Kesimpta® (ofatumumab) 20 mg injection

KESIMPTA AND VACCINES

Vaccine and vaccine-related information from the KESIMPTA Prescribing Information and pivotal trials

INDICATION

KESIMPTA is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

IMPORTANT SAFETY INFORMATION

Contraindication: KESIMPTA is contraindicated in patients with active hepatitis B virus infection.

WARNINGS AND PRECAUTIONS

Infections: An increased risk of infections has been observed with other anti-CD20 B-cell depleting therapies. KESIMPTA has the potential for an increased risk of infections including serious bacterial, fungal, and new or reactivated viral infections; some have been fatal in patients treated with other anti-CD20 antibodies. The overall rate of infections and serious infections in KESIMPTA-treated patients was similar to teriflunomide-treated patients (51.6% vs 52.7%, and 2.5% vs 1.8%, respectively). The most common infections reported by KESIMPTA-treated patients in relapsing MS (RMS) trials included upper respiratory tract infection (39%) and urinary tract infection (10%). Delay KESIMPTA administration in patients with an active infection until resolved.

Consider the potential increased immunosuppressive effects when initiating KESIMPTA after an immunosuppressive therapy or initiating an immunosuppressive therapy after KESIMPTA.

Please see additional Important Safety Information throughout this brochure.
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KESIMPTA and vaccinations

For new patients **planning to start KESIMPTA**

Live vaccines[1,2] live-attenuated (eg, chickenpox, measles)*	**Non-live and inactivated vaccines**[1-3] (eg, hepatitis A, polio, influenza, and SARS-CoV-2 vaccines)*
Administer at least **4 weeks** prior to initiation of KESIMPTA	Whenever possible, administer at least **2 weeks** prior to initiation of KESIMPTA

For patients **already taking KESIMPTA**

Live vaccines[1,2] live-attenuated (eg, chickenpox, measles)*	**Non-live and inactivated vaccines**[1-3] (eg, hepatitis A, polio, influenza, and SARS-CoV-2 vaccines)*
• Not recommended during treatment† • Administer live vaccines only after B-cell repletion	• In the pivotal trials, concomitant treatment with non-live vaccines was permitted • The use of non-live vaccines is not contraindicated with KESIMPTA therapy • KESIMPTA may interfere with the effectiveness of inactivated vaccines†

Vaccination of infants born to mothers treated with KESIMPTA during pregnancy[1*†]

- In infants of mothers treated with KESIMPTA during pregnancy, do not administer live or live-attenuated vaccines before confirming the recovery of B-cell counts. Depletion of B-cells in these infants may increase the risks from live or live-attenuated vaccines‡
- Inactivated vaccines may be administered, as indicated, prior to recovery from B-cell depletion, but an assessment of vaccine immune responses, including consultation with a qualified specialist, should be considered to determine whether a protective immune response was mounted‡

Currently available COVID-19 vaccines on the market, by Pfizer/BioNTech, Moderna, and Janssen, are non-live vaccines[3]

*As of March 2021, KESIMPTA has not been studied with vaccines.

†Post vaccination, an assessment of vaccine immune responses, including consultation with qualified specialists, should be considered to determine whether a protective immune response was mounted. It is unknown whether KESIMPTA may interfere with vaccine efficacy.

‡Data from RMS clinical studies indicate B-cell recoveries over the lower limit of normal in at least 50% of patients in 24 to 36 weeks post treatment discontinuation. Modeling and simulation for repletion corroborate these data, predicting median time to B-cell recovery of 40 weeks post treatment discontinuation.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

Hepatitis B Virus: *Reactivation:* No reports of hepatitis B virus (HBV) reactivation in patients with MS treated with KESIMPTA. However, HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, has occurred in patients treated with ofatumumab at higher intravenous doses for chronic lymphocytic leukemia (CLL) than the recommended dose in MS and in patients treated with other anti-CD20 antibodies.

