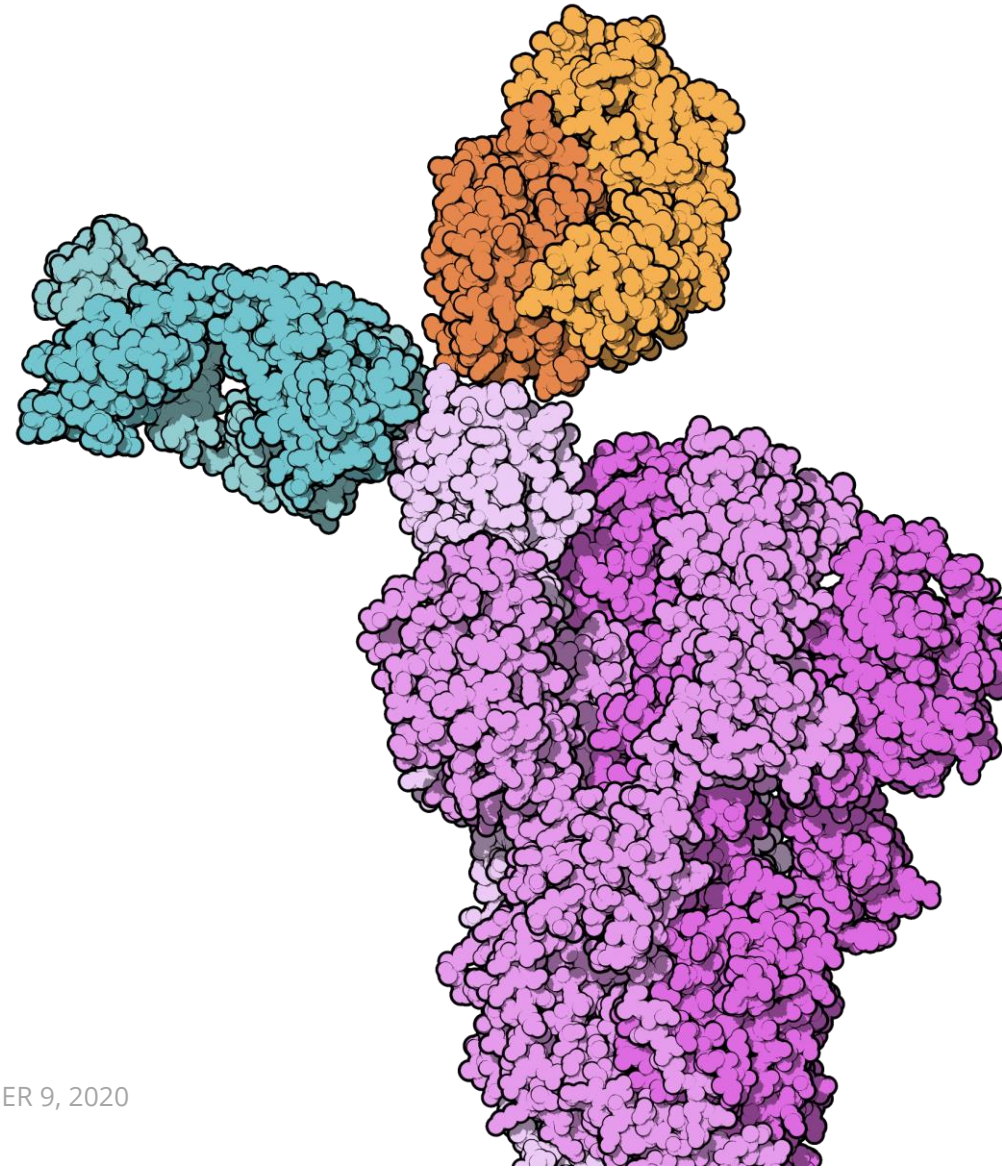
INPHARMD™ **MONOGRAPHS**

Casirivimab/imdevimab

The latest evidence on drug efficacy & recommendations.



InpharmD™

UPDATED DECEMBER 9, 2020

OVERVIEW

REGIMEN

Generic Name	Casirivimab/ imdevimab
Trade Name	N/A
Manufacturer	Regeneron
FDA Approval Date	Not approved; authorized for use on 11/21/2020
Dosage (Not Approved)	Injection solution: 300 mg/2.5 mL or 1,332 mg/11.1 mL (120 mg/mL) single-dose vials for each agent

PHARMACOLOGY

Casirivimab (IgG1κ) and imdevimab (IgG1λ) are two recombinant human monoclonal antibodies (mAbs) which are unmodified in the Fc regions. Each agent binds to the spike protein receptor binding domain (RBD) of SARS-CoV-2 at different areas to block the virus binding to ACE2, thereby blocking viral entry into cells.

PHARMACODYNAMICS

Casirivimab and imdevimab dosed at 1 and 3.33 times the recommended doses (1,200 mg casirivimab and 1,200 mg imdevimab; 4,000 mg casirivimab and 4,000 mg imdevimab) in ambulatory patients with COVID-19 showed a flat dose-response relationship for efficacy.

