FDA approves Novartis Kesimpta® (ofatumumab), the first and only self-administered, targeted B-cell therapy for patients with relapsing multiple sclerosis

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- Kesimpta delivers powerful efficacy with a favorable safety profile and can be self-administered at home, addressing significant unmet needs for people living with relapsing forms of multiple sclerosis (RMS)[1]
- Approval based on two Phase III ASCLEPIOS studies demonstrating significant reductions in risk of relapses, confirmed disability progression, Gd+ T1 brain lesions and new/enlarging T2 lesions[1]
- In a post hoc analysis, 47.0% and 87.8% of patients treated with Kesimpta achieved no evidence of disease activity (NEDA-3) within the first (0-12 months) and second year (12-24 months) of treatment, respectively[2]

EAST HANOVER, N.J., Aug. 20, 2020 /PRNewswire/ -- Novartis today announced that the US Food and Drug Administration (FDA) has approved Kesimpta® (ofatumumab, formerly OMB157) as an injection for subcutaneous use for the treatment of relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. Kesimpta is a targeted, precisely dosed and delivered B-cell therapy that has shown superior efficacy with a similar safety profile compared with teriflunomide and is a first-choice treatment option for RMS patients.[1] Kesimpta is the first B-cell therapy that can be self-administered once monthly at home via the Sensoready® autoinjector pen.[3]

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"This approval is wonderful news for patients with relapsing multiple sclerosis. In the key clinical studies, this breakthrough treatment produced a profound reduction in new brain lesions, reducing relapses and slowing underlying disease progression,"[1] said Professor Stephen L. Hauser, Director of the UCSF Weill Institute for Neurosciences and co-chair of the steering committee for the ASCLEPIOS I and II studies. "Through its favorable safety profile and well-tolerated monthly injection regimen, patients can self-administer the treatment at home, avoiding visits to the infusion center."[1]

One of the goals when managing RMS is to preserve neurological function to slow down the worsening of disability.[4] Despite the availability of several disease-modifying therapies (DMTs) for the treatment of RMS, the majority of individuals with RMS continue to experience disease activity.[5] Evidence suggests early initiation of high-efficacy treatment can improve long-term outcomes for patients with RMS.[6]

"Multiple sclerosis (MS) is a complex disease, and response to disease modifying treatment will vary among individuals," said Bruce Bebo, PhD, Executive Vice President of Research at the National MS Society. "This makes it important to have a range of treatments available with different mechanisms of action and routes of administration. We are pleased to have an additional option approved for the treatment of relapsing forms of MS."

Traditionally, B-cell treatments, which bind to and deplete B-cells associated with disease activity in MS, have predominantly been available in hospitals or infusion treatment centers, which can add costs to the healthcare system and present a lifestyle burden for some patients.[7,8] Kesimpta provides patients the flexibility of self-administering via once-monthly subcutaneous dosing requiring no premedication, eliminating the need to travel to an infusion center. The positive results from the APLIOS study—an open-label Phase II study to determine the bioequivalence of subcutaneous delivery of Kesimpta via a prefilled syringe and a Sensoready pen in patients with RMS—and the ASCLEPIOS studies show Kesimpta to be a highly effective B-cell therapy that can be easily self-administered at home.[1,3]

"At Novartis, we challenge treatment paradigms and strive to offer the best treatment choice for patients," said Marie-France Tschudin, President, Novartis Pharmaceuticals. "When treating patients with RMS, Kesimpta is a meaningful treatment option that delivers both high efficacy and safety with the ability for patients to have more freedom in managing their disease. The development of Kesimpta is a great example of our commitment, knowledge and understanding of multiple sclerosis, which enabled us to identify a targeted treatment that can significantly improve patient outcomes and experience."

