Dosage and Administration

Recommended Dosage in Adults with Ulcerative Colitis and Crohn’s Disease

Recommended Dosage: 300 mg infused intravenously over approximately 30 minutes.

Preparation and Administration Instructions for Subcutaneous Injection

Recommended Dose: 108 mg/0.68 mL solution in a single-dose prefilled syringe with needle safety device.

Patients may remain on ENTYVIO intravenous therapy or switch to subcutaneous ENTYVIO.

Important Administration Information

- Before initiating ENTYVIO, update immunizations according to current immunization guidelines.
- Intravenous Administration: ENTYVIO should be administered intravenously by a healthcare provider.
- Subcutaneous Injection: ENTYVIO prefilled syringe and ENTYVIO PEN are intended for subcutaneous use. A patient may self-inject or caregiver may inject after proper training.

Recommended Dosage: 300 mg infused intravenously over approximately 30 minutes.

Week 6: Patients may remain on ENTYVIO intravenous therapy or switch to subcutaneous injection after receiving two ENTYVIO intravenous doses administered at Week 0 and Week 2.

- Intravenous Infusion: 300 mg infused over approximately 30 minutes and then every eight weeks thereafter.
- Subcutaneous Injection: 108 mg subcutaneously once every two weeks.

- Discontinue ENTYVIO in patients who do not show evidence of therapeutic benefit by Week 14.
- Patients currently receiving and responding to ENTYVIO intravenous therapy after Week 6 may also be switched to subcutaneous injection. Administer the first subcutaneous dose in place of the next scheduled intravenous infusion and every two weeks thereafter.

Important Administration Information

- Patients who have had a known serious or severe hypersensitivity reaction to ENTYVIO or any of its excipients.

- Adverse reactions with subcutaneous ENTYVIO are similar to those reported with intravenous ENTYVIO with the exception of injection site reactions reported with subcutaneous ENTYVIO.

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals U.S.A., Inc. at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2024
**1 INDICATIONS AND USAGE**

ENTYVIO is indicated in adults for the treatment of:
- moderately to severely active ulcerative colitis (UC).
- moderately to severely active Crohn’s disease (CD).

**2 DOSAGE AND ADMINISTRATION**

### 2.1 Important Administration Information

**Before initiating ENTYVIO, update immunizations according to current immunization guidelines** [see Warnings and Precautions (5.5)].

**Intravenous Administration**
- ENTYVIO should be administered by a healthcare provider prepared to manage hypersensitivity reactions including anaphylaxis, if they occur [see Warnings and Precautions (5.1)]. Appropriate monitoring and medical support measures should be available for immediate use. Observe patients during infusion and until the infusion is complete.
- Reconstitute and dilute ENTYVIO lyophilized powder prior to administration as a 30-minute intravenous infusion [see Dosage and Administration (2.3)].

**Subcutaneous injection**
- ENTYVIO prefilled syringe and ENTYVIO PEN are intended for subcutaneous use under the guidance and supervision of a healthcare professional.
- Patients may self-inject or caregivers may inject subcutaneous ENTYVIO using either the ENTYVIO prefilled syringe or ENTYVIO PEN after training in subcutaneous injection technique. Provide proper training to patients and/or caregivers on the subcutaneous injection technique of ENTYVIO.

### 2.2 Recommended Dosage in Adults with Ulcerative Colitis and Crohn’s Disease

**Week 0:** Administer ENTYVIO 300 mg by intravenous infusion over approximately 30 minutes [see Dosage and Administration (2.3)].

**Week 2:** Administer ENTYVIO 300 mg by intravenous infusion over approximately 30 minutes.

**Week 6:** Patients may remain on ENTYVIO intravenous therapy or switch to subcutaneous injection after receiving two ENTYVIO intravenous doses administered at Week 0 and Week 2.
- **Subcutaneous Injection:** Administer ENTYVIO 108 mg subcutaneously once every 2 weeks.
- Discontinue therapy in patients who show no evidence of therapeutic benefit by Week 14.

Patients currently receiving and responding to ENTYVIO intravenous therapy after Week 6 may also be switched to subcutaneous injection. Administer the first subcutaneous dose in place of the next scheduled intravenous infusion and every two weeks thereafter.

