## Casirivimab/imdevimab and respiratory insufficiency

### Introduction

Casirivimab and imdevimab are two human recombinant IgG1 monoclonal antibodies that are supplied as individual vials in one product, known as Ronapreve or REGN-COV [1]. These two antibodies bind to two different epitopes of the spike protein receptor binding domain of the virus SARS-COV2, which prevents entry of the virus into human cells through the angiotensin-converting enzyme 2 (ACE2) receptor. The combination of antibodies is necessary for neutralising variants and preventing mutations of the virus. Casirivimab/imdevimab was granted marketing authorisation on 12 November 2021.

Casirivimab/imdevimab is indicated for *treatment of non-hospitalised adults or children older than 12 years with mild to severe COVID19 that weigh more than 40 kilogram, have a positive PCR test and have had symptoms less than 10 days with high risk of developing severe COVID-19 or hospitalisation* [2]. Treatment with casirivimab/imdevimab consists of one infusion in a standardised dose. According to the Dutch working group of antibiotic policy (SWAB) treatment with casirivimab/imdevimab can be considered in three patient groups:

- **Mild COVID19** (no indication for hospitalisation, no oxygen required)**:** Casirivimab/imdevimab treatment can be considered in patients with risk factors for fatal COVID-19 without antibodies (not vaccinated or immunocompromised). These risk factors are cardiovascular burden, comorbidities, immunosuppression, primary or secondary immunodeficiency, age above 70 years old and obesity.
- **Mild to severe COVID19** (indication for hospitalisation and oxygen required)**:** Casirivimab/imdevimab treatment can be considered in patients without antibodies.
- **Severe COVID19** (indication for hospitalisation to medium or intensive care unit (ICU) with the need for mechanical ventiolation of extracorporeal membrange oxygenation)**:** Casirivimab/imdevimab can be considered in patients without antibodies in case these patients will be hospitalised at the ICU immediately. Casirivimab/imdevimab should not be considered as a treatment for patients who have already been admitted to the ICU for a longer period of time.

Treatment with casirivimab/imdevimab of ambulatory or hospitalised patients is not recommended in hospitals or regions with more than 50% of COVID19 infections with the Omicron variant. Casirivimab/imdevimab is also being investigated for prophylactic use. However, the use of prophylactic casirivimab/imdevimab is currently not advised by the SWAB [2, 3].

In respiratory failure, the respiratory system fails in one or both of its gas exchanging functions [4]. Respiratory insufficiency, with dyspnoea as a symptom, can be caused by various underlying disorders, including respiratory tract infections and asthma. The incidence of respiratory failure is higher in infants than in adults [5]. Immunocompromised adults, including patients with cancer, organ transplantation and patients using immunosuppressing drugs, are at increased risk of respiratory failure. The incidence of respiratory failure across immunocompromised patients varies for different underlying disorders [6]. COVID19 is an acute respiratory disease caused by SARS-CoV2 with dyspnoea as a symptom in severe cases [7].

### Reports

From 19 August 2021 until 21 December 2021 Lareb received 17 reports of adverse drug reactions related to casirivimab/imdevimab. Out of these, eight reports concerned respiratory insufficiency and four reports concerned signs of respiratory insufficiency, such as dyspnoea, hypoxia and decreased oxygen saturation.

*Table 1. Reports of respiratory insufficiency or signs of respiratory insufficiency associated with administration of casirivimab/imdevimab*

