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

AUSTRALIAN PRODUCT INFORMATION

REGKIRONA (Regdanvimab)

1 NAME OF THE MEDICINE

Regdanvimab (rch)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

REGKIRONA vial contains 960 mg of regdanvimab in 16 mL.

Each mL of concentrate contains 60 mg of regdanvimab.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

REGKIRONA is a sterile, clear to opalescent and colourless to pale yellow solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

REGKIRONA has **provisional approval** for the treatment of adults with coronavirus disease 2019 (COVID-19) who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19 (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

The decision has been made on the basis of short term efficacy and safety data. Continued approval of this indication depends on the evidence of longer term efficacy and safety from assessment.

4.2 DOSE AND METHOD OF ADMINISTRATION

As part of risk stratification of patients the pivotal consideration is the comorbidities, alongside age, particularly multiple comorbidities.

REGKIRONA should not be used in patients hospitalised due to COVID-19.

Dose

The recommended dosage of REGKIRONA in adults is a single intravenous infusion of 40

mg/kg. The maximum dosage of REGKIRONA should not exceed 8,000 mg.

Method of Administration

For intravenous use only.

REGKIRONA should be diluted and administered intravenously over 60 minutes.

The rate of infusion may be slowed or interrupted if the patient develops any signs of infusion-related reactions (see Section 4.8 Adverse effects) or other adverse events and appropriate resuscitation equipment should be available (see Section 4.4 Special warnings and precautions for use).

REGKIRONA should be administered after a positive viral test for SARS-CoV-2 and within 7 days of symptom onset. (See Section 5.1 PHARMACODYNAMICS PROPERTIES, Clinical Trials)

REGKIRONA may only be administered in settings in which health care providers have immediate access to medicinal products to treat a severe infusion reaction, including anaphylaxis. Patients should be clinically monitored during administration and be observed for at least 1 hour after infusion is complete.

Preparation

REGKIRONA solution for infusion should be prepared by a qualified healthcare professional using aseptic technique:

- Remove REGKIRONA vial(s) from refrigerated storage and allow to equilibrate to room temperature (not exceeding 30°C) for approximately 20 minutes before preparation. DO NOT EXPOSE TO DIRECT HEAT. DO NOT SHAKE THE VIAL(S).
- REGKIRONA is a clear to opalescent, colourless to pale yellow solution for infusion. Inspect REGKIRONA vial(s) visually for particulate matter and discolouration prior to dilution. Should either be observed, the vial(s) must be discarded, and new vial(s) should be used for preparation.
- Calculate total volume of REGKIRONA to be administered. The volume of REGKIRONA is calculated as follows.

Calculation to determine the total volume of REGKIRONA to be administered:

$$\frac{\text{Patient's } \textbf{body weight} \text{ (kg) x REGKIRONA } \textbf{dose} \text{ (}\textbf{40}\text{ mg/kg)}}{\text{Vial concentration (}\textbf{60}\text{ mg/mL)}} = \textbf{Volume} \text{ of REGKIRONA(mL)}$$

Calculation to determine the total number of REGKIRONA vials needed:

$$\frac{\text{Total REGKIRONA volume (mL) to be administered}}{\text{Total volume per vial (16 mL/vial)}} = \text{Number of REGKIRONA vials needed}$$

Table 1: Sample calculations for patients receiving the recommended dose of 40 mg/kg of REGKIRONA for weights ranging from 40 kg to 120 kg

Body weight (kg)	Total dose (mg)	Volume (mL)	Vials (n)
40	1,600	27	2
60	2,400	40	3
80	3,200	53	4
100	4,000	67	5
120	4,800	80	5

Note: If a patient's weight is more than 200 kg, the dose calculation should use 200 kg. The maximal recommended dose is 8,000 mg.

- Dilute REGKIRONA in a bag containing sodium chloride 9 mg/mL (0.9%) solution for infusion. The total volume of the medicinal product and sodium chloride should be 250 mL.
    - In a 250 mL bag of sodium chloride, withdraw and discard the required volume (which is identical to the calculated volume of REGKIRONA) of sodium chloride 9 mg/mL (0.9%) from the infusion bag.
    - Withdraw the calculated volume of REGKIRONA from the vial(s) using a sterile syringe.
    - Transfer REGKIRONA to the infusion bag.
- Gently invert IV bag by hand approximately 10 times to mix. DO NOT SHAKE**.**

Administration

REGKIRONA solution for infusion should be administered by a qualified healthcare professional.

