WINREVAIR™

[Sotatercept 45/60 mg]

1. NAME OF THE MEDICINAL PRODUCT

WINREVAIR 45 mg Powder for Solution for Injection

WINREVAIR 60 mg Powder for Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

WINREVAIR 45 mg powder for solution for injection

Each vial contains 45 mg of sotatercept. After reconstitution, each mL of solution contains 50 mg sotatercept.

WINREVAIR 60 mg powder for solution for injection

Each vial contains 60 mg of sotatercept. After reconstitution, each mL of solution contains 50 mg sotatercept.

Sotatercept is a recombinant homodimeric fusion protein consisting of the extracellular domain of human activin receptor type IIA (ActRIIA) linked to the Fc domain of human IgG1, produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for injection (powder for injection).

White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

WINREVAIR, in combination with other pulmonary arterial hypertension (PAH) therapies, is indicated for the treatment of PAH in adult patients with WHO Functional Class (FC) II to III, to improve exercise capacity (see section 5.1).

4.2 Posology and method of administration

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

Posology

WINREVAIR is administered once every 3 weeks as a single subcutaneous injection according to patient weight.

Recommended starting dose

Haemoglobin (Hgb) and platelet count should be obtained prior to the first dose (see section 4.4). Initiation of treatment is contraindicated if platelet count is consistently < 50 x 10^9/L (see section 4.3). Treatment is initiated with a single dose of 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)*	Pack type
30.0 - 40.8	0.2	Pack containing 1 x 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	Pack containing 1 x 60 mg
174.2 - 180.0	1.1	

*The concentration of the reconstituted solution is 50 mg/ml (see section 6.6)

Recommended target dose

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 "*Dose adjustments due to increase in haemoglobin or decreased platelet count*").

Treatment should be continued at 0.7 mg/kg every 3 weeks unless dose adjustments are required.

Table 2. Injection volume for dose of 0.7 mg/kg

Patient weight range (kg)	Injection volume (mL)*	Pack type
30.0 - 31.7	0.4	Pack containing 1 x 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	Pack containing 1 x 60 mg
74.7 - 81.7	1.1	
81.8 - 88.9	1.2	
89.0 - 96.0	1.3	Pack containing 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	Pack containing 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	

*The concentration of the reconstituted solution is 50 mg/ml (see section 6.6)

Dose adjustments due to increase in haemoglobin or decreased platelet count

Hgb and platelet count should be monitored for the first 5 doses, or longer if values are unstable. Thereafter, Hgb and platelet count should be verified every 3 to 6 months and the dose adjusted if necessary (see sections 4.4 and 4.8).

Treatment should be delayed for 3 weeks (i.e., one dose delay) if any of the following occur:

- Hgb increases > 1.24 mmol/L (2 g/dL) from the previous dose and is above the ULN.
- Hgb increases > 2.48 mmol/L (4 g/dL) from baseline.
- Hgb increases > 1.24 mmol/L (2 g/dL) above ULN.
- Platelet count decreases < 50 x 10^9/L.

Hgb and platelet count should be obtained again before reinitiating treatment.

For treatment delays lasting > 9 weeks, treatment should be restarted at 0.3 mg/kg, and the dose should be escalated to 0.7 mg/kg after verifying acceptable Hgb and platelet count.

For treatment delays lasting > 9 weeks due to platelet counts consistently < 50 x 10^9/L, the physician should carry out a benefit/risk re-evaluation for the patient before reinitiating treatment.

Missed dose

If a dose is missed, administer as soon as possible. If the missed dose is not taken within 3 days of the scheduled date, adjust the schedule to maintain 3-week dosing intervals.

Elderly

No dose adjustment is required in elderly patients ≥ 65 years old (see section 5.2)

Renal impairment

No dose adjustment is required based on renal impairment (see section 5.2). Sotatercept has not been studied in PAH patients with severe renal impairment (estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2).

Hepatic impairment

No dose adjustment is required based on hepatic impairment (Child-Pugh Classification A to C). Sotatercept has not been studied in patients with hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of WINREVAIR in children and adolescents below 18 years of age have not yet been established. No data are available (see section 5.3).

Method of administration

WINREVAIR is for single use only.

It should be reconstituted before use. The reconstituted medicinal product is a clear to opalescent and colourless to slightly brownish-yellow solution.

WINREVAIR should be administered by subcutaneous injection in the abdomen (at least 5 cm away from navel), upper arm, or upper thigh. It should not be injected into sites that are scarred, tender, or bruised. The same injection site should not be used on two consecutive injections.

Refer to section 6.6 for instructions on the proper preparation and administration of WINREVAIR.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients with platelet counts consistently < 50 x 10^9/L before initiating treatment.