### 2.3 Preparation and Administration Instructions for Intravenous Infusion

**Reconstitution instructions**
1. Remove the flip-off cap from the single-dose vial and wipe with alcohol swab. Reconstitute ENTYVIO vial containing lyophilized powder with 4.8 mL of Sterile Water for injection. 0.9% Sodium Chloride Injection, or Lactated Ringer’s Injection, at room temperature (20°C to 25°C [68°F to 77°F]), using a syringe with a 21- to 25-gauge needle.
2. Insert the syringe needle into the vial through the center of the stopper and direct the stream of Sterile Water or Injection, 0.9% Sodium Chloride Injection, or Lactated Ringer’s Injection, to the glass wall of the vial to avoid excessive foaming.
3. Gently swirl the vial for at least 15 seconds to dissolve the lyophilized powder. Do not vigorously shake or invert.
4. Allow the solution to sit for up to 20 minutes at room temperature to allow for reconstitution and for any foam to settle; the vial can be swirled and inspected for dissolution during this time. If not fully dissolved after 20 minutes, allow another 10 minutes for dissolution. Do not use the vial if the drug product is not dissolved within 30 minutes.
5. Visually inspect the reconstituted ENTYVIO solution for particulate matter and coloration to determine if the vial is clear or opalescent, colorless to light brownish yellow and free of visible particulates. Do not administer reconstituted solution showing uncharacteristic color or containing particulates.
6. Once dissolved, gently invert vial three times.
7. Immediately, withdraw 5 mL (300 mg) of reconstituted ENTYVIO solution using a syringe with a 21- to 25-gauge needle. Discard any remaining portion of the reconstituted solution in the vial.

**Dilution instructions**
Add the 5 mL (300 mg) of reconstituted ENTYVIO solution to 250 mL of 0.9% Sodium Chloride Injection, or Lactated Ringer’s Injection, and gently mix the infusion bag. Do not add other medicinal products to the prepared infusion solution or intravenous infusion set. Once reconstituted and diluted, use the infusion solution as soon as possible. Discard any unused portion of the infusion solution.

**Administration Instructions**
After the infusion is complete, flush with 30 mL of 0.9% Sodium Chloride Injection, or Lactated Ringer’s Injection.

### Storage and Stability
Specific storage conditions and timing for the reconstituted solution in vial and diluted solution in the infusion bag are outlined in Table 1. Do not freeze the reconstituted solution in the vial or the diluted solution in the infusion bag.

**Table 1. Storage Conditions for Reconstituted Solution in Vial and Diluted Solution in Infusion Bag**

<table>
<thead>
<tr>
<th>Storage Conditions</th>
<th>Solution</th>
<th>Refrigeration</th>
<th>Room Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reconstituted Solution</strong> (in Sterile Water for Injection, 0.9% Sodium Chloride Injection, or Lactated Ringer’s Injection, inside vial)</td>
<td>8 hours</td>
<td>Use immediately after reconstitution</td>
<td></td>
</tr>
<tr>
<td><strong>Diluted Solution</strong> (in 0.9% Sodium Chloride Injection)</td>
<td>24 hours†</td>
<td>12 hours*</td>
<td></td>
</tr>
<tr>
<td><strong>Diluted Solution</strong> (in Lactated Ringer’s Injection)</td>
<td>6 hours*</td>
<td>Use immediately after dilution</td>
<td></td>
</tr>
</tbody>
</table>

* This time assumes the reconstituted solution is immediately diluted in the 0.9% Sodium Chloride Injection, or Lactated Ringer’s Injection, and held in the infusion bag only. Any time that the reconstituted solution was held in vial should be subtracted from the time the solution may be held in the infusion bag.
† This period may include up to 12 hours at room temperature (20°C to 25°C [68°F to 77°F]).

The combined storage time of reconstituted ENTYVIO solution in the vial and the diluted solution in the infusion bag with 0.9% Sodium Chloride Injection, is a total of 12 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 24 hours refrigerated (2°C to 8°C [36°F to 46°F]). This combined storage time may include up to eight hours of the reconstituted solution in the vial at 2°C to 8°C.

The combined storage time of reconstituted ENTYVIO solution in the vial and the diluted solution in the infusion bag with Lactated Ringer’s Injection, is a total of six hours refrigerated (2°C to 8°C [36°F to 46°F]).

### 2.4 Preparation and Administration Instructions for Subcutaneous Injection

- Inspect the solution visually for particulate matter and discoloration prior to administration. ENTYVIO in prefilled syringe or ENTYVIO PEN should be a clear to moderately opalescent, colorless to slightly yellow solution. Do not use ENTYVIO prefilled syringes or ENTYVIO PENs with visible particulate matter or discoloration.
- Administer each subcutaneous injection at a different anatomic location (such as thighs, any quadrant of abdomen, or upper arms) than the previous injection.
- Administration of ENTYVIO in the back of upper arm may only be performed by a healthcare professional or caregiver. Do not inject into moles, scars, bruises, or areas where the skin is tender, erythematous, or indurated.

**Missed Subcutaneous Dose**
If treatment with subcutaneous ENTYVIO is interrupted or if a scheduled dose(s) of subcutaneous ENTYVIO is missed, inject the next subcutaneous dose as soon as possible and then every 2 weeks thereafter.

In the event of incomplete dose administration (i.e., patient attempts administration of dose with ENTYVIO PEN, however it is uncertain if a full dose was administered), instruct the patient to call their pharmacy or healthcare provider.

### 3 DOSAGE AND STRENGTHS

**Intravenous Infusion**
- For injection: 300 mg of vedolizumab as a white to off-white lyophilized cake in a single-dose vial for reconstitution.