- Gather the recommended materials for infusion: Infusion set with in-line filter (PES (Polyethersulfone) filter with a pore size of 1.2 µm or less would be recommended).
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer as an IV infusion via pump over 60 minutes.
- The prepared solution for infusion should not be administered simultaneously with any other medicinal product.

Special Populations

Elderly

No dose adjustment of REGKIRONA is required in elderly patients (see Section 5.2 Pharmacokinetic properties).

Renal impairment

No dose adjustments are recommended (see Section 5.2 Pharmacokinetic properties).

Hepatic impairment

No dose adjustments are recommended (see Section 5.2 Pharmacokinetic properties).

Paediatric population

The safety and efficacy of regdanvimab in paediatric patients have not yet been established. No data are available.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or any of the excipients (see Section 6.1 LIST OF EXCIPIENTS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity including Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported with administration of regdanvimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, administration of regdanvimab should be discontinued and appropriate supportive treatment should be administered.

Infusion-related reactions have been observed with administration of regdanvimab (see Section 4.8 Adverse effects).

Signs and symptoms of infusion-related reactions may include fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia, palpitation), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vaso-vagal reactions (e.g., presyncope, syncope), dizziness and diaphoresis.

If an infusion-related reaction occurs, slowing or stopping the infusion should be considered and appropriate medicinal products and/or supportive care should be administered.

Antiviral Resistance

The clinical trials with regdanvimab were conducted in subjects who were predominantly infected with the wild-type virus and the Alpha (UK origin/B.1.1.7 lineage) variant. While it is expected that the tissue levels of regdanvimab, in most cases, will still be sufficient to neutralise SARS-CoV-2 virus, clinical efficacy data for regdanvimab against some circulating SARS-CoV-2 variants with decreased susceptibility is currently limited (see section 5.1). Healthcare professionals should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering treatment options.

Use in the Elderly

Of the 1642 patients with SARS-CoV-2 infection randomised in an ambulatory (non-hospitalised) clinical trial (Study CT-P59 3.2 Part 1 and Part 2), 13.7% were 65 years or older, and 2.7% were 75 years of age or older.

No age-dependent trends were observed in the pharmacokinetics, efficacy and safety of patients with mild-to-moderate COVID-19 aged 65 or older compared to younger patients based on subgroup analyses (see Section 5.2 Pharmacokinetic properties, Special patient populations).

Paediatric Use

The safety and efficacy of REGKIRONA have not been established in children (see Section 5.2 Pharmacokinetic properties).

Effects on Laboratory Tests

No dose-dependent relationship was observed for the laboratory abnormalities across regdanvimab-treated patients.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pharmacokinetic interactions

No interaction studies have been performed with regdanvimab.

Regdanvimab is a monoclonal antibody, which is not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medicinal products that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are considered unlikely.

Pharmacodynamic interactions

No interaction studies have been performed. Concomitant administration of regdanvimab with COVID-19 vaccines has not been studied.

The efficacy and safety of regdanvimab in subjects who have received a COVID-19 vaccine has not been established.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
No fertility studies have been performed.

Use in pregnancy (Category B2)
Reproductive and developmental studies have not been performed with regdanvimab.

Non-clinical reproductive toxicity studies have not been conducted with regdanvimab. In tissue cross-reactivity (TCR) studies with regdanvimab using human fetal and neonatal

tissues, binding to neonatal meningeal arachnoid cap cells in the spinal cord, and to nerve endings in fetal and neonatal tissues was detected. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, regdanvimab has the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of regdanvimab provides any treatment benefit or risk to the developing fetus.

REGKIRONA should not be used during pregnancy.

Use in lactation

It is not known whether regdanvimab is excreted in human milk or absorbed systemically after ingestion. Administration of regdanvimab while breast-feeding can be considered when clinically indicated.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There have been no studies to investigate the effect of regdanvimab on the ability to perform tasks that require judgement, motor or cognitive skills. A detrimental effect on such activities would not be anticipated from the pharmacology of regdanvimab. The clinical status of the patient and the adverse event profile of regdanvimab should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills.

REGKIRONA is predicted to have no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

Overall, 906 subjects have been exposed to regdanvimab in clinical trials in both healthy subjects and non-hospitalised patients. The safety of regdanvimab is based on exposure of ambulatory (non-hospitalised) patients with COVID-19.