| No | ID, sex, age, primary source | Drug, Dosage | Indication | Concomitant medication | Reported ADRs (MedDRA Lower Level Term) | Medical history or comorbidities | Latency after start<br>Action taken<br>Outcome |
|---|---|---|---|---|---|---|---|
| A | NL-LRB-00686376, male, 60-70 years, Physician | Casirivimab/ imdevimab (Regn-Cov2), 8 gram / Total | SARS CoV 2 infection COVID 19 antibody test negative | Dexamethasone, Alfacalcidol, Gliclazide, Magnesium sulfate, Tiotropium/ | Acute respiratory insufficiency | Not reported | 1 Hour<br>Not Applicable<br>Not Recovered |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | Olodaterol, Clopidogrel, Piperacillin/ Tazobactam, Quetiapine, Famotidine, Dalteparin, Levetiracetam, Metformin, Metoprolol, Paracetamol, Salbutamol/ Ipratropium, Insulin Aspart | | | |
| B | NL-LRB-00670053, female, 60-70 Years, Pharmacist | Casirivimab/ imdevimab (Regn-Cov2), 8000 milligram / Total | COVID 19 COVID 19 antibody test negative | Amlodipine, Atorvastatin, Colecalciferol, Metformin, Metoprolol, Pantoprazole, Ciclesonide Aerosol, Nadroparin, Codeine, Dexamethasone, Paracetamol, Piperacillin/ Tazobactam, Insulin Aspart | Respiratory insufficiency, Bronchospasm | Asthma, Diabetes, Hypothyroidism, Urolithiasis, Diaphragmatic hernia, Castleman's disease | 2 Hours Not Applicable Recovering |
| C | NL-LRB-00699436, female, 60-70 years, Physician | Casirivimab/ imdevimab (Regn-Cov2), 8 gram / Total | COVID 19 COVID 19 antibody test negative | Esomeprazole, Macrogol/ electrolytes, Insulin Glargine, Metformin, Multivitamin, Nadroparin, Acetylsalicylic acid, Hydroxocobalamin, Metoprolol, Dexamethasone, Prednisolone, Levothyroxine, Colecalciferol, Mycophenolate, Tacrolimus, Paracetamol, Pregabalin, Amitriptyline, Insulin Aspart, Insulin Degludec | Respiratory insufficiency | Kidney transplant | 2.5 Hours Not Applicable Recovering |
| D | NL-LRB-00705326, male, 70 Years and older, Physician | Casirivimab/ imdevimab (Regn-Cov2), 8 gram | COVID 19 | Acenocoumarol, Allopurinol, Clopidogrel, Colecalciferol, Dalteparin, Dexamethasone, Digoxin, Dutasteride, Hydrochlorothiazide, Macrogol/ electrolytes, Metoprolol, Pantoprazole, Paracetamol, Paroxetine, Simvastatin, Ipratropium, Salbutamol/ Ipratropium | Comatose, Respiratory insufficiency | Pulmonary hypertension, Cerebrovascular accident | 3 Hours Not Applicable Recovered |
| E | NL-LRB-00727180, male, 50-60 | Casirivimab/ imdevimab (Regn-Cov2), | COVID 19 COVID 19 | Omeprazole, Insulin Aspart, Calciumcarb/ | Acute respiratory insufficiency | Immunocompromised, | 4 Hours Not applicable Recovering |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | years, Physician | 1.2 gram / Total | antibody test negative | Colecalc, Nadroparin, Acetylsalicylic acid, Nitroglycerin, Isosorbide mononitrate, Metoprolol, Rosuvastatine, Ezetimibe, Lanette ointment, Clindamycin, Dexamethasone, Cotrimoxazole, Valaciclovir, Mycophenolate, Oxycodone, Paracetamol, Insulin Glargine | | Allogenic stem cell transplantation | |