**Subcutaneous Injection**
- Injection: 108 mg/0.68 mL vedolizumab as a clear to moderately opalescent, colorless to slightly yellow solution in a single-dose prefilled syringe with needle safety device.
- Injection: 108 mg/0.68 mL vedolizumab as a clear to moderately opalescent, colorless to slightly yellow solution in a single-dose prefilled pen (ENTYVIO PEN).

### 4 CONTRAINDICATIONS

ENTYVIO is contraindicated in patients who have had a known severe or serious hypersensitivity reaction to ENTYVIO or any of its excipients (such as docusate, bromocresol, urticaria, flushing, rash, and increased heart rate) [see Warnings and Precautions (5.1)].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Infusion-Related Reactions and Hypersensitivity Reactions

- Infusion-related reactions and hypersensitivity reactions have been reported, including anaphylaxis, dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate [see Adverse Reactions (6.1, 6.2)]. These reactions may occur with the first or subsequent infusions of ENTYVIO 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 institute appropriate treatment.

#### 5.2 Infections

Patients treated with ENTYVIO are at increased risk for developing infections [see Adverse Reactions (6.1)]. The most commonly reported infections in clinical trials occurring at a rate greater on ENTYVIO than placebo involved the upper respiratory and nasal mucosa (e.g., nasopharyngitis, upper respiratory tract infection). Serious infections have also been reported in patients treated with ENTYVIO, including anaphylaxis, dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate [see Adverse Reactions (6.1, 6.2)]. Infections may occur with the first or subsequent infusions of ENTYVIO 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 institute appropriate treatment.

For progressive multifocal leukoencephalopathy (PML), [see Warnings and Precautions (5.3)].
5.3 Progressive Multifocal Leukoencephalopathy
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 is caused by the John Cunningham (JC) virus and typically only occurs in patients who are immunocompromised. One case of PML in an ENTYVIO-treated patient with multiple contributory factors has been reported in the postmarketing setting (e.g., human immunodeficiency virus [HIV] infection with a CD4 count of 300 cells/mm³ and prior and concomitant immunosuppression). Although unlikely, a risk of PML cannot be ruled out.

Monitor patients on ENTYVIO for any new onset, or worsening, of neurological signs and symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of speech, swallowing, or walking, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months. If PML is suspected, withhold dosing with ENTYVIO and refer to a neurologist, if confirmed, discontinue dosing permanently.

5.4 Liver Injury
There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO. In general, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients. ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury [see Adverse Reactions (6.1)].

5.5 Live and Oral Vaccines
Prior to initiating treatment with ENTYVIO, all patients should be brought up to date with all vaccinations according to current immunization guidelines [see Dosage and Administration (2.1)]. Patients receiving ENTYVIO may receive non-live vaccines (e.g., influenza vaccine injection) and may receive live vaccines if the benefits outweigh the risks. There are no data on the secondary transmission of infection by live vaccines in patients receiving ENTYVIO [see Adverse Reactions (6.1)].

6 ADVERSE REACTIONS
The following topics are also discussed in detail in the Warnings and Precautions section:

• Infusion-Related Reactions and Hypersensitivity Reactions [see Warnings and Precautions (5.1)]
• Infections [see Warnings and Precautions (5.2)]
• Progressive Multifocal Leukoencephalopathy [see Warnings and Precautions (5.3)]
• Liver Injury [see Warnings and Precautions (5.4)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to intravenous ENTYVIO in 3,326 patients and healthy volunteers in clinical trials, including 1,356 exposed for greater than one year, and 835 exposed for greater than two years.

### Intravenous Infusion

The safety data described in Table 2 are derived from four controlled Phase 3 trials (UC Trials I and II and CD Trials I and III); data from adult patients receiving open-label intravenous ENTYVIO at Week 0 and 2 (prior to entry into UC Trial II and CD Trial III) and from Weeks 6 to 52 (non-responders at Week 6 of UC Trial I and CD Trial I) are included [see Clinical Studies (14.1, 14.2)]. In these trials, 1,434 patients received ENTYVIO 300 mg intravenously for up to 52 weeks, and 297 patients received placebo for up to 52 weeks. Of these, 79 patients had ulcerative colitis and 962 patients had Crohn’s disease. Patients were exposed for a mean duration of 259 days (330 days UC Trials I and II) and 247 days (CD Trials I and III).

### Adverse Reactions

Adverse reactions were reported in 52% of patients treated with intravenous ENTYVIO and 45% of patients treated with placebo (UC Trials I and II: 49% with ENTYVIO and 37% with placebo; CD Trials I and III: 55% with ENTYVIO and 47% with placebo). Serious adverse reactions were reported in 7% of patients treated with intravenous ENTYVIO compared to 4% of patients treated with placebo (UC Trials I and II: 8% with ENTYVIO and 7% with placebo; CD Trials I and III: 12% with ENTYVIO and 9% with placebo).

