicable

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 Pharmacodynamics

In patients with PAH, a significantly greater decrease from baseline in pulmonary vascular resistance (PVR) was observed in the sotatercept 0.7 mg/kg and 0.3 mg/kg treatment groups compared with the placebo group in the clinical studies (see [14. CLINICAL TRIALS](#)).

10.3 Pharmacokinetics

Following subcutaneous administration of sotatercept at the dose of 0.7 mg/kg once every three weeks (Q3W) in patients with PAH, the geometric mean (%CV) steady-state AUC and steady-state peak concentration (C_{max}) 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 following multiple Q3W dosing. The accumulation ratio of sotatercept AUC was approximately 2.2.

Absorption

Following SC administration, the absolute bioavailability of sotatercept is approximately 66%. The median time to peak drug concentration (T_{max}) of sotatercept is approximately 7 days (range from 2 to 8 days) following multiple (0.1 mg/kg every 4 weeks) SC doses.

Distribution

The population PK model estimated central and peripheral volumes of distribution (%CV) of sotatercept are approximately 3.6 L (24.7%) and 1.7 L (73.3%), respectively.

Metabolism

Sotatercept is catabolized by general protein degradation processes.

Elimination

Sotatercept clearance is approximately 0.18 L/day, estimated by population PK model. The geometric mean terminal half-life (%CV) is approximately 21 days (33.8%).

Special Populations and Conditions

Specific Populations

- **Age, Sex and Ethnic Origin:** No clinically significant differences in sotatercept pharmacokinetics (PK) were observed based on age (18 to 81 years of age), sex, or race.
- **Hepatic Insufficiency:** Sotatercept has not been studied in PAH patients with hepatic impairment (Child-Pugh Classification A to C).
- **Renal Insufficiency:** Sotatercept PK was comparable in PAH patients with mild to moderate renal impairment (eGFR ranging from 30 to 89 mL/min/1.73m²) to those with normal renal function (eGFR ≥90 mL/min/1.73m²). Sotatercept has not been studied in PAH patients with severe renal impairment (eGFR <30 mL/min/1.73m²). Studies in non-PAH patients with end-stage kidney disease (ESKD) did not reveal significant impact of severe renal impairment on sotatercept PK. sotatercept is not dialyzable during hemodialysis.
- **Body Weight:** The clearance (CL) and central volume of distribution (V_c) of sotatercept increased with increasing body weight. The body weight effect on PK of sotatercept is not clinically relevant if following recommended weight-based dosing regimen.

11 STORAGE, STABILITY AND DISPOSAL

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.

Do not reuse any of the supplies. This product is disposable and should only be used one time.

12 SPECIAL HANDLING INSTRUCTIONS

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: sotatercept

Chemical name: Activin receptor type IIA (ActRIIA-IgG1Fc)

Molecular formula and molecular mass: Approximately 78 kDa as a non-glycosylated homodimer.

Structural formula: Sotatercept is a recombinant human homodimeric fusion protein consisting of the extracellular domain (ECD) of human activin receptor type IIA (ActRIIA) linked to Fc domain of human IgG1. Each monomer consists of 344 amino acids. Sotatercept contains a total of 16 disulfide bonds.

Physicochemical properties: Sotatercept for injection is a sterile, preservative-free, white to off-white lyophilized powder available in 45 mg and 60 mg single-dose vials for SC administration after reconstitution. Sotatercept drug substance (DS) is formulated in 10 mM citrate buffer at a pH of 5.8 ± 0.5 at a final target bulk concentration of 75 mg/mL and is a clear to opalescent solution, colorless to slightly yellow solution that is essentially free of visible particulates.

Composition

Active Ingredient

sotatercept

Inactive Ingredients (List of excipients)

citric acid monohydrate, polysorbate 80, sucrose, and tri-sodium citrate dihydrate

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Pulmonary Arterial Hypertension Adult Subjects

The efficacy of WINREVAIR® was evaluated in adult patients with PAH in the STELLAR trial (NCT04576988). 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 randomized 1:1 to WINREVAIR® (target dose 0.7 mg/kg) (n=163) or placebo (n=160) administered subcutaneously once every 3 weeks, in addition to standard of care PAH therapies.