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Vaccine information

T-cells are also involved and play a fundamental role in viral infections by helping B-cells produce antibodies. They also orchestrate the response for other immune cells. Some T-cells kill infected cells to reduce the viral burden.[4,5]

Live-attenuated vaccines

- Also referred to as "live," these vaccines contain a weakened (or attenuated) version of the living virus or bacteria. Because they are so similar to natural infection, these vaccines create a strong and long-lasting immune response. Live-attenuated vaccines include those for chickenpox and measles[2]

Inactivated vaccines

- Inactivated virus or bacteria are rendered unable to enter cells and replicate. Inactivated vaccines usually don't provide immunity that's as strong as live vaccines and may require several doses over time to provide ongoing immunity. Inactivated vaccines include those for hepatitis A, polio, and influenza[2]

mRNA vaccines

- A type of non-live vaccine that does not contain a virus. Instead, mRNA translation produces a protein specific to a virus that triggers an immune response[5]

Viral-vector vaccines

- Instead of preventing infection by modifying the specific virus that causes it, these vaccines rely on modifications to a different virus. The viral vector enters the body's cells and stimulates an immune response to the intended virus. These vaccines either use live vectors that replicate (but are often attenuated) or those that are nonreplicating (considered non-live)[3,5]

Any vaccine used in patients taking KESIMPTA should be administered in accordance with the KESIMPTA Prescribing Information.

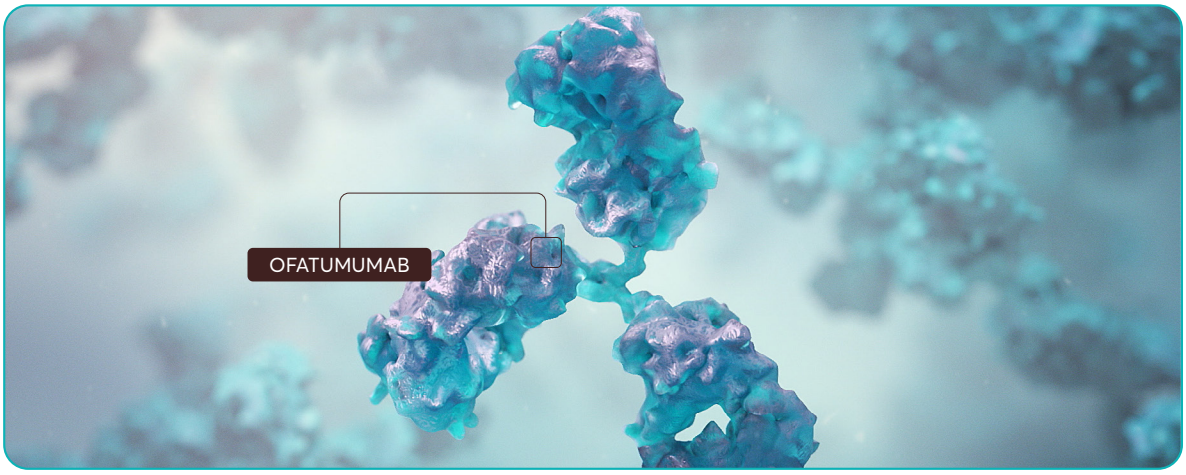
IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

Infection: KESIMPTA is contraindicated in patients with active hepatitis B disease. Fatal infections caused by HBV in patients who have not been previously infected have occurred in patients treated with ofatumumab at higher intravenous doses for CLL than the recommended dose in MS. Perform HBV screening in all patients before initiation of KESIMPTA. Patients who are negative for HBsAg and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], should consult liver disease experts before starting and during KESIMPTA treatment.

Progressive Multifocal Leukoencephalopathy: No cases of progressive multifocal leukoencephalopathy (PML) have been reported for KESIMPTA in RMS clinical studies; however, PML resulting in death has occurred in patients being treated with ofatumumab at higher intravenous doses for CLL than the recommended dose in MS. In addition, JC virus infection resulting in PML has also been observed in patients treated with other anti-CD20 antibodies and other MS therapies.