The most common adverse reactions (reported by ≥3% of patients treated with intravenous ENTYVIO in the UC Trials I and II and CD Trials I and III combined group and ≥1% higher than in placebo in combined placebo group) 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 (Table 2).

### Table 2. Adverse Reactions in ≥3% of Infusion-ENTYVIO-Treated Adult Patients and ≥1% Higher than in Placebo (UC Trials I and II and CD Trials I and III)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ENTYVIO IV† (N=1434)</th>
<th>Placebo‡ (N=297)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>13%</td>
<td>7%</td>
</tr>
<tr>
<td>Headache</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Cough</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Influenza</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Back pain</td>
<td>4%</td>
<td>3%</td>
</tr>
</tbody>
</table>

### Infusion-Related Reactions and Hypersensitivity Reactions

Serious infusion-related reactions and hypersensitivity reactions including anaphylaxis have been reported following intravenous ENTYVIO administration in clinical trials (see Warnings and Precautions (5.1)) in CD Trials I and II, UC Trials I and II, and in two of 297 patients treated with placebo. Infections are reported in the following sections.

### Infections

In UC Trials I and II and CD Trials I and III, the rate of infections was 0.85 per patient-year in patients treated with intravenous ENTYVIO and 0.7 per patient-year in the patients treated with placebo [see Warnings and Precautions (5.2)]. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, sinusitis, and urinary tract infection. Two percent of patients discontinued intravenous ENTYVIO due to infections.

In UC Trials I and II and CD Trials I and III, the rate of serious infections was 0.07 per patient-year in patients treated with intravenous ENTYVIO and 0.02 per patient-year in patients treated with placebo. Serious infections were more common in Crohn’s disease patients than ulcerative colitis patients, and anal abscesses were the most commonly reported serious adverse reaction in Crohn’s disease patients. Over 48 months, there was no increase in the rate of serious infections.

### Malignancies

In UC Trials I and II and CD Trials I and III, malignancies (excluding dysplasia and basal cell carcinoma) were reported in six of 1,434 (0.4%) patients treated with intravenous ENTYVIO, including colon cancer (n=2), transitional cell carcinoma (n=1), breast cancer (n=1), and adenocarcinoma of the gallbladder (n=1).
Fetal/Neonatal Adverse Reactions

ENTYVIO administered during pregnancy could affect immune responses in the in utero exposed newborn and infant. The clinical significance of low levels of ENTUVIO in utero-exposed infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown.

Data

Human Data

The vedolizumab pregnancy exposure registry conducted by OTIS/MotherToBaby study in the United States and Canada collected prospective observational data between 2015 and 2022 to assess the risk of major birth defects in live-born infants of women with ulcerative colitis (UC) or Crohn’s disease (CD) treated with vedolizumab during pregnancy. The study compared pregnant patients with UC or CD exposed to vedolizumab with pregnant patients with UC or CD exposed to other biological products. The registry included 99 women (58 with UC, 41 with CD) treated with vedolizumab during pregnancy, and 76 women (27 with UC, 49 with CD) exposed to other biological products during pregnancy.

The proportion of major birth defects among live-born infants in patients with UC or CD treated with vedolizumab and patients with UC or CD treated with other biological products was 7.4% (7/94) and 5.6% (4/71), respectively. Overall, there was no evidence of increased risk for major structural birth defects (adjusted RR 1.07, 95% CI: 0.33, 3.52).

The methodological limitations of the registry, including small sample size and the non-randomized design, resulted in a limited ability to estimate the risk of major birth defects and other maternal and infant outcomes. The conclusions from the pregnancy registry were consistent with the published literature and pharmacovigilance.

Animal Data

A reproduction study has been performed in pregnant rabbits at single intrauterine doses up to 100 mg/kg administered on gestation Day 7 (about 20 times the recommended human dosage) and has revealed no evidence of impaired fertility or harm to the fetus due to vedolizumab. A pre- and postnatal development study in monkeys showed no evidence of any adverse effect on pre- and postnatal development at intrauterine doses up to 100 mg/kg (about 20 times the recommended human dosage).

8.2 Lactation

Risk Summary

Data from a clinical lactation study show the presence of vedolizumab in human milk. The mean calculated daily infant dosage was 0.02 mg/kg/day orally (see Data). Systemic exposure for the infant is expected to be low because monoclonal antibodies are largely degraded in the gastrointestinal tract. There are no data on the effects of vedolizumab on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ENTUVIO and any potential adverse effects on the breastfed infant from ENTUVIO or from the underlying maternal condition.

Data

A milk-only lactation study was conducted in 9 adult lactating women being treated for active ulcerative colitis or Crohn’s disease with intravenous ENTUVIO every 8 weeks after reaching steady state and completing the induction phase (ENTUVIO administration at 0, 2, and 6 weeks) of treatment. Human milk samples were collected on Weeks 4 and 8 of the 8-week period and were assayed for vedolizumab (up to 0.07 mg/mL). The mean calculated daily infant oral dosage was 0.02 mg/kg/day calculated as a product of the average concentration over the 8-week dosing interval and the standardized milk consumption of 150 mL/kg/day.