Ofatumumab was first approved by the FDA in 2009 for the treatment of chronic lymphocytic leukemia (CLL) as an intravenous infusion with a high dose, administered by a healthcare provider. Ofatumumab was then investigated in an entirely new development program in RMS, as B-cells are known to play a critical role in the development of autoimmune diseases, such as MS.[7] The clinical development program for ofatumumab in RMS took 10 years and has involved more than 2,300 patients around the world as part of rigorous studies that were reflective of the broad patient population. Kesimpta was found to work through a distinct mode of action, and the treatment regimen (dosing)—which was specifically designed for RMS—plays a critical role in the outcome.[9] This is a different dosing regimen and route of administration than was previously approved for the CLL indication.

The approval of Kesimpta is based on results from the Phase III ASCLEPIOS I and II studies, in which Kesimpta demonstrated superiority versus teriflunomide in significantly reducing the annualized relapse rate (ARR, primary endpoint), 3-month confirmed disability progression (CDP), and the number of gadolinium-enhancing (Gd+) T1 and new or enlarging T2 lesions.[1] Results from these two studies were recently published in the August 6, 2020 issue of *The New England Journal of Medicine*.

Kesimpta is expected to be available in the United States in early September.* Additional regulatory filings are currently underway across the world, and regulatory approval for Kesimpta in Europe is expected by Q2 2021.

**Time of availability may vary as healthcare providers integrate Kesimpta into their practices.*

About ASCLEPIOS I and II studies

The ASCLEPIOS I and II studies are twin, identical design, flexible duration (up to 30 months), double-blind, randomized, multi-center Phase III studies evaluating the safety and efficacy of Kesimpta 20 mg monthly subcutaneous injections versus teriflunomide 14 mg oral tablets taken once daily in adults with RMS. The ASCLEPIOS I and II studies enrolled 1,882 patients with MS, between the ages of 18 and 55 years, with an Expanded Disability Status Scale (EDSS) score between 0 and 5.5.[1] The studies were conducted in over 350 sites in 37 countries.[10] Kesimpta demonstrated a significant reduction in ARR by 51% (0.11 vs 0.22) and 59% (0.10 vs 0.25) compared with teriflunomide (P<.001 in both studies) in ASCLEPIOS I and II, respectively (primary endpoint). Kesimpta also showed a relative risk reduction of 34.4% (P=.002) in 3-month CDP compared with teriflunomide in a pre-specified meta-analysis, as defined in ASCLEPIOS.[1]

Kesimpta showed significant reduction of both Gd+ T1 lesions and new or enlarging T2 lesions. It significantly

reduced the mean number of both Gd+ T1 lesions (98% and 94% relative reduction in ASCLEPIOS I and II, respectively, both *P*<.001) and new or enlarging T2 lesions (82% and 85% relative reduction in ASCLEPIOS I and II, respectively, both *P*<.001) vs teriflunomide.[1]

Kesimpta had a similar safety profile to teriflunomide, with the frequency of serious infections and malignancies also being similar across both treatment groups.[1] Upper respiratory tract infection, headache, injection-related reactions, and local injection site reactions were the most commonly observed adverse reactions with Kesimpta (incidence greater than 10%).[1] A separate post hoc analysis demonstrated that the odds of achieving no evidence of disease activity (NEDA-3; no relapses, no MRI lesions, and no disability worsening combined) with Kesimpta versus teriflunomide were >3-fold higher at Months 0–12 (47.0% vs 24.5% of patients) and >8-fold higher at Months 12–24 (87.8% vs 48.2% of patients).[2]

Overall Kesimpta, an antibody targeting CD20 positive B-cells, delivered superior efficacy and demonstrated a safety profile with infection rates similar to teriflunomide.[1]

