NEW DRUG APPROVAL

Brand Name	REGN-COV2
Generic Name	imdevimab
Drug Manufacturer	Regeneron Pharmaceuticals, Inc.

New Drug Approval

- FDA Approval Date: November 21, 2020 - **Emergency Use Authorization Only**
- Review Designation: N/A
- Type of Review: N/A
- Dispensing Restrictions: Per EUA, imdevimab may only be administered in settings in which healthcare 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.

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus (SARS-CoV-2). Most people infected with the COVID-19 virus will experience mild to moderate respiratory illness and recover without requiring special treatment. Older people, and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness. The COVID-19 virus spreads primarily through droplets of saliva or discharge from the nose when an infected person coughs or sneezes, so it's important that you also practice respiratory etiquette (for example, by coughing into a flexed elbow).

In December 2019, pneumonia of unknown cause occurred in Wuhan (China). On January 7, 2020, a novel corona virus, named as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), was identified in the throat swab sample of 1 patient. Globally, over 55 million confirmed cases of COVID-19 have been reported in all continents except Antarctica.

Efficacy

The data supporting this EUA for casirivimab and imdevimab are based on a randomized, double-blind, placebo-controlled clinical trial in 799 non-hospitalized adults with mild to moderate COVID-19 symptoms. Of these patients, 266 received a single intravenous infusion of 2,400 milligrams casirivimab and imdevimab (1,200 mg of each), 267 received 8,000 mg casirivimab and imdevimab (4,000 mg of each), and 266 received a placebo, within three days of obtaining a positive SARS-CoV-2 viral test.

The pre-specified primary endpoint in Phase 1/2 of trial R10933-10987-COV-2067 was the time weighted average (TWA) change from baseline in viral load (log10 copies/mL), as measured by RT-qPCR in nasopharyngeal swab samples, in subjects with a positive baseline RT-qPCR value, i.e., the modified full analysis set (mFAS). In the mFAS for the Phase 1/2 analysis, the difference in TWA from Day 1 through Day 7 for the pooled doses of casirivimab and imdevimab compared with placebo (n=665) was -0.36 log10 copies/mL ($p<0.0001$). The largest reductions in viral load relative to placebo occurred in patients with high viral load (-0.78 log10 copies/mL) or who were seronegative (-0.69 log10 copies/mL) at baseline. Reductions occurring from Day 1 through Day 11 were similar to those for Day 1 through Day 7.

However, the most important evidence that casirivimab and imdevimab administered together may be effective came from the predefined secondary endpoint of medically attended visits related to COVID-19, particularly

hospitalizations and emergency room visits within 28 days after treatment. For patients at high risk for disease progression, hospitalizations and emergency room visits occurred in 3% of casirivimab and imdevimab-treated patients on average compared to 9% in placebo-treated patients. The effects on viral load, reduction in hospitalizations and ER visits were similar in patients receiving either of the two casirivimab and imdevimab doses.

The casirivimab and imdevimab combination therapy continues to be evaluated in Phase 2/3 clinical trials for the treatment of COVID-19 in certain hospitalized and non-hospitalized patients, the Phase 3 open-label RECOVERY trial of hospitalized patients in the UK, and a Phase 3 trial for the prevention of COVID-19 in household contacts of infected individuals. To date, more than 7,000 people have participated in casirivimab and imdevimab clinical trials.

Safety

ADVERSE EVENTS

- Serious adverse events (SAEs) were reported in 4 (1.6%) patients in the casirivimab and imdevimab 2,400 mg group, 2 (0.8%) patients in casirivimab and imdevimab 8,000 mg group and 6 (2.3%) patients in the placebo group. None of the SAEs were related to study drug. SAEs that were reported as Grade 3 or 4 adverse events were pneumonia, hyperglycemia, nausea and vomiting (2,400 mg casirivimab and imdevimab), intestinal obstruction and dyspnea (8,000 mg casirivimab and imdevimab) and COVID-19, pneumonia, and hypoxia (placebo). Casirivimab and imdevimab are not authorized at the 8,000 mg dose (4,000 mg casirivimab and 4,000 mg imdevimab).
- One anaphylactic reaction was reported in the clinical program. The event began within 1 hour of completion of the infusion, and required treatment including epinephrine. The event was resolved. Infusion-related reactions, of grade 2 or higher severity, were reported in 4 subjects (1.5%) in the 8,000 mg (4,000 mg casirivimab and 4,000 mg imdevimab) arm. These infusion-related reactions events were moderate in severity; and include pyrexia, chills, urticaria, pruritus, abdominal pain, and flushing. One infusion-related reaction (nausea) was reported in the placebo arm and none were reported in the 2,400 mg (1,200 mg casirivimab and 1,200 mg imdevimab) arm. In two subjects receiving the 8,000 mg dose of casirivimab and imdevimab, the infusion-related reactions (urticaria, pruritus, flushing, pyrexia, shortness of breath, chest tightness, nausea, vomiting) resulted in permanent discontinuation of the infusion. All events resolved.

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 occur, immediately discontinue administration, and initiate appropriate medications and/or supportive care.
Infusion-related reactions have been observed with administration of casirivimab and imdevimab.
Signs and symptoms of infusion related reactions may include: fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness.
If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer 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 requiring high flow oxygen or mechanical ventilation with COVID-19. Therefore, casirivimab and imdevimab are not authorized for use in patients [see Limitations of Authorized Use]:

- who are hospitalized due to COVID-19, OR
- who 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.

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

Casirivimab (IgG1κ) and imdevimab (IgG1λ) are two recombinants human mAbs which are unmodified in the Fc regions. 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.

Dose & Administration

ADULTS

- 1,200 mg of casirivimab and 1,200 mg of imdevimab administered together as a single IV infusion over at least 60 minutes via pump or gravity.
- Must be diluted prior to administration.
- Should be given together as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset.

PEDIATRICS

The dosage in pediatric patients (12 years of age and older weighing at least 40 kg) is 1,200 mg of casirivimab and 1,200 mg of imdevimab administered together as a single intravenous infusion over at least 60 minutes.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

Casirivimab and imdevimab are not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of casirivimab and imdevimab.

HEPATIC IMPAIRMENT

The effect of hepatic impairment on PK of casirivimab and imdevimab is unknown.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Imdevimab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution available as:

- Injection: 300 mg/2.5 mL (120 mg/mL) or 1,332 mg/11.1 mL (120 mg/mL) in a single-dose vial.