8.4 Pediatric Use

Safety and effectiveness of ENTUVIO in pediatric patients have not been established.

8.5 Geriatric Use

Clinical trials of ENTUVIO did not include sufficient numbers of patients aged 65 and over. (72 patients with Crohn’s disease or ulcerative colitis aged 65 and over treated with ENTUVIO during controlled Phase 3 trials) to determine whether they respond differently from younger adult patients. However, no overall differences in safety or effectiveness were observed between these patients and younger adult patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

11 DESCRIPTION

Vedolizumab, an integrin receptor antagonist, is a humanized IgG, monoclonal antibody produced in Chinese hamster ovary cells that binds to the human α4β7 integrin. ENTUVIO has an approximate molecular weight of 147 kilodaltons.

Intravenous ENTUVIO

ENTUVIO (vedolizumab) for injection is supplied as a sterile, white to off-white, preservative-free, lyophilized cake for intravenous infusion. After reconstitution with 4.8 mL Sterile Water for Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer’s Injection, USP, the resulting concentration is 60 mg/mL, with a deliverable volume of 5 mL (500 mg) and the resulting pH is approximately 6.3.

Each single-dose vial contains 300 mg vedolizumab, arginine hydrochloride (131.7 mg), histidine (23 mg), histidine monohydrochloride (21.4 mg), polysorbate 80 (3 mg), and sucrose (500 mg).

Subcutaneous ENTUVIO

ENTUVIO (vedolizumab) injection is supplied as a sterile, clear to moderately opalescent, colorless to slightly yellow, preservative-free solution for subcutaneous administration.

Each single-dose prefilled syringe or single-dose prefilled pen (ENTUVIO PEN) contains 108 mg vedolizumab, arginine hydrochloride (17.77 mg), citric acid monohydrate (0.18 mg), histidine (3.86 mg), histidine monohydrochloride (1.86 mg), polysorbate 80 (1.35 mg), sodium citrate dihydrate (4.71 mg) and Sterile Water for Injection, USP, at a pH of 6.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vedolizumab is a humanized monoclonal antibody that specifically binds to the α4β7 integrin and blocks the interaction of α4β7 integrin with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and inhibits the migration of memory T-lymphocytes across the endothelium into inflamed gastrointestinal parenchymal tissue. Vedolizumab does not bind to or inhibit function of the α4β1 and αEβ7 integrins and does not antagonize the interaction of α4 integrins with vascular cell adhesion molecule-1 (VCAM-1).
The entyvio (vedolizumab) in these studies has not been fully characterized.

In the study of 14 healthy subjects, ENTYVIO did not affect the CD4+ lymphocyte cell counts, CD8+ lymphocyte cell counts, or the CD4+/CD8+ ratios in the CSF [see Clinical Pharmacology (12.3)].

A reduction in gastrointestinal inflammation was observed in rectal biopsy specimens from Phase 2 ulcerative colitis patients exposed to ENTYVIO for four or six weeks compared to placebo as assessed by histopathological analysis.

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of ENTYVIO or of other vedolizumab studies.

The bioavailability of vedolizumab following a 108 mg single-dose subcutaneous injection in healthy subjects was approximately 75%. Following a 108 mg single-dose subcutaneous injection in healthy subjects, the median T_max was 7 days with a range of 3 to 14 days and the mean C_max was 15.4 mcg/mL (SD ± 3.2).

The bioavailability of vedolizumab following a 108 mg single-dose subcutaneous injection relative to a 300 mg intravenous infusion in healthy subjects was approximately 75%. Following a 108 mg single-dose subcutaneous injection in healthy subjects, the median T_max was 7 days with a range of 3 to 14 days and the mean C_max was 15.4 mcg/mL (SD ± 3.2).

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of ENTYVIO or of other vedolizumab studies.

The incidence of anti-drug antibodies to ENTYVIO using a drug-tolerant ECL method for patients in SC UC Trial and SC CD Trial who had continuous treatment for 52 weeks was 3.4% (13 out of 381 total patients treated with subcutaneous ENTYVIO). Of the 13 patients who tested positive for anti-vedolizumab antibodies, 7 patients were persistently positive (4 at two or more consecutive study visits) and 7 patients developed neutralizing antibodies to vedolizumab. Two of the 7 patients with Crohn’s disease and none of the 6 patients with ulcerative colitis who had positive anti-vedolizumab antibodies achieved clinical remission at Week 52. There is insufficient data to assess the effect of anti-drug antibodies on pharmacokinetics, effectiveness, and safety of ENTYVIO in the SC UC and SC CD trials.