Table 6: Summary of patient demographics for clinical trials in Pulmonary Arterial Hypertension (WHO Group 1 FC II or III)

Study #	Study design	Dosage route of administration • duration	Study subjects (n)	Mean age (Range)	Sex
STELLAR (Phase 3)	multicenter placebo-controlled double-blind parallel-group	0.7 mg/kg placebo <i>subcutaneous</i> every 3 weeks	n=163 n=160	48.0 years (18 to 82 years)	79.3% F

The demographic and baseline clinical characteristics were generally comparable between the WINREVAIR® and placebo groups. Participants in this study were adults with a mean age of 47.9 years (range: 18 to 82 years); 89.2% of participants were White and 79.3% were female. PAH etiologies were idiopathic PAH (58.5%), heritable PAH (18.3%), and PAH associated with connective tissue diseases (CTD) (14.9%), PAH associated with simple congenital heart disease with repaired systemic-to-pulmonary shunts (5%), or drug or toxin-induced PAH (3.4%). 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). The placebo-adjusted median change increase in 6MWD for WINREVAIR® was 40.8 meters (95% CI: 27.5, 54.1; $p < 0.001$). The treatment effect was consistent across the different subgroups including sex, PAH diagnostic group, background therapy at baseline, prostacyclin infusion therapy at baseline, WHO FC, and baseline PVR.

Multicomponent 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 $\geq 30\%$ 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 included worsening-related listing for lung and/or heart transplant, need to initiate rescue therapy with an approved background PAH therapy or the need to increase the dose of infusion prostacyclin by $\geq 10\%$, need for atrial septostomy, hospitalization for worsening PAH (≥ 24 hours), or deterioration of PAH (worsened WHO FC and decrease in 6MWD $\geq 15\%$ with both events occurring at the same time or different times). 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).

Results for key secondary endpoints are presented in Table 7 below.

Table 7: Selected 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) ^a	N/A	<.001 ^b
Hodges-Lehmann location shift from placebo estimate in change from Baseline PVR at Week 24 (ASE) (dynes*sec/cm ⁵)	N/A	-234.6 (27.5) ^c	(-288.4, -180.8)	<.001 ^d
Hodges-Lehmann location shift from placebo estimate in change from Baseline NT-proBNP Levels at Week 24 (ASE) (pg/mL)	N/A	-441.6 (67.3) ^e	(-573.5, -309.6)	<.001 ^d
Proportion of Patients who Improve FC Class from Baseline at Week 24, n (%)	22 (13.8)	48 (29.4) ^a	N/A	<.001 ^b
Time to Death or the First Occurrence of a Worsening Event, n (%)	42 (26.3)	9 (5.5)	HR ^f : 0.163 (0.076, 0.347) ^f	<.001 ^g
Proportion of Patients who Maintained or Achieved a Low Risk Score ^h at Week 24 vs. Baseline, n (%)	29 (18.2)	64 (39.5)	N/A	<.001 ^b

ASE= asymptotic standard error.

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

^a 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.

^b Comparison with placebo uses Cochran-Mantel-Haenszel (CMH) method stratified by randomization factors.

^c 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.

^d Wilcoxon p-value refers to p-value from the aligned rank-stratified Wilcoxon test with randomization factors as strata.

^e 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.

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

^g Log-rank test comparison with placebo stratified by the randomization factors.

^h Utilizing French Risk score calculator.

Table 8: Death or Clinical Worsening Events

	Placebo (N=160)	WINREVAIR® (N=163)
Duration of exposure in days: median (min, max)	229.5 (21, 566)	252.0 (61, 518)
Total number of subjects who experienced death or at least one clinical worsening event, n (%)	42 (26.3)	9 (5.5)
HR (95% CI) ^a	N/A	0.163 (0.076, 0.347)
Assessment of death or first occurrence of clinical worsening events^b, 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 hospitalization (≥24 hours)	7 (4.4)	0 (0.0)
Deterioration of PAH ^c	15 (9.4)	4 (2.5)

^a Hazard ratio (HR) estimated by a Cox proportional hazards model stratified by randomization factors