4.4 Special Warnings and Precautions for Use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Erythrocytosis

Increases in Hgb have been observed in patients during treatment with sotatercept. Severe erythrocytosis may increase the risk of thromboembolic events and hyperviscosity syndrome. Use caution in patients with erythrocytosis who are at increased risk of thromboembolic events. Hgb should be monitored before each dose for the first 5 doses, or longer if values are unstable, and every 3 to 6 months thereafter to determine if dose adjustments are required (see sections 4.2 and 4.8).

Severe thrombocytopenia

Decreased platelet count has been observed in some patients taking Sotatercept including severe thrombocytopenia (platelet count < 50 x 10^9/L). Thrombocytopenia was reported more frequently in patients also receiving prostacyclin infusion (21.5%) compared to patients not receiving prostacyclin infusion (3.1%) (see section 4.8). Severe thrombocytopenia may increase the risk of bleeding events. Platelet count should be monitored before each dose for the first 5 doses, or longer if values are unstable, and every 3 to 6 months thereafter to determine whether dose adjustments are required (see section 4.2).

Serious bleeding

In clinical studies, serious bleeding events (including gastrointestinal, intracranial haemorrhage) have been observed in 4.3% of patients during

treatment with sotatercept (see section 4.8). Patients with serious bleeding events were more likely to be on prostacyclin background therapy and/or antithrombotic agents, have low platelet count, or be 65 years of age or older. Patients should be advised about any signs and symptoms of blood loss. A physician should evaluate and treat bleeding events accordingly. Sotatercept should not be administered if the patient is experiencing a serious bleeding event.

Limitation of the clinical data

The clinical studies did not include participants with human immunodeficiency virus (HIV)-, portal hypertension-, schistosomiasis-, or pulmonary veno occlusive disease (PVOD)-associated PAH.

Excipients with known effect

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium free'.

This medicinal product contains 0.20 mg of polysorbate 80 in each mL of reconstituted solution. Polysorbates may cause allergic reactions.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

No interaction studies have been performed.

4.6 Fertility, Pregnancy and Lactation

Women of childbearing potential

Pregnancy testing is recommended for women of childbearing potential before starting treatment. Women of childbearing potential should use effective

contraception during treatment and for at least 4 months after the last dose if treatment is discontinued (see section 5.3).

Pregnancy

There are no data from the use of sotatercept in pregnant women. Studies in animals have shown reproductive toxicity (increases in post-implantation losses, reduction in foetal body weights, and delays in ossification) (see section 5.3).

WINREVAIR is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether sotatercept/metabolites are excreted in human milk. A risk to newborns/infants cannot be excluded.

Breast-feeding should be discontinued during treatment and for 4 months after the last dose of treatment.

Fertility

Based on findings in animals, sotatercept may impair female and male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Sotatercept has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile

The most frequently reported adverse reactions were headache (24.5%), epistaxis (22.1%), telangiectasia (16.6%), diarrhoea (15.3%), dizziness (14.7 %), rash (12.3%), and thrombocytopenia (10.4%).

The most frequently reported serious adverse reactions were thrombocytopenia (< 1%) and epistaxis (< 1%).

The most common adverse reactions leading to discontinuation were epistaxis and telangiectasia

Tabulated list of adverse reactions

The safety of sotatercept was evaluated in the pivotal study STELLAR, a placebo-controlled study of 163 patients with PAH treated with sotatercept (see section 5.1). The median duration of treatment with sotatercept was 313 days.

Table 3 shows the adverse reactions reported with sotatercept in placebo-controlled clinical studies and post-marketing surveillance. These are listed in the table below by MedDRA system organ class and by frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), and very rare (< 1/10 000), and not known (cannot be estimated from available post-marketing data).

Table 3. Adverse reactions

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Very common	Thrombocytopenia[1,2] Increased haemoglobin[1]
Nervous system disorders	Very common	Dizziness

		Headache
Cardiac disorder	Not known	Pericardial effusion[1]
Respiratory, thoracic and mediastinal disorders	Very common	Epistaxis
Gastrointestinal disorders	Very common	Diarrhoea
	Common	Gingival bleeding
Skin and subcutaneous tissue disorders	Very common	Telangiectasia[1] Rash
	Common	Erythema
General disorders and administration site conditions	Common	Injection site pruritus
Investigations	Common	Increased blood pressure[1,3]

[1] See description of selected adverse reactions

[2] Includes 'thrombocytopenia' and 'platelet count decreased'

[3] Includes 'hypertension', 'blood pressure diastolic increased' and 'blood pressure increased'

Description of selected adverse reactions

Increased haemoglobin

In STELLAR, adverse reactions of increased Hgb ('haemoglobin increased' and 'polycythaemia') were reported in 8.6% of patients taking sotatercept. Based on laboratory data, moderate elevations in Hgb (> 1.24 mmol/L (2 g/dL) above ULN) occurred in 15.3% of patients taking sotatercept. Increases in Hgb were managed by dose adjustments (see sections 4.2 and 4.4).