Casirivimab and imdevimab bind to non-overlapping epitopes of the spike protein receptor binding domain (RBD) of SARS-CoV-2 with dissociation constants Kd = 45.8 pM and 46.7 pM, respectively. Casirivimab, imdevimab and the casirivimab + imdevimab combination blocked RBD binding to the human ACE2 receptor with IC50 values of 56.4 pM, 165 pM, and 81.8 pM, respectively.

In a SARS-CoV-2 virus neutralization assay in Vero E6 cells, casirivimab, imdevimab, and the casirivimab + imdevimab combination neutralized SARS-CoV-2 (USA-WA1/2020 isolate) with EC50 values of 37.4 pM (0.006 µg/mL), 42.1 pM (0.006 µg/mL), and 31.0 pM (0.005 µg/mL) respectively.

PHARMACOKINETICS

Distribution	The pharmacokinetic profiles of casirivimab and imdevimab is expected to be consistent with the profile of other IgG1 monoclonal antibodies.
Metabolism	No CYP metabolism; expected to be metabolized via proteolytic degradation
Half-Life Elimination	Unknown
Excretion	Renal: none

CLINICAL DATA OVERVIEW

Unpublished • n = 799 (of >900 enrolled) • Unpublished data from a press release

Preliminary Results from Initial Cohort Patients From 2067 Seamless Ph1/2/3 Trial in Outpatients

REGIMEN

Participants were then randomized to a lower dose (2.4 g) casirivimab/imdevimab antibody cocktail, higher dose (8 g) casirivimab/imdevimab antibody cocktail, or placebo.

CRITERIA

Inclusion:

adults with COVID-19, symptom onset of <7 days before randomization, positive RT-PCR test for SARS-CoV-2 within 72 hours of randomization

Exclusion:

hospitalized due to COVID-19

OUTCOMES

Primary:

proportion of patients with a COVID-19 related medical visit (through 29 days)

Secondary:

time to symptom alleviation; change from baseline viral load from day 1 to day 7

RESULTS

The overall primary endpoint of reduced COVID-19 related medical visits by day 29 was significantly lower with casirivimab/imdevimab (2.8% combined dose groups; 6.5% placebo; P=0.024).

Treatment with casirivimab and imdevimab reduced COVID-19 related medical visits by 72% in patients with one or more risk factor (including being over 50 years of age; body mass index greater than 30; cardiovascular, metabolic, lung, liver or kidney disease; or immunocompromised status) (combined dose groups; P=0.0065).

CONCLUSION

These unpublished, preliminary results from press releases from Regeneron show promise for casirivimab and imdevimab to reduce COVID-19 related medical visits in outpatients who presented within 7 days of symptom onset.

The efficacy of casirivimab + imdevimab combination has been assessed in rhesus macaque and Syrian golden hamster treatment models of SARS-CoV-2 infection. Therapeutic administration of the casirivimab + imdevimab combination at 25 mg/kg or 150 mg/kg into rhesus macaques (n=4 for each dosing group) 1-day post infection resulted in approximately 1-2 log10 reductions in genomic and sub-genomic viral RNA in nasopharyngeal swabs and oral swabs at Day 4 post-challenge in most animals, and reduced lung pathology relative to placebo-treated animals. Therapeutic administration of the casirivimab + imdevimab combination at 5 mg/kg and 50 mg/kg doses to hamsters 1-day post infection had no clear effects on viral load in lung tissue. The applicability of these findings to a clinical setting is not known.

ADVERSE EFFECTS

Organ site	
Serious Adverse Events	Pneumonia, hyperglycemia, nausea and vomiting, intestinal obstruction, dyspnea
Immunologic	Infusion-related reactions: pyrexia, chills, urticaria, pruritus, abdominal pain, and flushing (1.5%), hypersensitivity

DRUG INTERACTIONS

No known interactions.

STORAGE

Store unopened casirivimab and imdevimab vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.

Diluted casirivimab and imdevimab solution may be stored in the refrigerator at 2°C to 8°C (36°F to 46°F) for no more than 36 hours and at room temperature up to 25°C (77°F) for no more than 4 hours, including infusion time.

SAFETY CONSIDERATIONS

BOXED WARNINGS

Casirivimab and imdevimab are unapproved products. Casirivimab and imdevimab are authorized for the treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

Casirivimab and imdevimab must be administered TOGETHER by intravenous (IV) infusion only. Casirivimab and imdevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

Health care providers must submit a report on all medication errors and ALL SERIOUS ADVERSE EVENTS potentially related to casirivimab and imdevimab.

WARNINGS & PRECAUTIONS

Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions: There is a potential for serious hypersensitivity reaction, including anaphylaxis, with administration of casirivimab and imdevimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis (e.g. fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness) occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19: Benefit of treatment with casirivimab and imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Casirivimab and imdevimab are not authorized for use in patients who are hospitalized due to COVID-19, require oxygen therapy due to COVID-19, or who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

USE IN SPECIFIC POPULATIONS

Pregnancy: The Pregnancy: There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Casirivimab and imdevimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, Casirivimab and imdevimab have the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of casirivimab or imdevimab provide any treatment benefit or risk to the developing fetus.