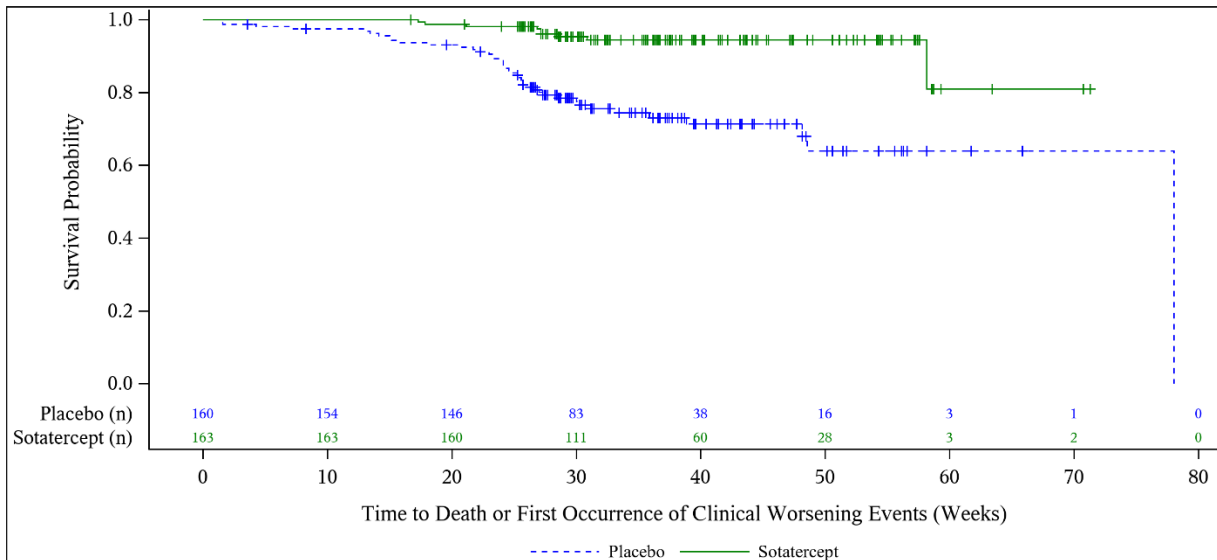
^b A subject can have more than one assessment recorded for their first event of clinical worsening. There were 3 placebo subjects and 0 sotatercept subjects who had more than one assessment recorded for their first event of clinical worsening.

^c 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. N/A = not applicable.

Percentages are calculated as (n/N)*100

Figure 1: Time to Death or First Occurrence of Clinical Worsening Events Kaplan-Meier Plot



n= Number of subjects at risk, +: Censored

14.3 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 neutralizing antibodies against sotatercept.

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 at the recommended dose regimen.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General toxicology

Single-dose studies

No acute toxicity was observed in repeated-dose SC toxicity studies at dosages up to 30 mg/kg in rats and 50 mg/kg in monkeys (single doses provided exposures approximately 15-fold and 38-fold, respectively, the human exposure at the MRHD based on estimated area under the curve [AUC]).

In rats administered a single IV dose of 10 mg/kg or 30 mg/kg of sotatercept, adrenal gland necrosis was observed 28-days after dosing. A NOAEL was not determined in this study.

Repeat-dose studies

In rats and monkeys, the longest duration SC toxicity studies were 3-months and 9-months in duration, respectively.

In rats administered once weekly doses of 0.3, 3, and 30 mg/kg for 3 months (equal to exposures 0.4-, 2-, or 18-fold the MRHD based on AUC), adverse findings included efferent duct/testicular degeneration, adrenal gland congestion/necrosis, and membranoproliferative glomerulonephritis and tubulointerstitial nephritis in the kidneys. The adrenal changes demonstrated reversibility following a 1-month recovery period. A NOAEL could not be determined for this study due to the adverse effects observed at all doses. In a subsequent rat 3-month toxicity study with 1 month recovery period that investigated the same dosing regimen, sotatercept-mediated renal toxicity (occurring at doses \geq 0.3 mg/kg Q1W) was non-reversible and developed into chronic progressive nephropathy.

In monkeys administered 1, 2.6, and 10 mg/kg once every 4 weeks and 10 mg/kg once every 2 weeks for 9 months, adverse changes were limited to glomerulonephritis and tubulointerstitial nephritis in the

kidneys that impacted the physical condition of individual animals. These kidney changes partially resolved following a 3-month recovery period. Additionally, inflammatory infiltrates occurred in the choroid plexus of the brain. The changes in the brain and kidneys were not associated with immune complex formation/deposition, they occurred due to the direct effects of sotatercept. The NOAEL was determined to be 1 mg/kg (equal to exposure at the MRHD based on AUC). In separate study, monkeys were administered 10, 30, or 50 mg/kg once every 2 weeks for 6 months. Two mid-dose animals (where the sotatercept AUC was 32-fold higher than at the MRHD) were euthanized following clinical signs of renal failure, with renal toxicity confirmed at necropsy. Findings in this study were consistent with the 9-month study.