Thrombocytopenia

Thrombocytopenia (‘thrombocytopenia’ and ‘platelet count decreased’) was reported in 10.4% of patients taking sotatercept. Severe reduction in platelet count < 50 x 10^9/L occurred in 2.5% of patients taking sotatercept. Thrombocytopenia was reported more frequently in patients also receiving prostacyclin infusion (21.5%) compared to patients not receiving prostacyclin infusion (3.1%). Thrombocytopenia was managed by dose adjustments (see sections 4.2 and 4.4).

Telangiectasia

Telangiectasia was observed in 16.6% of patients taking sotatercept. The median time to onset was 18.6 weeks. Discontinuations of treatment due to telangiectasia were 1% in the sotatercept group.

Increased blood pressure

Increased blood pressure was reported in 4.3% of patients taking sotatercept. 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.

Pericardial effusion

Cases of new-onset or worsening of pericardial effusions (including cardiac tamponade) have been reported in patients treated with sotatercept, despite improved or stable PAH haemodynamics. Most cases were reported in

patients with PAH associated with connective tissue disease, pre-existing pericardial effusion, or both; most also received prostacyclin analogues.

Elderly

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 sotatercept subgroup (52% vs 31.9% in patients < 65-year-old); however, there was no notable imbalance between age categories for any specific bleeding event. Serious bleeding occurred in 3.6% of patients < 65-year-old and in 8.0% of patients ≥ 65-year-old taking sotatercept.

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.

4.9 Overdose

In a phase 1 healthy volunteer study, one participant dosed at 1 mg/kg of sotatercept experienced increased Hgb associated with symptomatic hypertension that improved with phlebotomy.

In the event of overdose in a patient with PAH, increases in Hgb and blood pressure should be closely monitored, and supportive care should be provided

as appropriate (see sections 4.2 and 4.4). Sotatercept is not dialyzable during haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihypertensives, antihypertensives for pulmonary arterial hypertension. ATC code: C02KX06

Mechanism of action

Sotatercept is an activin signalling inhibitor with high selectivity for Activin-A, a dimeric glycoprotein which belongs to the transforming growth factor-β (TGF- β) superfamily of ligands. Activin-A binds to the activin receptor type IIA (ActRIIA) regulating key signalling for inflammation, cell proliferation, apoptosis, and tissue homeostasis.

Activin-A levels are increased in PAH patients. Activin binding to ActRIIA promotes proliferative signalling while there is a decrease in anti-proliferative bone morphogenetic protein receptor type II (BMPRII) signalling. The imbalance of ActRIIA-BMPRII signalling underlying PAH results in vascular cell hyperproliferation, causing pathological remodelling of the pulmonary arterial wall, narrowing the arterial lumen, increasing pulmonary vascular resistance, and leads to increased pulmonary artery pressure and right ventricular dysfunction.

Sotatercept consists of a recombinant homodimeric activin receptor type IIA-Fc (ActRIIA-Fc) fusion protein, which acts as a ligand trap that scavenges

excess Activin-A and other ligands for ActRIIA to inhibit activin signalling. As a result, sotatercept rebalances the pro-proliferative (ActRIIA/Smad2/3-mediated) and anti-proliferative (BMPRII/Smad1/5/8-mediated) signalling to modulate vascular proliferation.

Pharmacodynamic effects

A phase 2 clinical study (PULSAR) 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 dyn*sec/cm^5 (95% CI: -365.8, -173.0) for the sotatercept 0.7 mg/kg group and -151.1 dyn*sec/cm^5 (95% CI: -249.6, -52.6) for the sotatercept 0.3 mg/kg group.

In rat models of PAH, a sotatercept analogue reduced expression of pro-inflammatory markers at the pulmonary arterial wall, reduced leucocyte recruitment, inhibited proliferation of endothelial and smooth muscle cells, and promoted apoptosis in diseased vasculature. These cellular changes were associated with thinner vessel walls, reversed arterial and right ventricular remodelling, and improved haemodynamics.