Table 3. Mean ± SD Vedolizumab Concentrations in Patients* with Ulcerative Colitis and Crohn’s Disease

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Trough Serum Concentration at Week 6 (mcg/mL)</th>
<th>Trough Serum Concentration at Week 46 (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcerative Colitis</td>
<td>26.3 ± 12.9 (N=210)</td>
<td>11.2 ± 7.2 (N=77)</td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td>27.4 ± 19.2 (N=198)</td>
<td>13.0 ± 9.1 (N=72)</td>
</tr>
</tbody>
</table>

* Data from patients in UC Trials I and II and CD Trials I and III with pharmacokinetic data available; data from patients with anti-vedolizumab antibody were excluded.

† Steady-state trough serum concentration.

The bioavailability of vedolizumab following a 108 mg single-dose subcutaneous injection relative to a 300 mg single-dose intravenous infusion in healthy subjects was approximately 75%. Following a 108 mg single-dose subcutaneous injection in healthy subjects, the median T_max was 7 days with a range of 3 to 14 days and the mean C_max was 15.4 mcg/mL (SD ± 3.2).

The bioavailability of vedolizumab following a 108 mg single-dose subcutaneous injection in healthy subjects, the median T_max was 7 days with a range of 3 to 14 days and the mean C_max was 15.4 mcg/mL (SD ± 3.2).

The bioavailability of vedolizumab following a 108 mg single-dose subcutaneous injection relative to a 300 mg single-dose intravenous infusion in healthy subjects was approximately 75%. Following a 108 mg single-dose subcutaneous injection in healthy subjects, the median T_max was 7 days with a range of 3 to 14 days and the mean C_max was 15.4 mcg/mL (SD ± 3.2).

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of ENTYVIO or of other vedolizumab studies.

**Adults Treated with Subcutaneous ENTYVIO**

The incidence of anti-drug antibodies to ENTYVIO using a drug-tolerant ECL method for patients in SC UC Trial and SC CD Trial who had continuous treatment for 52 weeks was 3.4% (13 out of 381 total patients treated with subcutaneous ENTYVIO). Of the 13 patients who tested positive for anti-vedolizumab antibodies, 7 patients were persistently positive (at two or more consecutive study visits) and 7 patients developed neutralizing antibodies to vedolizumab.

Among the ENTYVIO-treated patients who developed persistent anti-vedolizumab antibodies, 14/20 patients had serum vedolizumab trough concentrations that were markedly reduced or undetectable and 15/20 patients did not achieve clinical remission at Week 52 in UC Trials I and II and CD Trials I and III. Because of the low occurrence of persistent anti-vedolizumab antibodies (1%, 201/2,427), the effect of these antibodies on the safety and effectiveness of ENTYVIO in these studies has not been fully characterized.

**Clinical Studies**

**14.1 Clinical Studies in Ulcerative Colitis**

**Intravenous Administration**

The safety and efficacy of intravenous ENTYVIO were evaluated in two randomized, double-blind, placebo-controlled trials (UC Trials I and II) in adult patients with moderately to severely active ulcerative colitis (UC) defined as Mayo score of 6 to 12 with endoscopy sub-score of two or three. The Mayo score ranges from 0 to 12 and has four subscales that are each scored from zero (normal) to three (most severe): stool frequency, rectal bleeding, findings on endoscopy, and physician global assessment. A clinical response is defined by marked erythema, lack of vascular pattern, friability, and erosions; an endoscopy subscore of three is defined by spontaneous bleeding and ulceration.

Enrolled patients in the U.S. had over the previous five-year period an inadequate response or intolerance to immunomodulator therapy (i.e., azathioprine or 6-mercaptopurine) and were not responders to or were intolerant to or had a contraindication to corticosteroid therapy for at least 8 weeks prior to entry; patients who had received natalizumab ever in the past, and patients that had received a TNF blocker in the past were excluded from enrolment. Concomitant use of natalizumab or a TNF blocker was not allowed.

**UC Trial I - Intravenous**

In UC Trial I, 374 patients were randomized in a double-blind fashion (3:2) to receive ENTYVIO 300 mg or placebo by intravenous infusion at Week 0 and Week 2. Efficacy assessments were at Week 6. Concomitant stable dosages of aminosalicylates and/or corticosteroids (prednisone dosage ≤30 mg/day or equivalent), and immunomodulators (azathioprine or 6-mercaptopurine) were permitted through Week 6. At baseline, patients received corticosteroids (54%), immunomodulators (azathioprine or 6-mercaptopurine) (30%), and/or aminosalicylates (74%). Thirty-nine percent of patients had an inadequate response, loss of response, or intolerance to a TNF blocker therapy. Eighteen percent of patients had an inadequate response, inability to taper or intolerance to the corticosteroid treatment only (i.e., had received prior immunomodulators or TNF blockers). The median baseline Mayo score was 9 in the ENTYVIO group and 8 in the placebo group.

A greater percentage of patients treated with intravenous ENTYVIO compared to patients treated with placebo achieved clinical response at Week 6 (defined in Table 4). A greater percentage of patients treated with intravenous ENTYVIO compared to patients treated with placebo also achieved clinical remission at Week 6 (defined in Table 4). In addition, a greater percentage of patients treated with ENTYVIO had improvement of endoscopic appearance of the mucosa at Week 6 (defined in Table 4).

