1. NAME OF THE MEDICINAL PRODUCT

Winrevair® 45 mg

Winrevair® 60 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Winrevair® 45 mg powder and solvent 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 and solvent 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 and solvent for solution for injection (powder for injection).

Powder: white to off-white powder.

Solvent: clear colourless water for injections.

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)*	Kit type
30.0 – 40.8	0.2	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	Kit containing 1 x 60 mg vial
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)*	Kit type
30.0 – 31.7	0.4	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	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	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	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	

*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.

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.

Winrevair powder and solvent for solution for injection is intended for use under the guidance of a healthcare professional (HCP). Patients and caregivers may administer the medicinal product when considered appropriate and when they receive training from a HCP in how to reconstitute, prepare, measure and inject Winrevair powder and solvent for solution for injection. A HCP should confirm at a subsequent visit, soon after training, that the patient or caregiver can perform these steps correctly. A HCP should also consider reconfirming the patient's or caregiver's administration technique if the dose is adjusted, if the patient requires a different kit, if the patient develops erythrocytosis (see section 4.4), or at any time at the discretion of the HCP.

Refer to section 6.6 for detailed 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). If a patient develops erythrocytosis, HCP should consider re-evaluating the patient's or caregiver's administration technique.

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.

The adverse reactions reported with sotatercept 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).

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
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.

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

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, multicentre, 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 septostomy	0 (0.0)	0 (0.0)
PAH-specific hospitalisation (≥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.

Paediatric population

See section 4.2 for information on paediatric use.

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×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

Sucrose
Trisodium citrate dihydrate
Citric acid monohydrate
Polysorbate 80

Solvent

Water for injections

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

The expiry date of the product is indicated on the packaging materials.

After reconstitution

Biochemical and biophysical in-use stability has been demonstrated for 4 hours at 30 °C in the injection syringe.

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 and solvent 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.

Prefilled syringe (type I glass cartridge closed with a bromobutyl rubber stopper) with 1 mL of solvent.

Winrevair 60 mg powder and solvent 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.

Prefilled syringe (type I glass cartridge closed with a bromobutyl rubber stopper) with 1.3 mL of solvent.

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

- Kits containing 1 vial with 45 mg powder, 1 prefilled syringe with 1.0 mL solvent, 1 dosing syringe with 0.1 mL graduations, 1 vial adaptor (13 mm), 1 needle for injection and 4 alcohol wipes.
- Kits containing 2 vials with 45 mg powder, 2 prefilled syringes with 1.0 mL solvent, 1 dosing syringe with 0.1 mL graduations, 2 vial adaptors (13 mm), 1 needle for injection and 8 alcohol wipes.
- Kits containing 1 vial with 60 mg powder, 1 prefilled syringe with 1.3 mL solvent, 1 dosing syringe with 0.1 mL graduations, 1 vial adaptor (13 mm), 1 needle for injection and 4 alcohol wipes.
- Kits containing 2 vials with 60 mg powder, 2 prefilled syringes with 1.3 mL solvent, 1 dosing syringe with 0.1 mL graduations, 2 vial adaptors (13 mm), 1 needle for injection and 8 alcohol wipes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Selecting the appropriate product kit

If a patient's weight requires the use of two 45 mg or two 60 mg vials, a 2-vial kit should be used instead of two 1-vial kit to eliminate the need for multiple injections (see section 6.5).

Reconstitution and administration instructions

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

See the separate Instructions for Use booklet provided in the kit for detailed step by step instructions on how to prepare and administer the medicinal product. An overview of the reconstitution and administration instructions is provided below.

Reconstitution

- Remove the kit from the refrigerator and wait 15 minutes to allow the prefilled syringe(s) and 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.
- Attach the vial adaptor to the vial.
- Visually inspect the prefilled syringe for any damage or leaks and the sterile water inside to ensure there are no visible particles.
- Break off the cap of the prefilled syringe and attach the syringe to the vial adaptor.
- Inject all of the sterile water from the attached syringe into the vial containing the powder:
    - The prefilled syringe provided with the vial 45 mg contains 1.0 mL of sterile water.
    - The prefilled syringe provided with the vial 60 mg contains 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.
- Unscrew the syringe from the vial adaptor and discard the emptied syringe.
- If prescribed a 2-vial kit, 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.

Dosing syringe preparation

- 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.
- Swab the vial adaptor with an alcohol wipe.
- Remove the dosing syringe from its packaging and attach the syringe to the vial adaptor.
- 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 the entire contents into the second vial, to ensure dose accuracy.
    - Turn the syringe and vial upside-down and withdraw the required amount of medicinal product.
- If necessary, push the plunger in to remove excess medicinal product or air from the syringe.

- Remove the syringe from the vial adaptor and attach the needle.

Administration
Winrevair is to be administered as a single subcutaneous injection.
- 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.
    - For administration by the patient or caregiver, train them to inject only in the abdomen or upper thigh (see "Instructions for Use" booklet).
- Perform subcutaneous injection.
- Discard the emptied syringe. 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.

7. MARKETING AUTHORISATION HOLDER AND IMPORTER

Merck Sharp & Dohme (Israel – 1996) Company Ltd., 34 Ha'charash St., Hod-Hasharon.

8. MARKETING AUTHORISATION NUMBER(S)

Winrevair 45 mg - 179-20-38120
Winrevair 60 mg - 179-21-38121

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