Clinical efficacy and safety

The efficacy of sotatercept was evaluated in adult patients with PAH in the pivotal STELLAR study. STELLAR was a double-blind, placebo-controlled,

multicenter, parallel-group clinical study in which 323 patients with PAH (WHO Group 1 Functional Class II or III) were randomised 1:1 to sotatercept (starting dose 0.3 mg/kg escalated to target dose 0.7 mg/kg) (n=163) or placebo (n=160) administered subcutaneously once every 3 weeks. Patients continued their treatment assignment in the long-term double-blind treatment period until all patients completed Week 24.

Participants in this study were adults with a median age of 48.0 years (range: 18 to 82 years), of which 16.7% were ≥ 65 years of age. Median weight was 68.2 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 aetiologies were idiopathic PAH (58.5%), heritable PAH (18.3%), and PAH associated with connective tissue diseases (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 was 48.6 % and in WHO FC III was 51.4%. The STELLAR study excluded patients diagnosed with HIV-associated PAH, PAH associated with portal hypertension, schistosomiasis-associated PAH, and PVOD.

The primary efficacy endpoint was the change from baseline at Week 24 in 6-Minute Walk Distance (6MWD). In the sotatercept 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. 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.

The secondary endpoints included improvements in multicomponent improvement (MCI), PVR, N-terminal pro-B-type natriuretic peptide (NT-proBNP), WHO FC, time to death or first occurrence of clinical worsening events.

MCI 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 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 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 ≥ 10%, need for atrial septostomy, hospitalisation for worsening PAH (≥ 24 hours), or deterioration of PAH (worsened WHO FC and decrease in 6MWD ≥ 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).

At Week 24, 38.9% of sotatercept-treated patients showed improvement in MCI versus 10.1% in the placebo group ($p < 0.001$). The median treatment difference in PVR between sotatercept and placebo group was -234.6 dyn*sec/cm^5 (95% CI: -288.4, -180.8; $p < 0.001$). The median treatment difference in NT-proBNP between the sotatercept and placebo groups was -441.6 pg/mL (95% CI: -573.5, -309.6; $p < 0.001$). Improvement in WHO FC from baseline occurred in 29% of patients in sotatercept versus 13.8% in placebo ($p < 0.001$).

Treatment with sotatercept resulted in an 82% reduction (HR 0.182, 95% CI: 0.075, 0.441; $p < 0.001$) in the occurrence of death or clinical worsening events compared to placebo (see Table 4). The treatment effect of sotatercept versus placebo started by Week 10 and continued for the duration of the study.

Table 4. Death or clinical worsening events

	Placebo (N=160)	Sotatercept (N=163)
Total number of subjects who experienced death or at least one clinical worsening event, n (%)	29 (18.1)	7 (4.3)
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 for atrial septosomy	0 (0.0)	0 (0.0)
PAH-specific hospitalization (≥ 24 hours)	8 (5.0)	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 2 participants receiving placebo and no participant receiving sotatercept who had more than one assessment recorded for their first event of clinical worsening. This analysis excluded the component “need to initiate rescue therapy with an approved PAH therapy or need to increase the dose of infusion prostacyclin by 10% or more”

†Deterioration of PAH 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.

Immunogenicity

At Week 24 in STELLAR, anti-drug antibodies (ADA) were detected in 44/163 (27%) of patients taking sotatercept. Among these 44 patients, 12 tested positive for neutralising antibodies against sotatercept. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed.

5.2 Pharmacokinetic properties

In patients with PAH, the geometric mean (%Coefficient of variation (CV %)) steady-state AUC and steady-state peak concentration (C_{max}) at the dose of 0.7 mg/kg every 3 weeks were 171.3 mcg x d/mL (34.2%) and 9.7 mcg/mL (30%), respectively. Sotatercept AUC and C_{max} increase proportionally with dose. Steady state is achieved after approximately 15 weeks of treatment. The accumulation ratio of sotatercept AUC was approximately 2.2.

Absorption

The subcutaneous (SC) formulation has an absolute bioavailability of approximately 66% based on population pharmacokinetics analysis. 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 dosing every 4 weeks.

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%).

Biotransformation

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 ethnic origin

No clinically significant differences in sotatercept pharmacokinetics (PK) were observed based on age (18 to 81 years of age), sex, or ethnic origin (82.9% Caucasian, 3.1% Black, 7.1% Asian, and 6.9% other).

Body weight

The clearance and central volume of distribution of sotatercept increase with increasing body weight. The recommended weight-based dosing regimen results in consistent sotatercept exposures.

Renal impairment

Sotatercept pharmacokinetics 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 renal disease (ESRD) patients and patients with normal renal function. Sotatercept is not dialyzable during haemodialysis. Sotatercept has not been studied in PAH patients with severe renal impairment (eGFR <30 mL/min/1.73m^2).

Hepatic impairment

Sotatercept has not been studied in PAH 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.