Lactation: There are no available data on the presence of casirivimab and imdevimab in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk.

Pediatrics: Safety and effectiveness in pediatric patients have not been established. The recommended dosing regimen is expected to result in comparable serum exposures of casirivimab and imdevimab in patients 12 years of age and older and weighing at least 40 kg as observed in adults.

Geriatrics: The difference in pharmacokinetics of casirivimab and imdevimab in geriatric patients compared to younger patients is unknown.

Renal Impairment: Casirivimab and imdevimab are not eliminated intact in the urine, so renal impairment is not expected to affect the exposure of bamlanivimab.

Hepatic Impairment: The effect of hepatic impairment on casirivimab and imdevimab pharmacokinetics are unknown.

Other Specific Populations: The effect of other covariates (e.g., sex, race, body weight, disease severity) on the pharmacokinetics of casirivimab and imdevimab is unknown.

DOSAGE & ADMINISTRATION

NON-FDA ADULT

For treatment of mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

High risk is defined as having at least one of the following: BMI ≥35 kg/m2, chronic kidney disease, diabetes, an immunosuppressive disease, currently receiving immunosuppressive treatment, or are ≥65 years of age. Additionally, high risk may be designated by being ≥5 years of age AND having: cardiovascular disease, hypertension, or chronic obstructive pulmonary disease/other chronic respiratory disease.

Dosage/Administration: a single IV infusion of 1,200 mg of casirivimab and 1,200 mg of imdevimab (combined dose of 2,400 mg) administered together over at least 60 minutes (maximum infusion rate 250 mL/hr). Casirivimab and imdevimab should be given as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset.

Administer via a polyvinylchloride (PVC), polyethylene (PE)-lined PVC, or polyurethane (PU) infusion set containing a 0.20 micron in-line or add-on polyethersulfone (PES) filter. Administer the infusion solution via pump or gravity over at least 60 minutes. Once infusion is complete, flush the infusion line with normal saline to ensure delivery of the required dose. Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

Preparation: Remove casirivimab and imdevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. Remove 20 mL of 0.9% Sodium Chloride from a 250 mL bag. Withdraw 10 mL (1,200 mg) of casirivimab and 10 mL (1,200 mg) imdevimab from their respective vials using two separate syringes; discard any product remaining in the vials. Transfer the casirivimab and imdevimab into the prefilled 0.9% Sodium Chloride injection bag for intravenous infusion (total bag volume 250 mL); the order of transfer does not appear to matter. Gently invert the infusion bag by hand approximately 10 times; do not shake.

> One 11.1 mL vial of one antibody may be prepared with four 2.5 mL vials of the other antibody to create one treatment course

NON-FDA PEDIATRIC

For patients who are 12-17 years old, high risk is defined as having: a BMI ≥85th percentile for their age and gender based on CDC growth charts, sickle cell disease, a congenital or acquired heart disease, neurodevelopmental disorder (e.g., cerebral palsy), a medical-related technological dependence (e.g., tracheostomy, gastrostomy), or asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

Dosage, administration, and preparation are the same as adults.

FDA-APPROVED

N/A

REFERENCES

1. Casirivimab and imdevimab [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; 2020.
2. Food and Drug Administration. Casirivimab and Imdevimab Emergency Use Authorization (EUA). https://www.fda.gov/media/143891/download. Published November 21, 2020.
3. Food and Drug Administration. Frequently Asked Questions on the Emergency Use Authorization of Casirivimab + Imdevimab. https://www.fda.gov/media/143894/download. Published November 21, 2020.
4. Regeneron. REGN-COV2 ANTIBODY COCKTAIL PROGRAM UPDATE. https://investor.regeneron.com/static-files/a596a85e-e72d-4529-8eb5-d52d87a99070. September 29, 2020.
5. Regeneron. Regeneron's COVID-19 outpatient trial prospectively demonstrates that REGN-COV2 antibody cocktail significantly reduced viral levels and need for further medical attention. Available: https://investor.regeneron.com/news-releases/news-release-details/regenerons-covid-19-outpatient-trial-prospectively-demonstrates. Published October 28, 2020.
6. ClinicalTrials.gov. Study assessing the efficacy and safety of anti-spike SARS CoV-2 monoclonal antibodies for prevention of SARS CoV-2 infection asymptomatic in healthy adults and adolescents who are household contacts to an individual with a positive SARS-CoV-2 RT-PCR assay. Available: https://clinicaltrials.gov/ct2/show/study/NCT04452318. Updated November 10, 2020.
7. ClinicalTrials.gov. Safety, tolerability, and efficacy of anti-spike (S) SARS-CoV-2 monoclonal antibodies for hospitalized adult patients with COVID-19. Available: https://clinicaltrials.gov/ct2/show/NCT04426695. Updated November 10, 2020.
8. Baum A, Ajithdoss D, Copin R, et al. REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters. Science. 2020;370(6520):1110-1115. doi:10.1126/science.abe2402