In Study CT-P59 3.2, a total of 867 patients were treated with a single IV infusion of regdanvimab (40 mg/kg [N=757] or 80 mg/kg [N=110]) while 760 patients received placebo. Treatment-emergent adverse events (TEAEs) were reported for 29.9% of regdanvimab-treated patients and 31.2% of placebo-treated patients who were followed for at least 28 days. The most frequently reported adverse reaction (≥3% of patients) in the regdanvimab treatment group was hypertriglyceridaemia (4.2% of regdanvimab-treated patients and 4.6% of placebo-treated patients).

Treatment-emergent serious adverse events (TESAEs) were reported in 4 regdanvimab-treated patients (0.5%) and 1 placebo-treated patient (0.1%). There were no TESAEs reported for >1 patient in the regdanvimab treatment group. Infusion-related reactions were the only TESAEs considered to be related to study treatment (1 [0.1%] patient, Grade 2) in the regdanvimab treatment group, and all other TESAEs were considered to be unrelated to study treatment.

Table 2: Summary of Treatment-Emergent Adverse Events Reported at an Incidence of ≥2% in Study CT-P59 3.2: Safety Set

System Organ Class Preferred Term	Regdanvimab (N=867)	Placebo (N=760)
Investigations		
Alanine aminotransferase increased	19 (2.2%)	32 (4.2%)
Blood creatine phosphokinase increased	21 (2.4%)	11 (1.4%)
C-reactive protein increased	20 (2.3%)	10 (1.3%)
Gamma-glutamyltransferase increased	9 (1.0%)	21 (2.8%)
Hepatic enzyme increased	23 (2.7%)	15 (2.0%)
Inflammatory marker increased	17 (2.0%)	19 (2.5%)
Metabolism and nutrition disorders		
Hyperglycaemia	17 (2.0%)	12 (1.6%)
Hypertriglyceridaemia	36 (4.2%)	35 (4.6%)
Vascular disorders		
Hypertension	17 (2.0%)	11 (1.4%)

Tabulated list of adverse reactions

Adverse reactions reported with regdanvimab based on experience from clinical trials in healthy subjects and mild to moderate COVID-19 patients as well as adverse reactions reported from post-marketing experience are listed in Table 3 by system organ class and frequency. Frequencies are defined as follows: 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3: Tabulated list of adverse reactions

System organ class Frequency	Adverse reaction
Injury, poisoning and procedural complications	
Uncommon	Infusion-related reactions[1]

[1] Infusion-related reaction (IRR) includes hypersensitivity and anaphylaxis, and symptoms reported as IRRs are described below in 'Infusion-related reactions'. Anaphylaxis was identified from post-marketing experience.

Description of selected adverse reactions

Infusion-related reactions

Immediate infusion-related reactions were noted for 0.6% of regdanvimab-treated patients and 1.2% of placebo-treated patients. Reported events of fever, pruritus, hypertension and dyspnoea were mild with two cases of fever being moderate and one case of hypertension being severe and palpitation, presyncope and urticaria were moderate in the regdanvimab-treated patients. All patients in the regdanvimab treatment group recovered from the events.

In post-marketing experience, one case of anaphylaxis was reported during infusion of regdanvimab with symptoms of dyspnoea, chest discomfort and cough.

Reporting suspected adverse events

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

4.9 OVERDOSE

There is no human experience of acute overdosage with regdanvimab. Single doses up to 8,000 mg have been administered in clinical trials without dose-limiting toxicity.

Treatment of overdose should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with regdanvimab.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antivirals for systemic use,

ATC code: not yet assigned

Mechanism of action

Regdanvimab is a recombinant human IgG1 monoclonal antibody that binds to the receptor binding domain (RBD) of the spike(s) protein of SARS-CoV-2 consequently blocking SARS-CoV-2 cell entry and infection.

Antiviral activity

The *in vitro* neutralisation activity of regdanvimab against SARS-CoV-2 (BetaCoV/Korea/KCDC03/ 2020) was assessed by plaque reduction neutralisation test (PRNT) using VeroE6 cells. Regdanvimab neutralised this SARS-CoV-2 strain with an IC_{50} value of 9.70 ng/mL and an IC_{90} value of 25.09 ng/mL.

Antiviral Resistance

In vitro virus passaging with authentic SARS-CoV-2 viruses in VeroE6 cells in the presence/absence of regdanvimab identified a S494P amino acid substitution located in the RBD of the spike protein as the escape mutant emerging between 1st and 4th passage. Pseudovirus assay results with Q493K, Q493R, S494L and S494P showed IC_{50} above 500 ng/mL.

The plaque reduction neutralisation test (PRNT) using authentic SARS-CoV-2 variant virus indicate that regdanvimab retained activity against the Alpha (UK origin/B.1.1.7 lineage), Zeta (Brazilian origin/P.2), Iota (New York origin/B.1.526) and Eta (Nigerian origin/B.1.525)

variants. Reduced neutralising activity against Gamma (Brazilian origin/P.1), Beta (South African origin/B.1.351), Epsilon (Californian origin/B.1.427 and B.1.429), Kappa (Indian origin/B.1.617.1) and Delta (Indian origin/B.1.617.2) variants were observed (Table 4). Microneutralisation data using authentic SARS-CoV-2 variant virus indicate that regdanvimab retains activity against the Alpha variant and has reduced activity against the Beta and Gamma variants (Table 4).

An *in vivo* efficacy study was conducted in Beta variant or wild type virus-challenged ferrets at 80 and 160 mg/kg (below the clinical exposure based on plasma AUC). In addition, *in vivo* efficacy studies were conducted in human ACE2 transgenic mice challenged with the Beta, Gamma or Delta variants where mice were treated with regdanvimab at doses of 5, 20, 40 and 80 mg/kg (below the clinical exposure based on plasma C_{max} and AUC). The *in vivo* animal efficacy studies demonstrated that clinically relevant dosages of regdanvimab effectively reduce the viral loads and prevent exacerbation of the infection against the Beta, Gamma and Delta variants.

Table 4: Authentic SARS-CoV-2 and Pseudovirus Neutralisation Data for Regdanvimab

Lineage with Spike Protein Substitution	Key Substitutions Tested[a]	Fold Reduction in Susceptibility (Authentic Virus)	Fold Reduction in Susceptibility (Pseudovirus)[f]
B.1.1.7 (UK)	N501Y/P681H	No change[b, d, e]	No change[b]
P.1 (Brazil)	K417T/E484K/N501Y	138[e]/168[d]	61/127
P.2 (Brazil)	E484K	No change[b, d]	Not determined
B.1.351 (South Africa)	K417N/E484K/N501Y	20[e]/310[d]	184/253
B.1.427 (California)	L452R	74[d]	Not determined
B.1.429 (California)	L452R	54[d]	31
B.1.526 (New York)[c]	E484K/A701V	No change[b, d]	7
B.1.525 (Nigeria)	E484K/Q677H	No change[b, d]	7
B.1.617.1 (India)	L452R/E484Q/P681R	24[d]	44
B.1.617.2 (India)	L452R/T478K/P681R	183[d]	28
AY.1 (India)	K417N/L452R/T478K	Not determined	64
C.37 (Peru)	L452Q/F490S	Not determined	16
B.1.621 (Columbia)	R346K/E484K/N501Y/P681H	Not determined	39

[a] For variants with more than one substitution of concern, only the one(s) with the greatest impact on activity is(are) listed
[b] No change: <5-fold reduction in susceptibility
[c] Not all isolates of the New York lineage harbours E484K substitution (as of February 2021)
[d] The study was conducted using plaque reduction neutralisation test
[e] The study was conducted using microneutralisation assay
[f] Key substitutions for global variants have been tested in a pseudovirus assay and multiple studies have been conducted for some variants

Although the potential escape mutant (S494P) have been observed after regdanvimab treatment in regdanvimab monotherapy treatment arms, none of these patients required oxygen therapy or hospitalisation or experienced mortality due to SARS-CoV-2 infection.

It is possible that regdanvimab resistance-associated variants could have cross-resistance to other monoclonal antibodies targeting the RBD of SARS-CoV-2. The clinical relevance is not known.

Clinical trials

Study CT-P59 3.2 Part 2 was a randomised, double-blind, placebo-controlled clinical trial studying regdanvimab for the treatment of adult patients with mild to moderate COVID-19 and was conducted in multiple countries including the European Union (79.5%), the United States (7.6%) and Asia (0.9%). This study enrolled adult patients who were not hospitalised, had at least one or more symptoms of COVID-19 for ≤7 days, oxygen saturation >94% on room air and not requiring supplemental oxygen therapy and they were enrolled from January 18, 2021 and clinical efficacy endpoints were analysed based on data up to the cut-off date of May 21, 2021. Patients who have received a COVID-19 vaccine were excluded from the trial. Treatment was initiated after obtaining a positive SARS-CoV-2 viral infection determination. Patients were randomised in a 1:1 manner to receive a single infusion of regdanvimab at doses of 40 mg/kg (N=656) or placebo (N=659) over 60 minutes.

The primary efficacy endpoint was the proportion of patients with clinical symptoms requiring hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28. This was analysed in all patients randomly assigned to the study drug, who are at increased risk of progressing to severe COVID-19 and/or hospitalisation (defined as having at least one of the following risk factors for severe COVID-19: age >50 years; BMI >30 kg/m^2; cardiovascular disease, including hypertension; chronic lung disease, including asthma; type 1 or type 2 diabetes mellitus; chronic kidney disease, including those on dialysis; chronic liver disease; and immunosuppressed, based on investigator's assessment).

Key secondary endpoints included the proportion of patients with clinical symptoms requiring hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 in all randomised patients, time to clinical recovery up to Day 14 in all randomised patients who are at increased risk of progressing to severe COVID-19 and/or hospitalisation (as defined above) and time to clinical recovery up to Day 14 in all randomised patients.

At baseline, the median age was 48 years (range: 18 to 87); 13.0% of patients aged 65 or older and 2.7% of patients aged 75 or older; 51.3% of patients were male; 86.1% were White, 21.0% were Hispanic or Latino, 1.1% were Asian and 0.5% were Black or African American. Patients had mild (53.0%) to moderate (46.4%) COVID-19; 66.9% of patients were at increased risk of progressing to severe COVID-19 and/or hospitalisation; the median time from the initial symptom onset was 4 days; mean viral load at baseline was 5.8 log10 copies/mL in the regdanvimab treatment group and 5.9 log10 copies/mL in placebo group.

Proportion of patients with clinical symptom requiring hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28

Table 5: Result of Primary Endpoint in Study CT-P59 3.2 Part 2

		Regdanvimab (40 mg/kg IV infusion)	Placebo	Relative Risk Reduction (95% CI)[c]
Proportion of Patients with Clinical Symptoms Requiring Hospitalisation, Oxygen Therapy, or Experiencing Mortality due to SARS-CoV-2 Infection up to Day 28	**Proportion (n, %)**	14/446 (3.1%)	48/434 (11.1%)	72.3% (50.4, 84.5)
	Difference (95% CI)[a]	-8.0 (-11.7, -4.5)		
	P-value[b]	<0.0001		

Note: Clinical symptom which requires hospitalisation, oxygen therapy, or experiencing mortality due to SARS-CoV-2 infection up to Day 28 is included. Criterion of hospitalisation is ≥24 hours of acute care. Criteria of oxygen therapy are at least 24 hours of supplemental oxygen care and SpO_2 measure in room air before applying supplemental oxygen showing ≤94%.

[a] The difference of proportions between two treatment groups estimated using CMH (Cochran-Mantel-Haenszel) weights, and the 95% stratified Newcombe confidence interval (CI) with CMH weights are presented. Analysis was stratified by Age (≥60 years vs. <60 years), baseline comorbidities (Yes vs. No) and region (United States vs. European Union vs. other).

[b] The p-value from stratified CMH test is presented. The CMH test is stratified by age (≥60 years vs. <60 years), baseline comorbidities (Yes vs. No) and region (United States vs. European Union vs. other).

[c] The MH estimate of common relative risk between two treatment groups, and the 95% CI using Greenland and Robins (1985) variance are calculated. For each, the relative risk reduction (%) calculated as ([1 - relative risk]*100) is presented. Analysis is stratified by Age (≥60 years vs. <60 years), baseline comorbidities (Yes vs. No) and region (United States vs. European Union vs. other).

Time to Clinical Recovery up to Day 14

Time to clinical recovery was defined as time from study drug administration to the time when symptoms, which were scored as 'moderate' or 'severe' at baseline reduced to 'mild' or 'absent', and symptoms scored as 'mild' or 'absent' at baseline were scored as 'absent'. Symptoms 'absent' in intensity at baseline should maintain as 'absent' for at least 48 hours. Symptoms that were absent at baseline but became 'severe', 'moderate', or 'mild' in intensity during the study were considered clinically recovered if it changed back to 'absent' for at least 48 hours. Missing symptoms at baseline were considered to be clinically recovered if they were 'absent' for at least 48 hours. Symptoms assessed were limited to feeling feverish, cough, shortness of breath or difficulty breathing, sore throat, body pain or muscle pain, fatigue, and headache.

In Study CT-P59 3.2 Part 2, the median time to clinical recovery (at least 48 hours) in all randomised patients who are at increased risk of progressing to severe COVID-19 and/or hospitalisation (as defined above) was significantly shorter for regdanvimab-treated patients as compared to placebo-treated patients (median, 9.27 days vs. not calculated). As less than 50% of the patients in the placebo group achieved clinical recovery up to Day 14, it was not possible to calculate the median time to clinical recovery up to Day 14. However, it can be considered that the patients in the regdanvimab treatment group demonstrated a

shortened time to clinical recovery of at least 4.73 days compared to the placebo group assuming the median time to clinical recovery in the placebo-treated patients as a minimum of 14 days. The difference in time to clinical recovery between the treatment groups was statistically significant (p<0.0001 [stratified log-rank test]; clinical recovery ratio [95% CI] = 1.58 [1.31, 1.90]).

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic profile of regdanvimab is linear and based on the PK analysis in healthy subjects, regdanvimab was approximately dose-proportional in terms of maximal and systemic exposure (C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$) over the dose range of 10 mg/kg to 80 mg/kg.

Absorption

Following the administration of the recommended dose regimen (a single dose of 40 mg/kg) in COVID-19 patients, the mean (CV%) C_{max} level was 1016.6 µg/mL (26.5%).

Distribution

The mean (CV%) apparent volume of distribution at steady-state (V_{ss}) after intravenous administration of regdanvimab 40 mg/kg was 83.4 mL/kg (26.2%) in COVID-19 patients.

Metabolism

Regdanvimab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Excretion

No major age- or weight-related differences in clearance or volume of distribution were observed in COVID-19 patients aged 18 years and older.

In studies with COVID-19 patients, the mean (± SD) clearance of regdanvimab 40 mg/kg was 0.2 ± 0. 05 mL/hr/kg.

The mean terminal half-life ranged from 16.6 days to 22.0 days for 10, 20, 40 and 80 mg/kg of regdanvimab administered to healthy subjects. In patients with COVID-19, the geometric mean terminal half-life for 40 mg/kg of regdanvimab was 15.6 days.

Special patient populations

Elderly

Based on pharmacokinetic subgroup analyses, there is no difference in pharmacokinetics of regdanvimab in elderly patients compared to younger patients.

Paediatric patients

The pharmacokinetics of regdanvimab in paediatric patients has not been evaluated.

Hepatic and renal impairment

The pharmacokinetics of regdanvimab has not been evaluated in patients with renal and/or hepatic impairment. Regdanvimab is not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of regdanvimab.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies have not been conducted with regdanvimab.

Carcinogenicity

Carcinogenicity studies have not been conducted with regdanvimab.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENT

Histidine
Histidine hydrochloride monohydrate
Polysorbate 80
Aginine hydrochloride
Water for injections

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG 374190). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened packs

Store in a refrigerator (2°C – 8°C).

Do not freeze. Keep the medicinal product in its outer carton in order to protect from light.

Opened packs
Chemical and physical in-use stability has been demonstrated for 72 hours at 2°C – 8°C or 4 hours at ≤30°C after dilution in sodium chloride 9 mg/mL (0.9%) solution for infusion.

To reduce microbiological hazard, use as soon as practicable after preparation. If storage is necessary, hold at 2°C – 8°C for not more than 72 hours when dilution has taken place in controlled and validated aseptic conditions. Product is for single use in one patient only. Discard any residue.

6.5 NATURE AND CONTENTS OF CONTAINER

Type I glass vial with a chlorobutyl rubber stopper containing 960 mg of regdanvimab in 16 mL.

Pack size of 1 vial.

REGKIRONA is supplied as a single-use vial. Contains no preservative

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure
Not relevant

CAS number
CAS- 2444308-95-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Celltrion Healthcare Australia Pty Ltd.

Suite 13.03, 31 Market Street
Sydney NSW 2000
Australia Phone: 1800 325 228

9 DATE OF FIRST APPROVAL

06 December 2021

10 DATE OF REVISION

Not applicable

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information