5.3 Preclinical safety data

No carcinogenicity or mutagenicity studies have been conducted with sotatercept.

Repeat dose toxicity

In rats and monkeys, the longest SC toxicity studies were 3 months and 9 months in duration, respectively. In rats, adverse findings included efferent duct/testicular degeneration, adrenal gland congestion/necrosis, and membranoproliferative glomerulonephritis and tubulointerstitial nephritis in the kidneys. Kidney changes were not reversible following a 1-month recovery period. In monkeys, adverse changes included increased interstitial matrix at the corticomedullary junction, decreased glomerular tuft size, glomerulonephritis and tubulointerstitial nephritis in the kidney. Kidney changes in monkeys partially resolved following a 3-month recovery period. At the no observed adverse effect level (NOAEL) in rats and monkeys, sotatercept exposures were ≤ 2-times the clinical exposure at the maximum recommended human dose (MRHD). Other findings that occurred at clinical exposure margins in monkeys included hepatic inflammatory infiltrates, lymphoid depletion in spleen, and inflammatory infiltrates in the choroid plexus.

Reproductive toxicity

In a female fertility study, oestrous cycle duration was increased, pregnancy rates were decreased, there were increases in pre-implantation and post-implantation loss and reductions in live litter size. At the NOAEL for female fertility endpoints, sotatercept exposure was 2-times the clinical AUC at the MRHD.

In males, there were non-reversible histologic changes in the efferent ducts, testes, and epididymides. Histomorphologic changes in rat testes correlated to decreased fertility index that reversed during the 13-week treatment-free

period. A NOAEL for testicular histologic changes was not established and the NOAEL for male fertility functional changes provides a systemic exposure 2-times the clinical exposure at the MRHD.

In embryo-fetal developmental toxicity studies, effects in rats and rabbits included reductions in numbers of live foetuses and fetal body weights, delays in ossification, and increases in resorptions and post-implantation losses. In rats only, there were also skeletal variations (increased number of supernumerary ribs and changes in the number of thoracic or lumbar vertebrae). At the NOAEL in rats and rabbits, sotatercept exposures were 2-times and 0.4-times, respectively, the clinical exposure at the MRHD.

In a pre- and postnatal development study in rats, no sotatercept related adverse effects were observed in first filial generation (F1) pups from dams dosed during gestation at estimated exposures up to 2-times the MRHD. In F1 pups from dams dosed during lactation, decreases in pup weight correlated with delays in sexual maturation. The NOAEL for effects on growth and maturation in pups provides a systemic exposure 0.6-times the clinical exposure at the MRHD.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Citric acid monohydrate

Sodium citrate

Polysorbate 80

Sucrose

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

3 years

After reconstitution

Biochemical and biophysical in-use stability has been demonstrated for 4 hours at 30˚C.

From a microbiological point of view, the medicinal product should be used immediately or no longer than 4 hours after reconstitution.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Do not freeze. Store in the original package in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

WINREVAIR 45 mg powder for solution for injection

2 mL capacity, type I glass vial sealed with a bromobutyl rubber stopper with polymer coating and aluminium seal with lime polypropylene flip-off cap containing 45 mg of sotatercept.

WINREVAIR 60 mg powder for solution for injection

2 mL capacity, type I glass vial sealed with a bromobutyl rubber stopper with polymer coating and aluminium seal with burgundy polypropylene flip-off cap containing 60 mg of sotatercept.

Winrevair powder for solution for injection is available as the following pack sizes:

- Pack containing 1 vial with 45 mg powder
- Pack containing 1 vial with 60 mg powder

6.6 Special precautions for disposal and other handling

Reconstitution and administration instructions

WINREVAIR powder for solution for injection should be reconstituted before use and administered as a single injection according to patient weight (see section 4.2).

Reconstitution

- Remove the pack from the refrigerator and wait 15 minutes to allow the medicinal product to come to room temperature prior to preparation.

- Check the vial to ensure the medicinal product is not expired. The powder should be white to off-white and may look like a whole or broken up cake.
- Remove the lid from the vial containing the 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 water

After reconstitution, the 45 mg vial can only provide up to a dose of 0.9 mL of medicinal product and the 60 mg vial can only provide up to a dose of 1.2 mL of medicinal product. The final concentration after reconstitution is 50 mg/mL.

- Gently swirl the vial to reconstitute the medicinal 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, the reconstituted solution should be clear to opalescent and colourless to slightly brownish-yellow, and should not have clumps or powder.
- If prescribed two vials, 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

WINREVAIR is to be administered as a single subcutaneous injection.