About APLIOS study

The APLIOS study is a 12-week, open-label, Phase II bioequivalence study to determine the onset of B-cell depletion with Kesimpta subcutaneous monthly injections and the bioequivalence of subcutaneous administration of Kesimpta via a prefilled syringe—as used in ASCLEPIOS I and II—and a Sensoready pen in patients with RMS. Patients were randomized according to injection device and site including the abdomen and the thigh. B-cell depletion was measured nine times over 12 weeks and Gd+ lesion counts were assessed at baseline and at Weeks 4, 8 and 12. Regardless of injection device or site, Kesimpta 20 mg subcutaneous monthly injections resulted in rapid, close to complete and sustained B-cell depletion; the proportion of patients with B-cell concentrations of <10 cells/µL was >65% after the first injection by Day 7, 94% by Week 4, and sustained >95% at all following injections. Kesimpta treatment reduced the mean number of Gd+ lesions from baseline (1.5) to 0.8, 0.3 and 0.1 by Weeks 4, 8 and 12, respectively; the proportion of patients free from Gd+ lesions at the corresponding time points were 66.5%, 86.7% and 94.1%, respectively.[3]

About Kesimpta® (ofatumumab, formerly OMB157)

Kesimpta is a targeted, precisely dosed and delivered B-cell therapy that provides the flexibility of self-administration for adults with RMS. It is an anti-CD20 monoclonal antibody (mAb) self-administered by a once-monthly injection, delivered subcutaneously.[1,3] Initial doses of Kesimpta are given at Weeks 0, 1 and 2, with the first injection performed under the guidance of a healthcare professional. As shown in preclinical studies, Kesimpta is thought to work by binding to a distinct epitope on the CD20 molecule inducing potent B-cell lysis and depletion.9 The selective mechanism of action and subcutaneous administration of Kesimpta allows precise delivery to the lymph nodes, where B-cell depletion in MS is needed, and preclinical studies have shown that it may preserve the B-cells in the spleen.[11] Once-monthly dosing of Kesimpta also allows rapid repletion of B-cells and offers more flexibility.[12] Ofatumumab was originally developed by Genmab and licensed to GlaxoSmithKline. Novartis obtained rights for ofatumumab from GlaxoSmithKline in all indications, including RMS, in December 2015.[13]

About Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system characterized by myelin destruction and axonal damage in the brain, optic nerves and spinal cord.[14] MS, which affects approximately 2.3 million people worldwide,[15] can be characterized into four main types of MS: clinically isolated syndrome (CIS), relapsing remitting (RRMS), secondary progressive (SPMS) and primary progressive

(PPMS).[16] The various forms of MS can be distinguished based on whether a patient experiences relapses (clearly defined acute inflammatory attacks of worsening neurological function), and/or whether they experience progression of neurologic damage and disability from the onset of the disease.[14]

Novartis in Neuroscience

Novartis has a strong ongoing commitment to neuroscience and to bringing innovative treatments to patients suffering from neurological conditions where there is a high unmet need. We are committed to supporting patients and physicians in multiple disease areas, including MS, migraine, Alzheimer's disease, Parkinson's disease, epilepsy and attention deficit hyperactivity disorder, and have a promising pipeline in MS, Alzheimer's disease, spinal muscular atrophy and specialty neurology.

Indication

What is KESIMPTA (ofatumumab) injection?

KESIMPTA is a prescription medicine used to treat adults with relapsing forms of multiple sclerosis (MS) including clinically isolated syndrome (CIS), relapsing-remitting disease, and active secondary progressive disease.

It is not known if KESIMPTA is safe or effective in children.

Important Safety Information

Who should not take KESIMPTA?

Do NOT take KESIMPTA if you have active hepatitis B virus (HBV) infection.

What is the most important information I should know about KESIMPTA?

KESIMPTA can cause serious side effects such as:

- **Infections.** Serious infections can happen during treatment with KESIMPTA. If you have an active infection, your healthcare provider (HCP) should delay your treatment with KESIMPTA until your infection is gone. KESIMPTA taken before or after other medicines that weaken the immune system may increase your risk of getting infections. Tell your HCP right away if you have any infections or get any symptoms including painful and frequent urination, nasal congestion, runny nose, sore throat, fever, chills, cough, or body aches.
- **HBV reactivation.** If you have ever had HBV infection, it may become active again during or after treatment with KESIMPTA (reactivation). If this happens, it may cause serious liver problems including liver failure or death. Before starting KESIMPTA, your HCP will do a blood test to check for HBV. They will also continue to monitor you during and after treatment with KESIMPTA for HBV. Tell your HCP right away if you get worsening tiredness or yellowing of your skin or the white part of your eyes.
- **Progressive Multifocal Leukoencephalopathy (PML).** PML may happen with KESIMPTA. PML is a rare, serious brain infection caused by a virus that may get worse over days or weeks. PML can result in death or severe disability. Tell your HCP right away if you have any new or worsening neurologic signs or symptoms. These may include weakness on one side of your body, loss of coordination in arms and legs, vision problems, changes in thinking and memory, which may lead to confusion and personality changes.
- **Weakened immune system.** KESIMPTA taken before or after other medicines that weaken the immune system could increase your risk of getting infections.

Before you take KESIMPTA, tell your HCP about all your medical conditions, including if you:

- Have or think you have an infection including HBV or PML.
- Have ever taken, currently take, or plan to take medicines that affect your immune system. These medicines could increase your risk of getting an infection.
- Have had a recent vaccination or are scheduled to receive any vaccinations.
    - You should receive any required 'live' or 'live-attenuated' vaccines at least 4 weeks before you start treatment with KESIMPTA. You should not receive 'live' or 'live-attenuated' vaccines while you are being treated with KESIMPTA and until your HCP tells you that your immune system is no longer weakened.
    - Whenever possible, you should receive any 'non-live' vaccines at least 2 weeks before you start treatment with KESIMPTA.
    - Talk to your HCP about vaccinations for your baby if you used KESIMPTA during your pregnancy.
- Are pregnant, think that you might be pregnant, or plan to become pregnant. It is not known if KESIMPTA will harm your unborn baby. Females who can become pregnant should use birth control (contraception) during treatment with KESIMPTA and for 6 months after your last treatment. Talk with your HCP about what birth control method is right for you during this time.
- Are breastfeeding or plan to breastfeed. It is not known if KESIMPTA passes into your breast milk. Talk to your HCP about the best way to feed your baby if you take KESIMPTA.

Tell your HCP about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use KESIMPTA?

See the detailed Instructions for Use that comes with KESIMPTA for information about how to prepare and inject a dose of KESIMPTA and how to properly throw away (dispose) of used KESIMPTA Sensoready pens or prefilled syringes.

- Use KESIMPTA exactly as your HCP tells you to use it.
- Your HCP will show you how to prepare and inject KESIMPTA the right way before you use it for the first time.
- **Do not** inject into areas where the skin is tender, bruised, red, scaly or hard. Avoid areas with moles, scars, or stretch marks.

KESIMPTA may cause serious side effects including:

- **Injection-related reactions.** Injection-related reactions are a common side effect of KESIMPTA. Injecting KESIMPTA can cause injection-related reactions that can happen within 24 hours (1 day) following the first injections and with later injections. Talk with your HCP if you have any of these signs and symptoms:
    - **at or near the injection site:** redness of the skin, swelling, itching and pain or
    - **that may happen when certain substances are released in your body**: fever, headache, pain in the muscles, chills, and tiredness.
- **Low immunoglobulins.** KESIMPTA may cause a decrease in some types of antibodies. Your HCP will do blood tests to check your blood immunoglobulin levels.

The most common side effects of KESIMPTA include:

- Upper respiratory tract infection, with symptoms such as sore throat and runny nose, and headache.
- Headache.

You are encouraged to report negative side effects of prescription drugs to the FDA.
Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see full Prescribing Information including Medication Guide.

About Novartis

Located in East Hanover, NJ Novartis Pharmaceuticals Corporation – an affiliate of Novartis – is reimagining medicine to improve and extend people's lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis employs about 15,000 people in the United States. For more information, please visit https://www.novartis.us.

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Dr. Hauser's statements reflect his professional opinion and not necessarily the views of The Regents of the University of California. Nothing in his statements shall be construed to imply any support or endorsement of Novartis, or any of its products, by The Regents of the University of California.

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