NEWS RELEASE

U.S. FDA Approves Subcutaneous Administration of Takeda's ENTYVIO® (vedolizumab) for Maintenance Therapy in Moderately to Severely Active Ulcerative Colitis

9/27/2023

– ENTYVIO Is the Only FDA-Approved Ulcerative Colitis Biologic That Offers the Choice of Intravenous or Subcutaneous Maintenance Therapy

OSAKA, Japan & CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Takeda **(TSE:4502/NYSE:TAK)** today announced that the U.S. Food and Drug Administration (FDA) has approved a subcutaneous (SC) administration of ENTYVIO® (vedolizumab) for maintenance therapy in adults with moderately to severely active ulcerative colitis (UC) after induction therapy with ENTYVIO intravenous (IV).1 ENTYVIO SC is expected to be available in the U.S. as a single-dose pre-filled pen (ENTYVIO Pen) by the end of October. Additionally, a Biologics License Application for an investigational SC administration of ENTYVIO for the treatment of adults with moderately to severely active Crohn's disease is currently under review by the FDA.

"With the FDA approval of subcutaneous ENTYVIO, patients and physicians who want ENTYVIO's clinical profile along with flexibility of administration now have two choices for maintenance treatment for adults with moderate to severe ulcerative colitis," said Brandon Monk, senior vice president, head, U.S. Gastroenterology Business Unit, Takeda. "Takeda is committed to meeting the varied medical needs, circumstances and personal preferences of people living with UC as they progress in their lifelong journey with the disease. ENTYVIO is the only FDA-approved biologic for maintenance therapy in ulcerative colitis offering the option of either intravenous or subcutaneous administration."

The approval of this new route of administration for ENTYVIO is based on the VISIBLE 1 study (SC UC Trial). VISIBLE 1 was a Phase 3, randomized, double-blind, placebo-controlled trial that assessed the safety and efficacy of an SC formulation of ENTYVIO as maintenance therapy in adult patients with moderately to severely active UC who achieved clinical response* at Week 6 following two doses of open-label vedolizumab intravenous therapy at Weeks 0 and 2.1 A total of 162 patients were randomized at Week 6 in a double-blind fashion (2:1) to one of the following regimens: ENTYVIO SC 108 mg or placebo by subcutaneous injection every 2 weeks. Eligible patients included patients who had demonstrated an inadequate response to, loss of response to, or intolerance to at least one 12-week regimen of azathioprine or 6-mercaptopurine, induction with a tumor necrosis factor (TNF) blocker, or corticosteroids. The primary endpoint was clinical remission at Week 52, which was defined as a total Mayo score of ≤2 and no individual subscore >1.

“The VISIBLE 1 trial demonstrated that ENTYVIO SC can provide physicians with an additional administration option for achieving remission in their moderate to severe ulcerative colitis patients. Since its approval in 2014, ENTYVIO has continued to build a robust safety and efficacy profile. I appreciate now having a subcutaneous administration option that provides a clinical profile consistent with ENTYVIO IV while also giving me and my appropriate UC patients a choice of how they receive their maintenance therapy,” said Bruce Sands, M.D., M.S., Chief of the Dr. Henry D. Janowitz Division of Gastroenterology at the Icahn School of Medicine at Mount Sinai. Dr. Sands is a paid consultant of Takeda Pharmaceuticals U.S.A., Inc. He has not been compensated for media work.

A statistically significant proportion of patients receiving ENTYVIO SC 108 mg maintenance therapy administered every 2 weeks achieved clinical remission** compared to patients receiving placebo (46% vs. 14%; $p<0.001$) at Week 52.1 In clinical studies, the ENTYVIO SC safety profile was generally consistent with the known safety profile of ENTYVIO IV, with the addition of injection site reactions (including injection site erythema, rash, swelling, bruising and hematoma) as an adverse reaction for ENTYVIO SC. The most common adverse reactions reported with ENTYVIO IV (incidence ≥3% and ≥1% higher than placebo) were nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, and pain in extremities.