- Before preparing the dosing syringe, visually inspect the reconstituted solution. The reconstituted solution should be clear to opalescent and colourless to slightly brownish-yellow, and should not have clumps or powder.
- Withdraw the appropriate volume for injection from one or two vials, based on the patient's weight.
- Select the injection site on the abdomen (at least 5 cm 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.
- Perform subcutaneous injection.
- Discard the emptied syringe into a sharps container. Do not reuse the syringe.

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

See section 4.4 for instructions on the traceability of biological medicinal products.

REGISTRATION NUMBER

WINREVAIR 45 mg : Box, 1 Vial – Reg No. DKIXXXXXXXXXXX

WINREVAIR 60 mg : Box, 1 Vial – Reg No. DKIXXXXXXXXXXX

HARUS DENGAN RESEP DOKTER

Registered by:

PT Organon Pharma Indonesia Tbk

Pasuruan, Indonesia

Distributed by:

PT Merck Sharp & Dohme Indonesia

Jakarta, Indonesia

Manufactured and packed by:

Patheon Italia S.p.A

Viale Gian Battista Stucchi 110

20900, Monza, Italy

Released by:

Merck Sharp & Dohme B.V.

Waarderweg 39, Haarlem, 2031 BN

Netherlands

EU-SPC (2024), S-WPC-MK-7962-082025

PI Version 1.0

You can report side effects directly through:

DPOC - PT Merck Sharp & Dohme Indonesia

Fax : +62-21-30078769

DISETUJUI OLEH BPOM: 05/03/2026 ID EREG10037312500208-209

Phone: +622130078700 (Press 9)
Pusat Farmakovigilans/MESO Nasional c.q. Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif Badan Pengawas Obat dan Makanan Republik Indonesia Melalui pos: Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560 Email: pv-center@pom.go.id Aplikasi pelaporan farmakovigilans Pusat Farmakovigilans/ MESO Nasional (e-meso) dengan alamat: https://e-meso.pom.go.id/

Informasi untuk Pasien

WINREVAIR 45 mg sebuk untuk larutan injeksi

WINREVAIR 60 mg serbuk untuk larutan injeksi

Sotatercept

1. Apa itu dan untuk apa Winrevair digunakan

Winrevair mengandung zat aktif sotatercept. Obat ini digunakan bersama dengan terapi lain untuk mengobati *pulmonary arterial hypertension* (PAH) pada orang dewasa dengan kelas fungsional II atau III menurut WHO.

PAH adalah jenis tekanan darah tinggi di arteri paru-paru. Pada PAH, arteri ini menyempit sehingga membuat jantung lebih sulit memompa darah melalui pembuluh tersebut dan dapat menyebabkan gejala seperti kelelahan, pusing, dan kesulitan bernapas.

Winrevair membantu memperbaiki kondisi pembuluh darah di paru-paru sehingga jantung dapat memompa darah dengan lebih efisien dan membantu meningkatkan kemampuan Anda untuk beraktivitas fisik.

2. Apa yang perlu Anda ketahui sebelum menggunakan Winrevair

Jangan gunakan Winrevair

- Jika Anda alergi terhadap sotatercept atau bahan lain dari obat ini (tercantum di bagian 6).
- Jika jumlah trombosit dalam darah Anda berulang kali sangat rendah.

Peringatan dan tindakan pencegahan

Winrevair dapat meningkatkan kadar hemoglobin dalam darah Anda, menurunkan jumlah trombosit dalam darah Anda, atau meningkatkan risiko pendarahan serius.

Bicaralah dengan dokter atau apoteker Anda sebelum dan saat menggunakan Winrevair jika Anda memiliki:

- **kadar hemoglobin tinggi dalam darah Anda** (protein dalam sel darah merah yang membawa oksigen). Hal ini dapat meningkatkan kemungkinan terbentuknya bekuan darah yang dapat menyumbat pembuluh darah. Dokter Anda akan memeriksa kadar hemoglobin dengan tes darah rutin sebelum masing-masing dari 5 dosis pertama Winrevair Anda, atau lebih lama sebelum setiap dosis jika diperlukan, dan secara teratur saat Anda menggunakan obat ini.
- **jumlah trombosit rendah dalam darah Anda** (sel darah yang membantu darah membeku). Hal ini dapat menyebabkan mudah memar, pendarahan terus-menerus dari luka dan mimisan. Dokter Anda akan memeriksa jumlah trombosit Anda dengan tes darah rutin sebelum masing-masing dari 5 dosis pertama Winrevair Anda, atau lebih lama sebelum setiap dosis jika diperlukan, dan secara teratur saat Anda menggunakan obat ini. Jika jumlah trombosit dalam darah Anda berulang kali sangat rendah, dokter Anda tidak akan memulai pengobatan Anda.
- **tanda dan gejala pendarahan serius:**
  - sakit kepala terus-menerus
  - mual
  - lemas
  - tinja berwarna hitam atau merah gelap
  - darah dalam tinja
  - darah merah terang saat muntah atau batuk