Trial data



In the ASCLEPIOS I and II pivotal Phase 3 studies, concomitant treatment with non-live vaccines was permitted[6]

- Some patients received non-live vaccines concomitantly with ofatumumab. However, vaccine response in those patients was not measured during the study and data are not available[6]
- After starting KESIMPTA, the use of inactivated or non-live vaccines are not contraindicated with KESIMPTA therapy. Patients may be vaccinated with inactivated vaccines. KESIMPTA may interfere with effectiveness of inactivated vaccines[1]
- ASCLEPIOS I and II studied KESIMPTA vs oral teriflunomide in RMS patients (N=927 and N=955, respectively). Primary endpoint, annualized relapse rate. Maximum duration 120 weeks, median duration 85 weeks[1]

RMS=relapsing multiple sclerosis.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

Progressive Multifocal Leukoencephalopathy (cont): If PML is suspected, withhold KESIMPTA and perform an appropriate diagnostic evaluation. If PML is confirmed, KESIMPTA should be discontinued.

Vaccinations: Administer all immunizations according to immunization guidelines: for live or live-attenuated vaccines at least 4 weeks and, whenever possible at least 2 weeks prior to starting KESIMPTA for inactivated vaccines. The safety of immunization with live or live-attenuated vaccines following KESIMPTA therapy has not been studied. Vaccination with live or live-attenuated vaccines is not recommended during treatment and after discontinuation until B-cell repletion.

Vaccination of Infants Born to Mothers Treated with KESIMPTA During Pregnancy. For infants whose mother was treated with KESIMPTA during pregnancy, assess B-cell counts prior to administration of live or live-attenuated vaccines. If the B-cell count has not recovered in the infant, do not administer the vaccine as having depleted B-cells may pose an increased risk in these infants.

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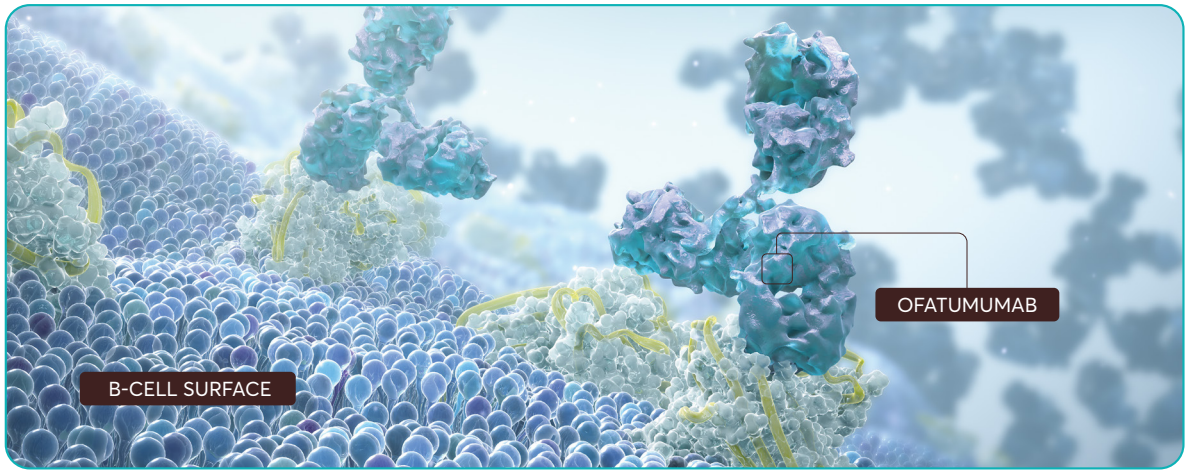
Immune response considerations