| F | NL-LRB-00720164, male, 30-40 Years, Physician | Casirivimab/ imdevimab (Regn-Cov2), 8 gram / Total | COVID 19 COVID 19 antibody test negative | Insulin Aspart, Nadroparin, Dexamethasone, Piperacillin/ Tazobactam, Paracetamol, Beclometasone/ Formoterol, Codeine, Metoclopramide, Sarilumab, Amoxicillin | Respiratory insufficiency | Not reported | Several hours Not Applicable Not Recovered (6 days after the reaction started) |
| G | NL-LRB-00718716, male, 60-70 years, Physician | Casirivimab/ imdevimab (Regn-Cov2) | COVID 19 COVID 19 antibody test negative | Not reported | Respiratory failure, Fever (38.2°C), Chills, Tachycardia | Not reported | 30 Minutes Not Applicable Not Recovered (2 days after the reaction started) |
| H | NL-LRB-00727144, male, 70 Years and older, Physician | Casirivimab/ imdevimab (Regn-Cov2), 1 dosage form | COVID 19 pneumonia | Edoxaban | Respiratory insufficiency, Oxygen saturation decreased | Gout, Type 2 diabetes mellitus, Atrial flutter, Mycotic aneurysm, Adenoma, Hypertension, Chronic kidney disease | 3 Hours Not Applicable Fatal |
| I | NL-LRB-00710128, male, 60-70 years, Physician | Casirivimab/ imdevimab (Regn-Cov2), 1 dosage form | COVID 19 antibody test negative | Not reported | Pyrexia, Tachycardia, Blood pressure increased, Breathing rate increased, Oxygen saturation decreased, Dyspnoea | Not reported | 4 Hours Not Applicable Recovered |
| J | NL-LRB-00722980, male, 70 Years and older, Physician | Casirivimab/ imdevimab (Regn-Cov2), Total | COVID 19 | Calciumcarb/ Colecalc, Phenprocoumon, Furosemide, Metoprolol, Dutasteride/ Tamsulosin, Ranibizumab, Dexamethasone | Dyspnoea | Immunocompromised | 30 Minutes Drug Withdrawn Recovered |
| K | NL-LRB-00725530, female, 70 Years and older, Physician | Casirivimab/ imdevimab (Regn-Cov2), 1 dosage form / Total | COVID 19 | Acetylsalicylic acid, Allopurinol, Atenolol, Calciumcarb/ Colecalc, Cetirizine, Clopidogrel, | Pyrexia (40.5°C), Hypertension, Hypoxia, Tachycardia | Allergy to iodinated contrast agent, Allergy to mesalamine | 4 Hours Not Applicable Fatal |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | Levothyroxine, Fentanyl transdermal, Fosinopril, Furosemide, Fentanyl Nasal spray, Metformin, Isosorbide mononitrate, Prednisone, Simvastatin, Morphine | | | |
| L | NL-LRB-00732241, female, 60-70 years, Physician | Ronapreve (Regn-Cov2) | COVID 19<br>COVID 19 antibody test negative | Ceftriaxon | Dyspnoea, Pyrexia, Chills, Bronchospasm, Tachypnoea | Not reported | 1 Hour<br>Not applicable<br>Recovering (1 day after the reaction started) |