Carcinogenicity: No carcinogenicity studies have been conducted with sotatercept.

Mutagenesis: No mutagenicity studies have been conducted with sotatercept.

Genotoxicity: No genotoxicity studies have been conducted with sotatercept.

Reproductive and Developmental Toxicology:

In a fertility and early embryonic development study in female rats, sotatercept was administered SC once weekly at doses of 5, 15, or 50 mg/kg beginning 2 weeks prior to mating and through gestation day 7. Two high-dose females were euthanized during gestation due to hind limb swelling and/or limb impairment. Enlarged and discoloured adrenal glands were observed in females given ≥ 15 mg/kg. 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 estrous cycle duration occurred at 50 mg/kg only (21-fold the MRHD, based on estimated AUC). The NOAEL for female fertility and early embryonic development was determined to be 5 mg/kg.

In a fertility study in male rats, sotatercept was administered SC once weekly at doses of 0.3, 3, or 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. At 30 mg/kg there was also reduced lack of sperm in the epididymides. Reversible decreases in fertility occurred at 30 mg/kg (20-fold the MRHD, based on estimated AUC). A NOAEL was not determined for this study.

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 (equal to 2, 4, and 15-fold the MRHD based on AUC, respectively) and to rabbits on gestation days 7 and 14 at doses of 0.5, 1.5, or 5 mg/kg (equal to 0.4, 0.6 and 4-fold the MRHD based on AUC, respectively). Sotatercept was detected in fetal rabbit plasma, confirming that sotatercept crosses the placenta. Effects in both species included reductions in numbers of live fetuses and fetal body weights, delays in ossification, and increases in resorptions and post-implantation losses. 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 rats and rabbits, the NOAELS for developmental toxicity were 5 mg/kg and 0.5 mg/kg, which provided exposures 2-fold and 0.4-fold the MRHD based on AUC, respectively.

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 (equal to 0.6,

2 and 4-fold the MRHD based on AUC, respectively) during lactation days 1, 8, and 15. The maternal NOAEL was 5 mg/kg or 10 mg/kg when administered during gestation or lactation, respectively. 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 (NOAEL 5 mg/kg, 2-fold the MRHD based on AUC). In F1 pups from dams dosed during lactation, decreases in pup weight correlated with delays in sexual maturation at estimated exposures (based on AUC) \geq 2-fold the MRHD (NOAEL 1.5 mg/kg, 0.6-fold the MRHD based on AUC).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

WINREVAIR®

Sotatercept for injection

Read this carefully before you start taking **WINREVAIR®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **WINREVAIR®**.

What is WINREVAIR® used for?

- **WINREVAIR®** is a prescription medicine to treat adults with pulmonary arterial hypertension (PAH). PAH is a type of high blood pressure in the arteries of your lungs.

How does WINREVAIR® work?

WINREVAIR® is an activin receptor type IIA-Fc (ActRIIA-Fc) fusion protein which works to lower the blood pressure in your lungs.

What are the ingredients in WINREVAIR®?

Medicinal ingredient: sotatercept

Non-medicinal ingredients: citric acid monohydrate, polysorbate 80, sucrose, and tri-sodium citrate dihydrate at pH 5.8.

WINREVAIR® comes in the following dosage forms:

Solution for injection: 45 mg or 60 mg for subcutaneous use.

To help avoid side effects and ensure proper use, talk to your healthcare professional before WINREVAIR® is administered. Talk about any health conditions or problems you may have, including if you:

- Have or have had any medical conditions, and about any allergies.
- Are pregnant or if you are planning to get pregnant. **WINREVAIR®** may harm your unborn baby.
- Become pregnant or think you may be pregnant while taking **WINREVAIR®**.
- Are breastfeeding or plan to breastfeed. It is not known if **WINREVAIR®** passes into breast milk.

Pregnancy

- Your healthcare professional should do a pregnancy test before you start taking **WINREVAIR®**.
- You should use effective birth control when taking **WINREVAIR®**.
- You should continue using effective birth control for at least 4 months after your last dose if you stop taking **WINREVAIR®**. Ask your healthcare professional about birth control methods that would work well for you.
- You or your healthcare professional should report any exposure to **WINREVAIR®** during pregnancy by calling 1-800-567-2594.