- kram perut yang terus-menerus
- nyeri punggung yang parah
- pendarahan menstruasi yang sangat berat

Berikut ini adalah tanda dan gejala pendarahan serius yang dapat terjadi jika Anda mengonsumsi Winrevair dan lebih mungkin terjadi jika Anda mengonsumsi Winrevair dengan obat-obatan tertentu. Dokter Anda akan memberi tahu Anda cara mengenalinya. Bicaralah dengan dokter Anda jika Anda melihat salah satu dari tanda atau gejala ini. Pendarahan serius dapat menyebabkan perlunya rawat inap, perlunya transfusi darah atau perawatan lain, dan dapat mengancam jiwa.

Anak-anak dan remaja

Jangan berikan obat ini kepada anak-anak dan remaja di bawah usia 18 tahun. Tidak diketahui apakah obat ini aman dan bekerja pada orang di bawah usia 18 tahun.

Obat-obatan lain dan Winrevair

Beri tahu dokter atau apoteker Anda jika Anda sedang menggunakan, baru saja menggunakan atau mungkin menggunakan obat-obatan lain.

Kehamilan, menyusui, dan kesuburan

Jika Anda sedang hamil atau menyusui, merasa mungkin hamil, atau berencana untuk memiliki bayi, mintalah saran dari dokter atau apoteker sebelum menggunakan obat ini.

Kehamilan:

Winrevair dapat membahayakan bayi Anda yang belum lahir.

Obat ini tidak dianjurkan selama kehamilan. Dokter Anda harus melakukan tes kehamilan sebelum Anda memulai pengobatan dan Anda harus menggunakan alat kontrasepsi yang efektif selama pengobatan dan setidaknya 4 bulan setelah dosis terakhir Winrevair. Tanyakan kepada dokter atau apoteker Anda tentang metode kontrasepsi yang akan bekerja dengan baik untuk Anda.

Segera beri tahu dokter Anda jika Anda hamil atau merasa mungkin hamil saat menggunakan obat ini.

Menyusui:

Tidak diketahui apakah Winrevair masuk ke dalam ASI. Jangan menyusui selama pengobatan dan setidaknya 4 bulan setelah dosis terakhir Winrevair. Bicarakan dengan dokter atau apoteker Anda tentang cara terbaik untuk memberi makan bayi Anda.

Kesuburan:

Winrevair dapat menurunkan kesuburan wanita dan pria.

Mengemudi dan menggunakan mesin

Obat ini mungkin tidak memengaruhi kemampuan Anda dalam mengemudi dan menggunakan mesin.

Winrevair mengandung natrium

Obat ini mengandung kurang dari 1 mmol natrium (23 mg) per dosis, yang berarti pada dasarnya 'bebas natrium'.

Winrevair mengandung polisorbat 80

Obat ini mengandung 0,20 mg polisorbat 80 dalam setiap mL larutan yang telah dilarutkan kembali / rekonstitusi. Polisorbat dapat menyebabkan reaksi alergi. Beri tahu dokter Anda jika Anda memiliki alergi yang diketahui.

3. Bagaimana Anda diberi Winrevair

Jadwal pemberian dosis yang dianjurkan adalah satu suntikan setiap 3 minggu.

Dokter Anda akan memantau dosis Anda

- Dosis Winrevair Anda tergantung pada berat badan dan tes darah Anda. Anda akan diberikan dosis pertama sebesar 0,3 mg/kg, kemudian dosis Anda akan ditingkatkan menjadi 0,7 mg/kg.
- Sebelum masing-masing dari 5 dosis pertama Anda, atau lebih lama sebelum setiap dosis jika diperlukan, dan secara teratur saat mengonsumsi Winrevair, dokter Anda akan melakukan tes darah. Hal ini agar dokter Anda dapat memantau Anda dan menemukan dosis terbaik untuk Anda.
- Dokter Anda dapat mengubah dosis Anda, menunda pengobatan, atau menghentikan pengobatan tergantung pada bagaimana Anda merespons Winrevair.

Bagaimana Anda diberi Winrevair

Anda akan diberikan Winrevair, sebagai suntikan tepat di bawah kulit Anda (subkutan (SC)) hanya di tempat suntikan ini:

- **perut** (abdomen), setidaknya 5 cm dari pusar, atau
- **paha atas**, atau
- **lengan atas**

Jika Anda diberi Winrevair lebih banyak dari yang seharusnya

Produk ini diberikan oleh dokter atau profesional perawatan kesehatan lainnya, sangat tidak mungkin Anda akan diberi dosis Winrevair yang salah. Namun, jika Anda memiliki kekhawatiran, Anda harus segera memberi tahu dokter, apoteker, atau perawat Anda.