The cases were reported by healthcare professionals from different hospitals. It concerns eight male and four female patients between 37 and 87 years old (median: 66.5 years old). In all cases, the reaction occurred within several hours after casirivimab/imdevimab administration. In eight cases, it was specifically reported that the patient did not have antibodies to SARS-CoV2 and in four cases it was reported that the patient's immunity was impaired. In ten cases the reaction was considered serious, which included life threatening in six cases, ICU admission in four cases and a fatal outcome in two cases. In ten cases oxygen therapy or mechanical ventilation had to be started or oxygen requirement increased rapidly with decreasing oxygen saturation. In five cases the reporter mentioned that the reaction could have been related to COVID19 but the rapid worsening was remarkable. In six cases the patient was recovering at the moment of reporting.

The patient in case A was admitted to the ICU and received oxygen. His deterioration might have been caused by COVID aggravation but the acute onset after administration of casirivimab/imdevimab was remarkable. Differential diagnosis was fluid overload, even though there was no oedema and minimal crepitation noticed.
The patient in case B was admitted to the ICU with an oxygen saturation below 80%. The patient was treated with furosemide, nitroglycerin and mechanical ventilation. The reporter mentioned that the reaction could be COVID19 aggravation with signs of fluid overload and comorbidities may also have contributed to the reaction.
The conditions of the patient in case C progressed from oxygen 0-2L/min to nasal high flow oxygen (Optiflow®) requirement and ICU admission. A thoracic CT scan showed pulmonary embolisms. The patient was also treated with tocilizumab.
The conditions of the patient in case D progressed from 3L/min oxygen requirement to 10L/min. The reporter mentioned that pulmonary embolisms were not likely and there were no signs of a bacterial infection. This patient became comatose several hours after aggravation of respiratory insufficiency which could not be explained by clinical parameters, saturation or blood pressure. There were no neurologic abnormalities. The patient spontaneously recovered without sequel after several days. The symptoms were considered as atypical delirium or conversion.
The patient in case E was hospitalised and progressed from 0L oxygen to 15L/min oxygen in several hours. No signs of pulmonary embolism were seen on a thoracic CT scan. The patient was treated with sarilumab.
In case J, a thoracic CT scan showed signs of fluid overload and the patient was treated with furosemide.
The patient in case F progressed from 3L/min oxygen to 15L/min oxygen in several hours. The reporter mentioned it could be aggravation of COVID19 but the rapid progression is nevertheless remarkable.
In case G the conditions of the patient rapidly progressed and did not improve with 15L/min oxygen. The patient was intubated and admitted to the ICU. The reporter mentioned that the reaction could be aggravation of COVID19 but the acute progression is remarkable.
The conditions of the patient in case H progressed from 97% oxygen saturation without oxygen therapy 2 hours after casirivimab/imdevimab administration in the afternoon to 69% 3 hours later with 10L/min oxygen and 15L/min oxygen overnight. The patient died the next morning (no obduction). The reporter mentioned that pulmonary embolisms were unlikely in this patient and the rapid progression was remarkable and not typical for COVID19.
The patient in case I had a mild decrease in oxygen saturation and increased breathing rate. The patient recovered after 2 hours.

The conditions of the patient in case K rapidly worsened after casirivimab/imdevimab administration. Body temperature rose to 40.5ºC in 1.5 hours with a decrease in oxygen saturation from 96% with 2L/min oxygen to 84% with 15L/min oxygen, hypertension (blood pressure: 213/147) and a heartrate of 120 per minute. The patient was treated with furosemide and morphine and died within 30 minutes. The reporter mentioned that the relationship with casirivimab/imdevimab is not clear but the rapid progression was remarkable.
The patient in case L was hospitalised and required oxygen therapy. The patient was recovering 1 day after the reaction occurred.

**Other sources of information**

*Summary of Product Characteristics (SmPC)*

A Dutch SmPC of casirivimab/imdevimab is not available yet. In the product information published by the European Medicines Agency (EMA) respiratory insufficiency or clinical worsening are not mentioned as possible adverse drug reactions [1]. In section 4.4 (Special warnings and precautions for use) infusion-related reactions are mentioned as reactions that have been observed within 24 hours of infusion. This is in line with the time to onset in the described cases. However, the described symptoms of an infusion-related reaction in the product information do not contain dyspnoea.

In a document with conditions of use of casirivimab/imdevimab, which was released by the European Medicines Agency before marketing authorisation, infusion-related reactions are described in section 5.3 (Special warnings and precautions for use) in more detail, including the symptoms: difficulty breathing, reduced oxygen saturation and bronchospasm [8].

A United States Food and Drug Administration (FDA) label is not available yet. In a fact sheet for health care providers of emergency use authorization of casirivimab/imdevimab published by the FDA signs and symptoms of infusion-related reactions include difficulty breathing, reduced oxygen saturation and bronchospasm [9]. Additionally, events of clinical worsening after casirivimab/imdevimab administration are mentioned, including hypoxia and increased respiratory difficulty sometimes leading to hospitalisation. It is unknown if these events were related to progression of COVID19 or related to casirivimab/imdevimab.