Immune response

- B-cells are part of a complex immune response to both viruses and vaccinations[4,5]
- T-cells are also involved and play a fundamental role in viral infections by helping B-cells produce antibodies. They also orchestrate the response for other immune cells. Some T-cells kill infected cells to reduce the viral burden[4,5]
- Data from an RMS clinical study also showed that T-cells remained largely unaffected in ofatumumab-treated patients. T-cells are an important part of a response to viral infections, including COVID-19[4,7]

KESIMPTA is a targeted and precisely delivered B-cell therapy

- When delivered subcutaneously, KESIMPTA is thought to promote preferential depletion of B-cells in the lymph nodes[8]
- Preclinical evidence suggests that KESIMPTA may preserve B-cells in the spleen that help maintain immune function[9]

The precise mechanism by which KESIMPTA exerts its therapeutic effects is unknown.

For questions related to KESIMPTA and COVID-19, please contact your Novartis sales specialist.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

Injection-Related Reactions: Injection-related reactions with systemic symptoms occurred most commonly within 24 hours of the first injection, but were also observed with later injections. There were no life-threatening injection reactions in RMS clinical studies.

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IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

Injection-Related Reactions (cont): The first injection of KESIMPTA should be performed under the guidance of an appropriately trained health care professional. If injection-related reactions occur, symptomatic treatment is recommended.

Reduction in Immunoglobulins: As expected with any B-cell depleting therapy, decreased immunoglobulin levels were observed. Monitor the levels of quantitative serum immunoglobulins during treatment, especially in patients with opportunistic or recurrent infections and after discontinuation of therapy until B-cell repletion. Consider discontinuing KESIMPTA therapy if a patient with low immunoglobulins develops a serious opportunistic infection or recurrent infections, or if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.

Fetal Risk: Based on animal data, KESIMPTA can cause fetal harm due to B-cell lymphopenia and reduce antibody response in offspring exposed to KESIMPTA in utero. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 B-cell depleting antibodies during pregnancy. Advise females of reproductive potential to use effective contraception while receiving KESIMPTA and for at least 6 months after the last dose.

Most common adverse reactions (>10%) are upper respiratory tract infection, headache, injection-related reactions, and local injection-site reactions.

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References: 1. Kesimpta [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2020. **2.** Principles of vaccination. Updated June 29, 2020. Centers for Disease Control and Prevention website. https://www.cdc.gov/vaccines/pubs/pinkbook/prinvac.html. Accessed March 5, 2021. **3.** Interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States. Centers for Disease Control and Prevention website. Updated March 3, 2021. https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html. Accessed March 5, 2021. **4.** Vabret N, Britton GJ, Gruber C, et al. Immunology of COVID-19: current state of the science. *Immunity*. 2020;52(6):910-941. doi:10.1016j.immuni.2020.05.002 **5.** Understanding How COVID-19 Vaccines Work. Updated March 8, 2021. Centers for Disease Control and Prevention website. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/how-they-work.html. Accessed March 17, 2021. **6.** Data on file. OMB157 Clinical Study Report ASCLEPIOS I&II. Novartis Pharmaceuticals Corp; 2019. **7.** Weindl H, Fox E, Goodyear A, et al. Effect of Subcutaneous ofatumumab on lymphocyte subsets in patients with RMS: analysis from the APLIOS study. Poster presented at: 6th Congress of the European Academy of Neurology, May 23-26, 2020. Paris, France (Virtual). LB129. **8.** Torres JB, Roodselaar J, Sealey M, et al. Distribution and efficacy of ofatumumab and ocrelizumab in humanized-CD20 mice following subcutaneous or intravenous administration. Poster P2.2-052. Poster presented at: 71st American Academy of Neurology Annual Meeting; May 4-10, 2019; Philadelphia, PA. **9.** Theil D, Smith P, Huck C, et al. Imaging mass cytometry and single-cell genomics reveal differential depletion and repletion of B-cell populations following ofatumumab treatment in cynomolgus monkeys. *Front Immunol*. 2019;10:1-11.

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