Breast-feeding

- Do not breastfeed while taking WINREVAIR®.
- Do not breastfeed for at least 4 months after your last dose if you stop taking WINREVAIR®. Talk to your healthcare professional about the best way to feed your baby.

Fertility

- WINREVAIR® may decrease female and male fertility.

Children

- It is not known if WINREVAIR® is safe and effective in children under 18 years of age.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

It is unknown if WINREVAIR® interacts with other medicines or supplements.

How to take WINREVAIR® (kit):

Read the separate **Instructions For Use** booklet that comes with your kit.

- Take WINREVAIR® exactly as your healthcare professional tells you to.
- You will take WINREVAIR® every 3 weeks as an injection just under your skin (subcutaneous) only in these injection sites:
 - **stomach** (abdomen) at least 2 inches away from the belly button, or
 - **upper thigh**
- You should inject WINREVAIR® right away after mixing the medicine powder with the sterile water, but no later than 4 hours after mixing.

How will you receive WINREVAIR®? (vial)

- You will be given WINREVAIR® every 3 weeks as an injection just under your skin (subcutaneous) only in these injection sites:
 - **stomach** (abdomen) at least 2 inches away from the belly button
 - **upper thigh**
 - **upper arm**

Your dose:

- Your dose of WINREVAIR® depends on your body weight and blood tests.
- Your healthcare professional will tell you how much WINREVAIR® to take and when to take it.
- Do not change your dose or stop taking WINREVAIR® without talking to your healthcare professional.
- Do not take WINREVAIR® more often than your healthcare professional tells you to. If you are not sure when to take WINREVAIR®, call your healthcare professional.

Your healthcare professional will monitor your dose:

- Your healthcare professional will do a blood test before your first 5 doses of WINREVAIR®, longer if needed, and then from time to time to check your levels of hemoglobin (a protein in red blood cells

that carries oxygen) and platelets (blood cells that help blood clot). After each of these blood tests, your healthcare provider may delay treatment or change your dose if needed.

- Before your first dose and regularly while taking WINREVAIR®, your healthcare professional will do blood tests. These are done so that your healthcare professional can monitor you and find the best dose for you.
- Your healthcare professional may adjust your dose, delay treatment, or stop treatment depending on how you respond to WINREVAIR®.

Overdose:

If you take too much WINREVAIR®, call your healthcare professional.

If you think you, or a person you are caring for, have taken too much WINREVAIR®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose (kit):

- If you miss your prescribed dose of WINREVAIR®, take it within 3 days and follow your original schedule for your next dose. If not taken within 3 days, call your healthcare professional for guidance.

Missed Dose (vial):

- If you miss your appointment to be given WINREVAIR®, call your healthcare professional immediately to reschedule your appointment.

What are possible side effects from using WINREVAIR®?

These are not all the possible side effects you may have when taking WINREVAIR®. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effects of WINREVAIR® are:

- nose bleeds (epistaxis)
- telangiectasia (also called spider veins or tiny blood vessels that look like pink or red lines on the skin)
- headache
- diarrhea

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Serious bleeding: persistent headache, nausea, weakness, black or tarry stool, blood in your stool, bright red blood from vomiting or coughing, persistent abdominal cramps, severe back pain, or abnormally heavy menstrual bleeding, more likely to happen if you take WINREVAIR with certain medicines. Your healthcare professional will inform you on how to recognize them.		√	
RARE			
Erythrocytosis: high level of hemoglobin (a protein in red blood cells that carries oxygen): This can raise the chance of a blood clot forming that can block a blood vessel.		√ Your healthcare professional will do blood tests to check your hemoglobin levels before starting and regularly during treatment with WINREVAIR®.	
Severe Thrombocytopenia: low number of platelets (blood cells that help blood clot): easy bruising, continued bleeding from cuts, and nosebleeds.		√ Your healthcare professional will do blood tests to check your platelet level before starting and regularly during treatment with WINREVAIR®.	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store WINREVAIR® in the refrigerator at 2°C to 8°C. Do not freeze.
- Store in the original container to help protect from light.
- Contact your healthcare professional if the unused injection kit has been out of the refrigerator for an extended period of time.
- After you mix the medicine powder with the sterile water (provided in the kit), it is recommended that you inject it right away, but no later than 4 hours after mixing.

Keep out of reach and sight of children.

If you want more information about WINREVAIR®:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html> or the manufacturer's website www.merck.ca, or by calling 1-800-567-2594.

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