*Literature*

Several studies investigating safety and efficacy of casirivimab/imdevimab have been published. No specific signs of respiratory insufficiency as an adverse drug reaction have been described.
Horby et al. studied the efficacy and safety of 8000mg casirivimab/imdevimab in hospitalised COVID19 patients in an open-label multicentre randomised clinical trial [10]. In this study, the frequency of sudden worsening in respiratory status was lower in the casirivimab/imdevimab (21% of 4839 patients) compared to the patients receiving usual care (22% of 4946 patients). Out of 7 suspected serious adverse reactions, acute desaturation was reported for one patient.
Weinreich et al, studied three dosages (1200mg, 2400mg and 8000mg) of casirivimab/imdevimab in non-hospitalised COVID19 patients in a double-blind randomised phase 1-3 trial [11]. In this study, patients in the casirivimab/imdevimab groups had less hospitalisation, shorter hospital stays and lower ICU admissions than patients in the placebo group. Serious adverse events occurred more frequently in the placebo group (4.0% of 1843 patients) than in the three casirivimab/imdevimab groups (1200mg: 1.1% of 827 patients; 2400mg: 1.3% of 1849 patients; 8000mg: 1.7% of 1012 patients). These serious adverse events included respiratory disorders (placebo: 1.0%, 1200mg: 0.12% ;2400mg: 0.22%; 8000mg: 0.30%). Infusion related reactions of grade 2 or higher were not observed in the placebo group and were observed in 2 patients in the 1200mg group, in 1 patient in the 2400mg group and 3 patients in the 8000mg group.
Razonable et al. studied real-world outcomes of 696 patients who received casirivimab/imdevimab compared to untreated controls in a retrospective cohort study [12]. In this study, casirivimab/imdevimab treatment was associated with a lower hospitalisation rate. Mild adverse events were reported in seven patients, which included shortness of breath in two patients. No serious adverse events were reported.
In conclusion, trials have shown *lower* rates of respiratory insufficiency in the treated study arms so far, implying that the reaction is related to the underlying disease rather than the medication.

*Mechanism*

Respiratory insufficiency could be related to casirivimab/imdevimab administration, it could be a symptom of COVID19 progression, it could be related to underlying diseases and might be a consequence of a combination of these contributing factors. In theory, the respiratory insufficiency described in the cases could be a symptom of an infusion related reaction since the reaction occurred within several hours after administration in all described cases. However, it is remarkable that no other signs of infusion-related reactions such as rash, urticaria and flushing have been described in the cases reported to Lareb. Several potential mechanisms for infusion related reactions induced by monoclonal antibody therapy have been described in literature [13], these include classical IgE mediated anaphylaxis with mast cell and /or basophil activation, IgG-mediated and basophil-dependent anaphylaxis, complement activation and anaphylatoxin-mediated mast cell triggering and cytokine release storm by target cells and macrophages.

*Databases*

*Table 2. Reports of Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) respiratory failure associated with casirivimab/imdevimab in the Lareb, World Health Organisation (WHO) and European Eudravigilance databases on 17 December 2021 [14, 15].*

| Database | MedDRA Preferred Term | Number of reports | ROR (95% CI) |
|---|---|---|---|
| Lareb | Respiratory failure | 6 | Not assessable |
| | Acute respiratory failure | 2 | Not assessable |
| WHO | Respiratory failure | 39 | 9.3 (6.8 – 12.8) |
| | Acute respiratory failure | 39 | 37.5 (27.3 – 51.4) |
| Eudravigilance | Respiratory failure | 15 | 16.5 (9.8 – 27.7) |
| | Acute respiratory failure | 4 | 20.0 (7.4 – 53.6) |

*Prescription data*

On 13 December 2021 RIVM had distributed 7742 packages of 300mg casirivimab + 300mg imdevimab to 92 hospitals across the Netherlands since 14 June 2021. The exact number of patients treated with casirivimab/imdevimab in the Netherlands is unknown.

