

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

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– ENTYVIO is Now Available in the U.S. in Both IV and Subcutaneous Administrations for Maintenance Treatment of Adults with Moderately to Severely Active Ulcerative Colitis or Crohn's Disease

OSAKA, Japan & CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Takeda ( **TSE:4502/NYSE:TAK** ) today announced that the U.S. Food and Drug Administration (FDA) has approved ENTYVIO® (vedolizumab) subcutaneous (SC) administration for maintenance therapy in adults with moderately to severely active Crohn's disease (CD) after induction therapy with intravenous (IV) ENTYVIO.1 The subcutaneous administration of ENTYVIO was also approved by FDA in September 2023 for the maintenance treatment of adults with moderately to severely active ulcerative colitis (UC) and is available in the U.S. as a single-dose prefilled pen (ENTYVIO Pen).\*

The approval is based on the VISIBLE 2 Study (SC CD Trial), a Phase 3, randomized, double-blind, placebo-controlled trial, which assessed the safety and efficacy of an SC formulation of ENTYVIO as maintenance therapy in adult patients with moderately to severely active CD who had clinical response\*\* at Week 6 following two doses of open-label vedolizumab intravenous therapy at Weeks 0 and 2.1 The primary endpoint was clinical remission\*\*\* at Week 52, which was defined as a total Crohn's Disease Activity Index (CDAI) score of  $\leq 150$ .

"Crohn's disease is a complex and usually progressive disease for which an appropriate management plan is critical. My primary goal as a clinician is always to get patients to achieve remission. In VISIBLE 2, about half of patients

treated with ENTYVIO SC achieved long-term clinical remission,” said Timothy Ritter, MD, senior medical director, Department of Research and Education, GI Alliance Research and assistant professor of medicine, TCU School of Medicine. “The data from VISIBLE 2 reaffirm the well-established efficacy profile of ENTYVIO, regardless of route of administration.”

In VISIBLE 2, a total of 409 patients were randomized at Week 6 in a double-blind fashion (2:1) to ENTYVIO 108 mg administered by SC injection or placebo every 2 weeks.<sup>1</sup> Eligible patients included patients who had experienced an inadequate response to, loss of response to, or intolerance to at least one of the following: corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate), or tumor necrosis factor (TNF) blockers (including primary non-responders).

A statistically significant proportion of patients receiving ENTYVIO SC 108 mg maintenance therapy administered every 2 weeks achieved long-term clinical remission\*\*\* compared to patients receiving placebo (48% vs. 34%;  $p < 0.01$ ) at Week 52.<sup>1</sup> 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, pruritus, swelling, bruising, hematoma, pain, urticaria and edema) as an adverse reaction for ENTYVIO SC. The most common adverse reactions reported with ENTYVIO IV (incidence  $\geq 3\%$  and  $\geq 1\%$  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.

“The approval of subcutaneous ENTYVIO in Crohn’s disease delivers on our goal of providing treatment options that can help patients achieve remission of their ulcerative colitis or Crohn’s disease, while also providing them flexibility and choice of route of administration. With ENTYVIO Pen, patients have the option of administering their maintenance treatment at home or on the go,” said Brandon Monk, senior vice president, head, U.S. Gastroenterology Business Unit, Takeda. “Our development of a subcutaneous option demonstrates Takeda’s commitment to meeting the very real needs of those living with gastrointestinal diseases.”

\*Please refer to “U.S. FDA Approves Subcutaneous Administration of Takeda’s ENTYVIO® (vedolizumab) for Maintenance Therapy in Moderately to Severely Active Ulcerative Colitis”, dated September 27, 2023.

\*\*Clinical response is defined as a  $\geq 70$ -point decrease in Crohn’s Disease Activity Index (CDAI) score from baseline (Week 0).<sup>1</sup>

\*\*\*Clinical remission is defined as CDAI score of  $\leq 150$  at Week 52.<sup>1</sup>

Takeda does not expect a material impact on the consolidated financial statements 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).<sup>1,2</sup> Vedolizumab SC has been granted marketing authorization in the United States, European Union and more than 50 countries. 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.<sup>3</sup> 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).<sup>4</sup> MAdCAM-1 is preferentially expressed on blood vessels and lymph nodes of the gastrointestinal tract.<sup>5</sup> The alpha4beta7 integrin is expressed on a subset of circulating white blood cells.<sup>4</sup> These cells have been shown to play a role in mediating the inflammatory process in ulcerative colitis and Crohn's disease.<sup>4,6,7</sup> By inhibiting alpha4beta7 integrin, vedolizumab may limit the ability of certain white blood cells to infiltrate gut tissues.<sup>4</sup>

## 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  $\geq 3\%$  and  $\geq 1\%$  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. Upon initiation or discontinuation of ENTYVIO in patients treated with CYP450 substrates, monitor drug concentrations or other therapeutic parameters, and adjust the dosage of the CYP substrate as needed.

## 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).<sup>8</sup> Both UC and CD are chronic, relapsing, remitting, inflammatory conditions of the gastrointestinal tract.<sup>9,10</sup> UC only involves the large intestine as opposed to CD, which can affect any part of the GI tract from mouth to anus.<sup>11,12</sup> CD can also affect the entire thickness of the bowel wall, while UC only involves the innermost lining of the large intestine.<sup>11,12</sup> UC can present with symptoms of abdominal discomfort or loose bowel movements, including blood.<sup>11,13</sup> CD can present with symptoms of abdominal pain, diarrhea, and weight loss.<sup>12</sup> 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.<sup>11,14,9</sup>

## 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 more than 35 years of experience in gastroenterology, Takeda has made significant strides in addressing patient needs with treatments for inflammatory bowel disease (IBD), eosinophilic esophagitis (EoE), 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](http://www.takeda.com).

## Important Notice

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## 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](http://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

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