*Clinical response is defined as a reduction in complete Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.1
**Clinical remission is defined as a complete Mayo score of ≤2 points and no individual subscore >1 point at Week 52.1

Takeda does not expect a material impact on the full year consolidated reported forecast for the year ending March 31, 2024 (Fiscal Year 2023), as a result of this approval.

About ENTYVIO® (vedolizumab)

Vedolizumab is a biologic therapy and is approved for intravenous (IV) and subcutaneous (SC) administration (approvals vary by market).1,2 Vedolizumab SC has been granted marketing authorization in the United States, European Union and more than 50 countries (vedolizumab SC is not currently approved for Crohn's disease in the U.S.). Vedolizumab IV has been granted marketing authorization in more than 70 countries, including the United States and European Union. Globally, vedolizumab IV and SC have more than one million patient years of exposure to date.3 Vedolizumab is a humanized monoclonal antibody designed to specifically antagonize the alpha4beta7 integrin, inhibiting the binding of alpha4beta7 integrin to intestinal mucosal addressin cell adhesion molecule 1 (MAdCAM-1), but not vascular cell adhesion molecule 1 (VCAM-1).4 MAdCAM-1 is preferentially expressed on blood vessels and lymph nodes of the gastrointestinal tract.5 The alpha4beta7 integrin is expressed on a subset of circulating white blood cells.4 These cells have been shown to play a role in mediating the inflammatory process in ulcerative colitis and Crohn’s disease.4,6,7 By inhibiting alpha4beta7 integrin, vedolizumab may limit the ability of certain white blood cells to infiltrate gut tissues.4

INDICATIONS

For adult patients with moderately to severely active ulcerative colitis (UC) or Crohn’s disease (CD) when other therapies have not worked well enough or cannot be tolerated.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

ENTYVIO is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to ENTYVIO or any of its excipients.

WARNINGS AND PRECAUTIONS

- Infusion-Related and Hypersensitivity Reactions: Infusion-related reactions and hypersensitivity reactions including anaphylaxis, dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate have been reported. These reactions may occur with the first or subsequent infusions and may vary in their time of onset from during infusion or up to several hours post-infusion. If anaphylaxis or other serious infusion-related or hypersensitivity reactions occur, discontinue administration of ENTYVIO immediately and initiate appropriate treatment.
- Infections: Patients treated with ENTYVIO are at increased risk for developing infections. Serious infections have been reported in patients treated with ENTYVIO, including anal abscess, sepsis (some fatal), tuberculosis,

salmonella sepsis, Listeria meningitis, giardiasis, and cytomegaloviral colitis. ENTYVIO is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding ENTYVIO in patients who develop a severe infection while on treatment with ENTYVIO. Exercise caution in patients with a history of recurring severe infections. Consider screening for tuberculosis (TB) according to the local practice.

- Progressive Multifocal Leukoencephalopathy (PML): PML, a rare and often fatal opportunistic infection of the central nervous system (CNS), has been reported with systemic immunosuppressants, including another integrin receptor antagonist. PML typically only occurs in patients who are immunocompromised. One case of PML in an ENTYVIO-treated patient with multiple contributory factors has been reported. Although unlikely, a risk of PML cannot be ruled out. Monitor patients for any new or worsening neurological signs or symptoms that may include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. If PML is suspected, withhold dosing with ENTYVIO and refer to neurologist; if confirmed, discontinue ENTYVIO dosing permanently.
- Liver Injury: There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO. ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury.
- Live and Oral Vaccines: Prior to initiating treatment with ENTYVIO, all patients should be brought up to date with all immunizations according to current immunization guidelines. Patients receiving ENTYVIO may receive non-live vaccines and may receive live vaccines if the benefits outweigh the risks.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥3% and ≥1% higher than placebo) were: nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, pain in extremities, and injection site reactions with subcutaneous administration.

DRUG INTERACTIONS

Because of the potential for increased risk of PML and other infections, avoid the concomitant use of ENTYVIO with natalizumab products and with TNF blockers.

INDICATIONS

Adult Ulcerative Colitis (UC):

ENTYVIO is indicated in adults for the treatment of moderately to severely active UC.

Adult Crohn's Disease (CD):

ENTYVIO is indicated in adults for the treatment of moderately to severely active CD.

DOSAGE FORMS & STRENGTHS:

- ENTYVIO Intravenous (IV) Infusion: 300 mg vedolizumab
- ENTYVIO Subcutaneous (SC) Injection: 108 mg vedolizumab

Please click for **Full U.S. Prescribing Information** .

About Ulcerative Colitis and Crohn's Disease

Ulcerative colitis (UC) and Crohn's disease (CD) are two of the most common forms of inflammatory bowel disease (IBD).8 Both UC and CD are chronic, relapsing, remitting, inflammatory conditions of the gastrointestinal tract.9,10 UC only involves the large intestine as opposed to CD, which can affect any part of the GI tract from mouth to anus.11,12 CD can also affect the entire thickness of the bowel wall, while UC only involves the innermost lining of the large intestine.11,12 UC can present with symptoms of abdominal discomfort or loose bowel movements, including blood.11,13 CD can present with symptoms of abdominal pain, diarrhea, and weight loss.12 The cause of UC or CD is not fully understood; however, research suggests that an interplay between environmental factors, genetics, and intestinal microbiota may contribute to the development of UC or CD.11,14,9

Takeda's Commitment to Gastroenterology

With this latest milestone, Takeda continues to demonstrate a commitment to meeting the very real needs of those living with gastrointestinal (GI) diseases. We believe that GI and liver diseases are life-disrupting conditions.Beyond a fundamental need for effective treatment options, we understand that improving patients' lives also depends on their needs being recognized. With nearly 30 years of experience in gastroenterology, Takeda has made significant strides in addressing patient needs with treatments for inflammatory bowel disease (IBD), acid-related diseases, short bowel syndrome (SBS) and motility disorders. We are making significant strides toward closing the gap on new areas of unmet need. Together with researchers, patient groups and more, we are working to advance scientific research and clinical medicine in GI.

About Takeda

Takeda is focused on creating better health for people and a brighter future for the world. We aim to discover and

deliver life-transforming treatments in our core therapeutic and business areas, including gastrointestinal and inflammation, rare diseases, plasma-derived therapies, oncology, neuroscience, and vaccines. Together with our partners, we aim to improve the patient experience and advance a new frontier of treatment options through our dynamic and diverse pipeline. As a leading values-based, R&D-driven biopharmaceutical company headquartered in Japan, we are guided by our commitment to patients, our people and the planet. Our employees in approximately 80 countries and regions are driven by our purpose and are grounded in the values that have defined us for more than two centuries. For more information, visit **www.takeda.com**.

Important Notice

For the purposes of this notice, "press release" means this document, any oral presentation, any question-and-answer session and any written or oral material discussed or distributed by Takeda Pharmaceutical Company Limited ("Takeda") regarding this release. This press release (including any oral briefing and any question-and-answer in connection with it) is not intended to, and does not constitute, represent or form part of any offer, invitation or solicitation of any offer to purchase, otherwise acquire, subscribe for, exchange, sell or otherwise dispose of, any securities or the solicitation of any vote or approval in any jurisdiction. No shares or other securities are being offered to the public by means of this press release. No offering of securities shall be made in the United States except pursuant to registration under the U.S. Securities Act of 1933, as amended, or an exemption therefrom. This press release is being given (together with any further information which may be provided to the recipient) on the condition that it is for use by the recipient for information purposes only (and not for the evaluation of any investment, acquisition, disposal or any other transaction). Any failure to comply with these restrictions may constitute a violation of applicable securities laws. The companies in which Takeda directly and indirectly owns investments are separate entities. In this press release, "Takeda" is sometimes used for convenience where references are made to Takeda and its subsidiaries in general. Likewise, the words "we", "us" and "our" are also used to refer to subsidiaries in general or to those who work for them. These expressions are also used where no useful purpose is served by identifying the particular company or companies.

Forward-Looking Statements

This press release and any materials distributed in connection with this press release may contain forward-looking statements, beliefs or opinions regarding Takeda's future business, future position and results of operations, including estimates, forecasts, targets and plans for Takeda. Without limitation, forward-looking statements often include words such as "targets", "plans", "believes", "hopes", "continues", "expects", "aims", "intends", "ensures", "will", "may", "should", "would", "could", "anticipates", "estimates", "projects" or similar expressions or the negative thereof. These forward-looking statements are based on assumptions about many important factors, including the following, which could cause actual results to differ materially from those expressed or implied by the forward-

looking statements: the economic circumstances surrounding Takeda's global business, including general economic conditions in Japan and the United States; competitive pressures and developments; changes to applicable laws and regulations, including global health care reforms; challenges inherent in new product development, including uncertainty of clinical success and decisions of regulatory authorities and the timing thereof; uncertainty of commercial success for new and existing products; manufacturing difficulties or delays; fluctuations in interest and currency exchange rates; claims or concerns regarding the safety or efficacy of marketed products or product candidates; the impact of health crises, like the novel coronavirus pandemic, on Takeda and its customers and suppliers, including foreign governments in countries in which Takeda operates, or on other facets of its business; the timing and impact of post-merger integration efforts with acquired companies; the ability to divest assets that are not core to Takeda's operations and the timing of any such divestment(s); and other factors identified in Takeda's most recent Annual Report on Form 20-F and Takeda's other reports filed with the U.S. Securities and Exchange Commission, available on Takeda's website at: **https://www.takeda.com/investors/sec-filings/** or at **www.sec.gov**. Takeda does not undertake to update any of the forward-looking statements contained in this press release or any other forward-looking statements it may make, except as required by law or stock exchange rule. Past performance is not an indicator of future results and the results or statements of Takeda in this press release may not be indicative of, and are not an estimate, forecast, guarantee or projection of Takeda's future results.

Medical Information

This press release contains information about products that may not be available in all countries, or may be available under different trademarks, for different indications, in different dosages, or in different strengths. Nothing contained herein should be considered a solicitation, promotion or advertisement for any prescription drugs including the ones under development.

References

1 ENTYVIO (vedolizumab) Prescribing Information. Takeda Pharmaceuticals U.S.A., Inc.
2 ENTYVIO Summary of Product Characteristics (SmPC). Available at: **https://www.ema.europa.eu/en/documents/product-information/entyvio-epar-product-information_en.pdf**. Last updated: April 2023. Last accessed: August 2023.
3 Data on file. Takeda Pharmaceuticals.
4 Soler D, Chapman T, Yang LL, et al. J Pharmacol Exp Ther. 2009;330(3):864-875.
5 Briskin M, Winsor-Hines D, Shyjan A, et al. Am J Pathol. 1997;151:97-110.
6 Eksteen B, Liaskou E, Adams DH. Inflamm Bowel Dis. 2008;14:1298-1312.
7 Wyant T, Fedyk E, Abhyankar B. J Crohns Colitis. 2016;10(12):1437-1444. doi:10.1093/ecco-jcc/jjw092.
8 Baumgart DC, Carding SR. Lancet. 2007;369:1627-1640.

9 Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Lancet. 2017; 389(10080):1741-1755.
10 Krugliak N, Torres J, Rubin DT. Gastroenterology. 2022;162:1396-1408.
11 Ordas I, Eckmann L, Talamini M, et al. Lancet. 2012;380:1606-1619.
12 Feuerstein JD, Cheifetz AS. Mayo Clin Proc. 2017;92:1088-1103.
13 Sands BE. Gastroenterology. 2004;126:1518-1532.
14 Kobayashi T, Siegmund B, Le Berre C, et al. Nat Rev Dis Primers. 2020;6(74).

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