**Discussion and conclusion**

The Netherlands Pharmacovigilance Centre Lareb received twelve cases of respiratory insufficiency or signs of respiratory insufficiency within several hours after casirivimab/imdevimab administration, leading to hospitalisation or ICU admission in some cases and a fatal outcome in two cases. Several reporters also contacted Lareb by phone to share their concern about this new possible adverse drug reaction. Reporters mentioned that COVID19 progression could play a role in these events but the acute progression of symptoms after casirivimab/imdevimab administration was remarkable. Some reporters also mentioned that underlying disease, other than COVID19, could play a role in the course of events. Casirivimab/imdevimab was only recently granted marketing authorisation in Europe and literature about safety is sparse. Acute respiratory worsening has been described in clinical trials with a lower rate in patients with casirivimab/imdevimab than in patients receiving usual care. Difficulty in breathing, reduced oxygen saturation and bronchospasm have been described in pre-authorisation documents of EMA and FDA as potential symptoms of an infusion-related reaction that may occur within 24 hours after administration. The FDA also mentioned clinical worsening after casirivimab/imdevimab has been observed. The current European SmPC of casirivimab/imdevimab does not include clinical worsening or symptoms of respiratory insufficiency as a potential adverse drug reaction or infusion-related reaction. Infusion-related reactions following monoclonal antibody administration have been described in literature with several potential mechanisms. These reactions often include other symptoms such as rash or flushing and it is remarkable that no other symptoms of infusion-related reactions than respiratory insufficiency were described in the cases reported to Lareb. The association between respiratory insufficiency and casirivimab/imdevimab is disproportionally present in the Eudravigilance and WHO database.

The exact cause of respiratory insufficiency in the described reports remains unclear since multiple factors may have contributed, including COVID19 progression. Respiratory insufficiency is currently not mentioned in all available literature of casirivimab/imdevimab, including the European SmPC. Since

casirivimab/imdevimab was only recently granted marketing authorisation, the association between respiratory insufficiency and casirivimab/imdevimab should be further investigated, including the exact difference with aggravation of COVID19. Attention to this potential reaction is warranted.

**References**


1. Casirivimab/imdevimab (Ronapreve) Summary of Product characteristics. European Medicines Agency; 2021.
2. Medicamenteuze behandeling voor patiënten met COVID-19 (infectie met SARS–CoV-2): Stichting Werkgroep Antibioticabeleid; 2021 [16-12-2021]. Available from: https://swab.nl/nl/covid-19#to_9.
3. O'Brien MP, Forleo-Neto E, Musser BJ, Isa F, Chan K-C, Sarkar N, et al. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. *New England Journal of Medicine*. 2021;**385(13)**:1184-95.
4. Lamba TS, Sharara RS, Singh AC, Balaan M. Pathophysiology and Classification of Respiratory Failure. *Crit Care Nurs Q*. 2016;**39(2)**:85-93.
5. Vo P, Kharasch VS. Respiratory failure. *Pediatr Rev*. 2014;**35(11)**:476-84; quiz 85-6.
6. Azoulay E, Mokart D, Kouatchet A, Demoule A, Lemiale V. Acute respiratory failure in immunocompromised adults. *Lancet Respir Med*. 2019;**7(2)**:173-86.
7. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol*. 2021;**19(3)**:141-54.
8. Casirivimab/imdevimab (Regeneron) - Annex I - Conditions for use. European Medicines Agency; 2021.
9. Emergency Use Authorization casirivimab/imdevimab (REGEN-COV) Fact sheet for health care providers. United States Food and Drug Administration; 2021.
10. Group RC, Horby PW, Mafham M, Peto L, Campbell M, Pessoa-Amorim G, et al. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *medRxiv*. 2021:2021.06.15.21258542.
11. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19. *New England Journal of Medicine*. 2021;**385(23)**:e81.
12. Razonable RR, Pawlowski C, O'Horo JC, Arndt LL, Arndt R, Bierle DM, et al. Casirivimab-Imdevimab treatment is associated with reduced rates of hospitalization among high-risk patients with mild to moderate coronavirus disease-19. *EClinicalMedicine*. 2021;**40**:101102.
13. Maggi E, Vultaggio A, Matucci A. Acute infusion reactions induced by monoclonal antibody therapy. *Expert Rev Clin Immunol*. 2011;**7(1)**:55-63.
14. WHO Global Individual Case Safety Reports database (Vigilyze). : World Health Organisation. Uppsala Monitoring Centre; 2021 [16-12-2021]. Available from: https://tools.who-umc.org/webroot/ (access restricted)
15. Eudravigilance Database: European Medicines Agency; [Available from: http://bi.eudra.org (access restricted).


*This signal has been raised on February 24, 2022. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl*