ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Regkirona 60 mg/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 960 mg of regdanvimab*.
Each mL of concentrate contains 60 mg of regdanvimab.

* Regdanvimab is a recombinant human IgG1 monoclonal antibody produced through recombinant DNA technology in a mammalian cell line (Chinese Hamster Ovary).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)
Clear to opalescent, colourless to pale yellow solution with pH of 5.7– 6.3 and osmolality of 250 - 300 mOsmol/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Regdanvimab is indicated for the treatment of adults with coronavirus disease 2019 (COVID-19) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 (see section 5.1).

4.2 Posology and method of administration

Regdanvimab should only be administered in settings in which health care providers have immediate access to appropriate resuscitation equipment and medicinal products to treat a severe infusion reaction, including anaphylaxis, and where patients can be clinically monitored during administration and be observed for at least 1 hour after infusion is complete (see section 4.4).

Posology

The recommended dosage of regdanvimab in adults is a single IV infusion of 40 mg/kg. Regdanvimab should be administered within 7 days of onset of symptoms of COVID-19 (see section 5.1).

The volume of Regkirona is calculated as follows.

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

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

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.

Special populations

Elderly
No dose adjustment of regdanvimab is required in elderly patients (see section 5.2).

Renal impairment
No dose adjustments are recommended.

Hepatic impairment
No dose adjustments are recommended.

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

Method of administration

For intravenous use only.

Regdanvimab 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 or other adverse reactions and appropriate treatment should be initiated as necessary (see section 4.4).

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

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.

Hypersensitivity including infusion-related reactions and anaphylactic reactions

Hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been observed during and following administration of regdanvimab (see section 4.8).

Patients should be clinically monitored during administration and be observed for at least 1 hour after infusion is complete.

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. Clinical efficacy data for regdanvimab against some circulating SARS-CoV-2 variants with decreased *in vitro* susceptibility is currently limited (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

No interaction studies have been performed with regdanvimab.

Regdanvimab is a monoclonal antibody, which is not renally excreted or metabolised 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Reproductive and developmental studies have not been performed with regdanvimab.

Nonclinical reproductive toxicity studies have not been conducted with regdanvimab (see section 5.3). In tissue cross-reactivity (TCR) studies with regdanvimab using human foetal and neonatal tissues, no binding of clinical concern was detected in the foetal tissues. 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 foetus. It is unknown whether the potential transfer of regdanvimab provides any treatment benefit or risk to the developing foetus.

Regdanvimab should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the foetus.

Breast-feeding

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.

Fertility

No fertility studies have been performed.

4.7 Effects on ability to drive and use machines

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

4.8 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.

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 2 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 2: 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 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. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immune sera and immunoglobulins, antiviral monoclonal antibodies, ATC code: J06BD06

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 cellular entry and SARS-CoV-2 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.

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 3). Microneutralisation data using authentic SARS-CoV-2 variant virus indicate that regdanivimab retains activity against the Alpha variant and has reduced activity against the Beta and Gamma variants (Table 3).

Table 3: 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 (Alpha, UK)	N501Y/P681H	No change[b, d, e]	No change[b]
P.1 (Gamma, Brazil)	K417T/E484K/N501Y	137.88[e]/167.90[d]	61.42
P.2 (Zeta, Brazil)	E484K	No change[b, d]	8.66
B.1.351 (Beta, South Africa)	K417N/E484K/N501Y	19.75[e]/310.06[d]	184.29
B.1.427 (Epsilon, California)	L452R	73.89[d]	34.97
B.1.429 (Epsilon, California)	L452R	54.08[d]	34.97
B.1.526 (Iota, New York)[c]	E484K/A701V	No change[b, d]	6.84
B.1.525 (Eta, Nigeria)	E484K/Q677H	No change[b, d]	7.22
B.1.617.1 (Kappa, India)	L452R/E484Q/P681R	23.89[d]	44.14
B.1.617.2 (Delta, India)	L452R/T478K/P681R	182.99[d]	27.70
AY.1 (Delta plus, India)	K417N/L452R/T478K	Not determined	63.65
C.37 (Lambda, Peru)	L452Q/F490S	Not determined	15.50

Lineage with Spike Protein Substitution	Key Substitutions Tested[a]	Fold Reduction in Susceptibility (Authentic Virus)	Fold Reduction in Susceptibility (Pseudovirus)[f]
B.1.621 (Mu, Columbia)	R346K/E484K/N501Y/ P681H	Not determined	38.65
B.1.1.529 (Omicron, South Africa)	K417N/T478K/E484A/ N501Y	Not determined	Not calculated[g]

[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
[g] Not calculated (IC_{50} > 1 mg/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. Pseudovirus assay results with Q493K, Q493R, S494L and S494P showed IC_{50} above 500 ng/mL.

In Study CT-P59 3.2 (Phase 3), sequencing data collected at study visits were available for 557 patients with COVID-19 (240 regdanvimab-treated patients and 317 placebo-treated patients). At an allele fraction of ≥15%, N501Y was the most frequently detected variant present in 76.7% (184/240) of patients in the regdanvimab group and 79.5% (252/317) of patients in the placebo group. At baseline, no patients had a combination of L452R, T478K and P681R mutations (associated with the Delta variant). Three patients (none from the regdanvimab group and 3 patients from the placebo group) had the combination of K417N, E484K and N501Y mutations (the Beta variant), and 10 patients (5 patients from each group) had the combination of K417T, E484K and N501Y mutations (the Gamma variant).

Variants with *in vitro* reduced susceptibility at spike protein amino acid positions Q493K/R or S494P/L at an allele fraction of ≥15% were detected for 17.9% (43/240) of patients in the regdanvimab group and none in the placebo group at posttreatment. Phenotyping assessments were done with variants in RBD at an allelic frequency of ≥15% and all variants in epitope found in genotyping from the regdanvimab-treated patients in Study CT-P59 3.2 (Phase 3) including F342S, R403G/T, Y449H, Y453C, L455F/S, K458R, F486I, L492S, Q493L, S494T and F490I using a luciferase-based pseudovirus assay. The reduction in susceptibility was below five-fold for all of these except for L455F/S, F486I, Q493L and S494T variants. For these variants, the fold-change was >20.

Clinical efficacy

A Phase 3 of Study CT-P59 3.2 was a randomised, double-blind, placebo-controlled clinical trial studying regdanvimab for the treatment of unvaccinated 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. Treatment was initiated after obtaining a positive SARS-CoV-2 viral infection determination.

A total of 1315 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).

Among all randomised patients, 66.9% of patients were at increased risk of progressing to severe COVID-19 and/or hospitalisation. Among patients at increased risk of progressing to severe COVID-19 and/or hospitalisation, the baseline median age was 54 years (range: 18 to 87); 19.4% of patients aged 65 or older and 4.0% of patients aged 75 or older; 53.6% of patients were male; 88.6% were White, 19.9% were Hispanic or Latino, 0.8% were Asian and 0.8% were Black or African American. The median time from the initial symptom onset was 4 days; mean viral load at baseline was 5.8 $\log_{10}$ copies/mL in the regdanvimab treatment group and 5.9 $\log_{10}$ copies/mL in placebo group. Forty-seven percent and 52.4% of patients had mild and moderate COVID-19, respectively. The most common risk factors were advanced age (age >50 years) (66.1%), cardiovascular disease, including hypertension, (50.3%) and obesity (BMI >30 kg/m^2) (47.2%).

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

Table 4: Result of Primary Endpoint in Study CT-P59 3.2 (Phase 3)

		Regdanvimab (40 mg/kg IV infusion)	Placebo
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%)
	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).

In addition, a total of 3 patients died (1 regdanvimab-treated patient and 2 placebo-treated patients) due to worsening of COVID-19.

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.

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]).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Regkirona in the treatment of Coronavirus disease 2019 (COVID-19) in one or more subsets of the paediatric population (see section 4.2 and section 5.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption and distribution

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 1017 μg/mL (27%).

The mean (CV%) apparent volume of distribution at steady-state (V_{ss}) after intravenous administration of regdanvimab 40 mg/kg was 83 mL/kg (26%) in COVID-19 patients.

Elimination

Regdanvimab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. No major age- or weight-related differences in clearance or volume of distribution were observed in COVID-19 patients.

In studies with COVID-19 patients, the mean (CV%) clearance of regdanvimab 40 mg/kg was 0.20 mL/hr/kg (24%).

In patients with COVID-19, the mean (CV%) terminal half-life for 40 mg/kg of regdanvimab was 17 days (37%).

Linearity

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.

Other special 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

Non-clinical data revealed no special hazard for humans based on conventional studies of tissue cross-reactivity and repeated dose toxicity.

In a 3-week repeat-dose toxicity study in cynomolgus monkeys, transient moderate to marked decreases in neutrophils and haematology parameter changes were observed in 20% of animals at a dose of about 9 times the human clinical exposure.

In the TCR studies with regdanvimab using human adult, neonatal, and cynomolgus tissues, specific positive stainings in meningeal arachnoid cap cells in the brain and/or spinal cord tissues were observed. These findings were not associated with neurological symptoms and histopathological findings in the toxicity study, indicating that this TCR finding is less likely to have clinical relevance.

Carcinogenicity, genotoxicity and reproductive toxicology studies have not been conducted with regdanvimab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine monohydrochloride monohydrate
Polysorbate 80
L-arginine monohydrochloride
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 6.6.

6.3 Shelf life

Unopened vials

30 months

Diluted solution for infusion

Chemically 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.

From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

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

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

6.5 Nature and contents of container

Type I glass vial with a chlorobutyl rubber stopper.

Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

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 (see section 4.2).
- 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.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

Celltrion Healthcare Hungary Kft.
1062 Budapest
Váci út 1-3. WestEnd Office Building B torony
Hungary

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1597/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 November 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

CELLTRION Inc.
23, Academy-ro,
Yeonsu-gu,
Incheon, 22014
REPUBLIC OF KOREA

Name and address of the manufacturer(s) responsible for batch release

NUVISAN GmbH
Wegenerstr. 13,
Neu-Ulm, Bayern, 89231
GERMANY

NUVISAN FRANCE SARL
2400 route des Colles,
06410 BIOT,
FRANCE

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

VIAL CARTON (CONCENTRATE FOR SOLUTION FOR INFUSION)

1. NAME OF THE MEDICINAL PRODUCT

Regkirona 60 mg/mL concentrate for solution for infusion
regdanvimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL contains 60 mg of regdanvimab

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, L-arginine monohydrochloride, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

1 vial (960 mg/16 mL)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For intravenous use after dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celltrion Healthcare Hungary Kft.
1062 Budapest
Váci út 1-3. WestEnd Office Building B torony
Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1597/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL (CONCENTRATE FOR SOLUTION FOR INFUSION)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Regkirona 60 mg/mL sterile concentrate
regdanvimab
IV use after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

960 mg/16 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Regkirona 60 mg/mL concentrate for solution for infusion
regdanvimab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Regkirona is and what it is used for
2. What you need to know before you are given Regkirona
3. How Regkirona is given to you
4. Possible side effects
5. How to store Regkirona
6. Contents of the pack and other information

1. What Regkirona is and what it is used for

The active substance of Regkirona is regdanvimab. It is a monoclonal antibody used for the treatment of COVID-19, a disease caused by a virus called SARS-CoV-2.

Regkirona is given to adult patients with COVID-19 who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

This medicine stops the virus from entering human cells by binding to the spike protein of SARS-CoV-2. When it attaches to the spike protein, the interaction between the virus and the cellular receptor is blocked and the ability of the virus to enter the body's cells is reduced. This can help your body to resist the virus infection, and may help to prevent the disease from getting worse.

2. What you need to know before you are given Regkirona

Do not use Regkirona:
- if you are allergic to regdanvimab or any of the other ingredients of this medicine (listed in section 6).

➔ **Talk to your doctor or nurse as soon as possible,** if this applies to you.

Warnings and precautions

Reactions after receiving the medicine
This medicine can cause allergic reactions or other reactions after the medicine is given to you. See also section 4, "Possible side effects". Symptoms can include:
- Fever
- Difficulty breathing
- Shortness of breath, rapid breathing or rapid heartbeat
- Chills

- Feeling tired
- Irregular, rapid or slow heart rate
- Chest discomfort or pain
- Weakness
- Confusion
- Feeling sick (nausea)
- Headache
- Shortness of breath, wheezing
- Low or high blood pressure
- Swelling of the face, lips, or throat (angioedema)
- Rash including nettle rash
- Itching
- Muscle aches
- Feeling faint
- Dizziness
- Sweating

➔ **Seek urgent medical advice** if you get any of these symptoms.

Children and adolescents
This medicine is not to be given to children and adolescents under 18 years of age because there are no data to show that this medicine is safe and works in this age group.

Other medicines and Regkirona
Tell your doctor or nurse about any other medicines you are taking, or have recently taken.

It is not yet known if this medicine affects other medicines, or if it is affected by them. Your healthcare team will monitor you for signs of medicines affecting each other.

Pregnancy and breast-feeding
If you are **pregnant, think you may be pregnant** or are **planning** to have a baby**, ask your doctor** for advice before receiving Regkirona. Your doctor will advise you whether the benefits of treatment with Regkirona are greater than any likely risks for you and your baby.

It is not known whether the ingredients of Regkirona can pass into breast milk. **If you are breast-feeding, you must check with your doctor** before you receive Regkirona.

Driving and using machines
Regkirona is not expected to have any effect on your ability to drive or use tools or machines.

3. How Regkirona is given to you

This medicine will be given to you by a nurse or doctor, as a drip into a vein (an intravenous infusion) lasting 60 minutes.

The recommended dose is a single dose of 40 mg/kg. This medicine should be given within 7 days of symptom onset.

This medicine can cause infusion reactions after the medicine is given to you. You will be closely monitored during your treatment and for at least 1 hour after infusion is complete.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or nurse if you notice any of the following side effects:

- **Uncommon:** may affect up to 1 in 100 people
  - Allergic reactions due to an infusion (e.g. fever, difficulty breathing, irregular, rapid or slow heart rate, high blood pressure, rash including nettle rash, itching, feeling faint)

In general, these types of reactions occur within minutes to several hours following completion of the infusion.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Regkirona

Keep this medicine out of sight and reach of children

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C). Keep the vial in the outer carton in order to protect from light. Do not freeze.

Do not use this medicine if you notice any particulate matter or discoloration prior to administration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines that you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Regkirona contains
- The active ingredient is called regdanvimab. The vial contains 960 mg of regdanvimab in 16 mL (60 mg/mL).
- The other ingredients are L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, L-arginine monohydrochloride and water for injections.

What Regkirona looks like and contents of the pack
This medicine is a clear to opalescent, colourless to pale yellow liquid solution in a glass vial with a rubber stopper and flip-off aluminium seal supplied as a concentrate for solution for infusion.

Regkirona is available in packs containing 1 vial.

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This leaflet was last revised in {**MM/YYYY**}.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only.
Please refer to the Summary of Product Characteristics for further information.

Instructions for healthcare professionals

Regkirona 60 mg/mL concentrate for solution for infusion
regdanvimab

Each single-use vial contains 960 mg of regdanvimab in 16 mL.

Regdanvimab should only be administered in settings in which health care providers have immediate access to appropriate resuscitation equipment and medicinal products to treat a severe infusion reaction, including anaphylaxis.

Monitor the patient for side effects during and at least 1 hour after the infusion is complete.

If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medicinal products and/or supportive therapy.

Dilute the concentrate with sodium chloride solution for infusion

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:

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

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.**
- This product is preservative-free and therefore, the diluted solution for infusion should be administered immediately. After aseptic dilution in sodium chloride 9 mg/mL (0.9%) solution for infusion, the prepared infusion solution of Regkirona in sodium chloride 9 mg/mL (0.9%) solution for infusion is physically and chemically stable for 72 hours at 2°C - 8°C or 4 hours at ≤30°C.
- From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions. If refrigerated, allow the solution for infusion to equilibrate to room temperature (not exceeding 30°C) for approximately 20 minutes prior to administration.

Administer the infusion

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.

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