**Table 4. Proportion of Patients Meeting Efficacy Endpoints at Week 6 (UC Trial I)**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo N=149</th>
<th>ENTYVIO N=225</th>
<th>p-value</th>
<th>Treatment Difference and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Response* 1a</td>
<td>26%</td>
<td>47%</td>
<td>&lt;0.001</td>
<td>22% (12%, 32%)</td>
</tr>
<tr>
<td>Clinical Remission† 1b</td>
<td>5%</td>
<td>17%</td>
<td>0.001</td>
<td>12% (5%, 18%)</td>
</tr>
<tr>
<td>Improvement of Endoscopic Appearance of the Mucosa‡ at Week 6</td>
<td>25%</td>
<td>41%</td>
<td>0.001</td>
<td>16% (6%, 26%)</td>
</tr>
</tbody>
</table>

* Clinical response: reduction in complete Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding sub-score of ≥1 point or absolute rectal bleeding sub-score of ≥1 point.

† Clinical remission: complete Mayo score of ≤2 points and no individual subscore >1 point.

‡ Improvement of endoscopic appearance of the mucosa: Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern, mild friability).

**UC Trial II - Intravenous**

In order to be randomized to treatment in UC Trial II, patients had to have received intravenous ENTYVIO at least once in clinical response at Week 6. Patients could have come from either UC Trial I or from a group who received ENTYVIO open-label.

In UC Trial II, 373 patients were randomized in a double-blind fashion (1:1:1) to one of the following regimens beginning at Week 6: intravenous ENTYVIO 300 mg every eight weeks, intravenous ENTYVIO 300 mg every four weeks or placebo every four weeks. Efficacy assessments were at Week 52. Concomitant aminosalicylates and corticosteroids were permitted through Week 6. At baseline, patients received corticosteroids (76%), immunomodulators (azathioprine or 6-mercaptopurine) (30%), and/or aminosalicylates (74%). Thirty-nine percent of patients had an inadequate response, loss of response, or intolerance to a TNF blocker therapy. Eighteen percent of patients had an inadequate response, inability to taper or intolerance to corticosteroid treatment only (i.e., had received prior immunomodulators or TNF blockers). The median baseline Mayo score was 9 in the ENTYVIO group and 8 in the placebo group.

A greater percentage of patients treated with intravenous ENTYVIO compared to patients treated with placebo achieved clinical response at Week 6 (defined in Table 4). A greater percentage of patients treated with intravenous ENTYVIO compared to patients treated with placebo also achieved clinical remission at Week 6 (defined in Table 4). In addition, a greater percentage of patients treated with ENTYVIO had improvement of endoscopic appearance of the mucosa at Week 6 (defined in Table 4).
were permitted through Week 52. Concomitant immunomodulators (azathioprine or 6-mercaptopurine) were permitted outside the U.S. but were not permitted beyond Week 6 in the U.S.

At Week 6, patients were receiving corticosteroids (61%), immunomodulators (azathioprine or 6-mercaptopurine) (32%), and aminosalicylates (75%). Thirty-two percent of patients had an inadequate response, loss of response or intolerance to a TNF blocker therapy. At Week 6, the median Mayo score was 8 in the ENTYVO every eight week group, the ENTYVO every four week group, and the placebo group. Patients who had achieved clinical response at Week 6 and were receiving corticosteroids were required to begin a corticosteroid-tapering regimen at Week 6.

In UC Trial II, a greater percentage of patients in groups treated with intravenous ENTYVO as compared to those who achieved clinical remission at Week 52, and had clinical response (clinical response at both Weeks 6 and 52) (Table 5). In addition, a greater percentage of patients in groups treated with intravenous ENTYVO as compared to placebo were in clinical remission at both Weeks 6 and 52, and had improvement of endoscopic appearance of the mucosa at Week 52 (Table 5). In the subgroup of patients who achieved clinical response at Week 6 and were receiving corticosteroid medication at baseline, a greater proportion of patients in groups treated with intravenous ENTYVO as compared to placebo discontinued corticosteroids and were in clinical remission at Week 52 (Table 5). The ENTYVO every four week dosing regimen did not demonstrate additional clinical benefit over the every eight dosing week regimen. The every four week dosing regimen is not the recommended dosing regimen (see Dosage and Administration).