Jika Anda melewatkan janji temu untuk diberikan Winrevair

Jika Anda melewatkan janji temu untuk diberikan Winrevair, segera hubungi dokter Anda untuk menjadwalkan ulang janji temu Anda. Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter, apoteker, atau perawat Anda.

4. Kemungkinan efek samping

Seperti semua obat, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

Efek samping yang serius:

Bicaralah dengan dokter atau apoteker Anda **segera** jika Anda merasakan:

- Mudah memar, pendarahan berkepanjangan dari luka dan mimisan. Ini bisa menjadi tanda-tanda rendahnya jumlah trombosit (trombositopenia). Ini akan terlihat dalam tes darah Anda.

  Selain itu, dokter Anda akan melakukan tes darah rutin untuk mengetahui apakah Anda memiliki:

- Kadar hemoglobin yang tinggi.

  Efek samping serius di atas dapat memengaruhi lebih dari 1 dari 10 orang.

Kemungkinan efek samping lainnya:

Bicaralah dengan dokter atau apoteker Anda jika Anda merasakan salah satu dari berikut ini:

Sangat umum (dapat memengaruhi lebih dari 1 dari 10 orang):

- Sakit kepala
- Mimisan (epistaksis)
- *Spider veins* atau pembuluh darah kecil yang tampak seperti garis merah muda atau merah pada kulit (*telangiectasia*)
- Diare
- Pusing
- Ruam kulit

Umum (dapat memengaruhi hingga 1 dari 10 orang):

- Tekanan darah tinggi
- Kemerahan pada kulit

- Gusi berdarah
- Gatal di tempat suntikan

Tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang tersedia)

- Penumpukan cairan di sekitar jantung (efusi perikardium)

Pelaporan efek samping

Jika Anda mengalami efek samping apa pun, bicarakan dengan dokter, apoteker, atau perawat Anda. Ini termasuk kemungkinan efek samping yang tidak tercantum dalam brosur ini.

5. Cara menyimpan Winrevair

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tertera pada botol dan karton setelah "EXP". Tanggal kedaluwarsa mengacu pada hari terakhir bulan tersebut.

Simpan dalam lemari es (2 °C – 8 °C). Jangan dibekukan. Simpan dalam kemasan asli untuk melindungi dari cahaya.

Setelah rekonstitusi (pencampuran serbuk dengan air steril), gunakan obat ini segera atau tidak lebih dari 4 jam setelah rekonstitusi.

Jangan membuang obat apa pun melalui air limbah. Semua produk obat atau bahan limbah yang tidak digunakan termasuk bahan yang digunakan untuk rekonstitusi dan

pemberian harus dibuang sesuai dengan persyaratan setempat. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

Kandungan Winrevair

- Zat aktifnya adalah sotatercept. Setiap vial mengandung 45 mg atau 60 mg sotatercept. Setelah dilarutkan / rekonstitusi, setiap mL larutan mengandung 50 mg sotatercept.
- Bahan lainnya adalah asam sitrat monohidrat, natrium sitrat (lihat bagian 2 "Winrevair mengandung natrium"), polisorbat 80 (lihat bagian 2 "Winrevair mengandung polisorbat 80") dan sukrosa.

Seperti apa bentuk Winrevair dan isi kemasannya

Winrevair adalah serbuk untuk larutan injeksi (serbuk untuk injeksi). Serbuk berwarna putih hingga putih pucat ini tersedia dalam vial kaca 2 mL yang mengandung 45 mg atau 60 mg sotatercept.

WINREVAIR tersedia dalam:

WINREVAIR (Sotatercept 45 mg), Dus, 1 Vial – Reg No. DKIXXXXXXXXXXXX

WINREVAIR (Sotatercept 60 mg), Dus, 1 Vial – Reg No. DKIXXXXXXXXXXXX

HARUS DENGAN RESEP DOKTER

Didaftarkan oleh:

PT Organon Pharma Indonesia Tbk

Pasuruan, Indonesia

Didistribusikan oleh:

PT Merck Sharp & Dohme Indonesia

Jakarta, Indonesia

Diproduksi dan dikemas oleh:

Patheon Italia S.p.A
Viale Gian Battista Stucchi 110
20900, Monza, Italy

Dirilis oleh:

Merck Sharp & Dohme B.V.
Waarderweg 39, Haarlem, 2031 BN
Netherlands

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Anda dapat melaporkan efek samping secara langsung melalui:

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