Table 5. Proportion of Patients Meeting Efficacy Endpoints at Week 52* (UC Trial II)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo†</th>
<th>ENTYVO 108 mg IV Every 8 Weeks</th>
<th>ENTYVO 108 mg IV Every 4 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Remission†</td>
<td>N=126</td>
<td>N=122</td>
<td>16%</td>
</tr>
<tr>
<td>Clinical Response at both Weeks 6 and 52</td>
<td>N=126</td>
<td>N=122</td>
<td>24%</td>
</tr>
<tr>
<td>Improvement of Endoscopic Appearance of the Mucosa‡ at Week 52</td>
<td>N=126</td>
<td>N=122</td>
<td>20%</td>
</tr>
<tr>
<td>Clinical Remission at Week 52</td>
<td>N=126</td>
<td>N=122</td>
<td>9%</td>
</tr>
<tr>
<td>Corticosteroid-free Clinical Remission§</td>
<td>N=126</td>
<td>N=122</td>
<td>14%†</td>
</tr>
</tbody>
</table>

* Patients must have achieved clinical response at Week 6 to continue into UC Trial II. This group includes patients that were in clinical remission at Week 52.
† The placebo group includes those patients who received ENTYVO at Week 0 and Week 2 and were randomized to receive placebo from Week 6 through Week 52.
‡ Improvement of endoscopic appearance of the mucosa: Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern, mild friability) at Week 52.
§ Corticosteroid-free clinical remission: Assessed in the subgroup of patients who were receiving corticosteroids at baseline and who were in clinical response at Week 6 (n=72 for placebo and n=20 for ENTYVO every eight weeks). Corticosteroid-free clinical remission was defined as the proportion of patients in this subgroup that discontinued corticosteroids by Week 52 and were in clinical remission at Week 52.

Intravenous Administration

The safety and efficacy of intravenous ENTYVO were evaluated in three randomized, double-blind, placebo-controlled clinical trials (CD Trials I, II, and III) in adult patients with moderately to severely active Crohn’s disease (CD) (Crohn’s Disease Activity Index [CDAI] score of 220 to 450) and/or a C-reactive protein (CRP) of ≥12 mg/L. The safety and efficacy of intravenous ENTYVO were evaluated in three randomized, double-blind, placebo-controlled clinical trials (CD Trials I, II, and III) in adult patients with moderately to severely active Crohn’s disease (CD) (Crohn’s Disease Activity Index [CDAI] score of 220 to 450). Enrolled patients were randomized to intravenous therapy with either 300 mg of intravenous ENTYVO at Week 0 and 2 or placebo. The primary analysis population was defined as all randomized patients with over the previous five-year period the patients were corticosteroid dependent (i.e., unable to successfully taper corticosteroids without a return of the symptoms of CD) or had an inadequate response or intolerance to corticosteroids. Patients that had received natalizumab ever in the past, and patients that had received a TNF blocker in the past 30 to 60 days were excluded from enrollment. Concomitant use of natalizumab or a TNF blocker was not allowed.

CD Trial I - Intravenous

In CD Trial I, 368 patients were randomized in a double-blind fashion (3:2) to receive ENTYVO 300 mg or placebo by intravenous infusion at Week 0 and Week 2. Efficacy assessments were at Week 6. Concomitant stable dosages of aminosalicylates, corticosteroids (prednisone ≤30 mg/day or equivalent), and immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) were permitted through Week 6.

At baseline, patients were receiving corticosteroids (24%), immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) (42%), and/or aminosalicylates (42%). Forty-eight percent of the patients had an inadequate response, loss of response, or intolerance to a TNF blocker therapy prior to enrollment. Seventeen percent of patients had inadequate response, inability to taper, or intolerance to prior corticosteroid treatment only (i.e., had not received prior immunomodulators or TNF blockers). The median baseline CDAI score was 324 in the intravenous ENTYVO group and 313 in the placebo group.

In CD Trial I, a statistically significantly higher percentage of patients treated with intravenous ENTYVO achieved clinical remission (defined as CDAI ≤150) as compared to placebo at Week 6 (Table 7). The difference in the percentage of patients who demonstrated clinical response (defined as a ≥100-point decrease in CDAI score from baseline), was however, not statistically significant at Week 6.

CD Trial II - Intravenous

Compared to CD Trial I, CD Trial II enrolled a higher number of patients who had over the previous five-year period had an inadequate response, loss of response, or intolerance to one or more TNF blockers (76%); this was the primary analysis population. In CD Trial II,
416 patients were randomized in a double-blind fashion (1:1:1) to receive either intravenous ENTYVIO 300 mg or placebo at Week 0, 2, and 6. Efficacy assessments were at Weeks 6 and 10. Concomitant aminosalicylates, corticosteroids, and immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) were permitted through Week 6. At baseline, patients were receiving corticosteroids (54%), immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) (34%), and aminosalicylates (31%). The median baseline CDAI score was 517 in the ENTYVIO group and 391 in the placebo group. For the primary endpoint (clinical remission at Week 6), treatment with intravenous ENTYVIO did not result in statistically significant improvement over placebo (Table 7). Secondary endpoints including assessments at Week 10 were not tested because the primary endpoint was not statistically significant.

### Table 7. Proportion of Patients in Clinical Remission at Week 6 (CD Trials I and II)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>ENTYVIO IV</th>
<th>p-value</th>
<th>Treatment Difference and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD Trial I: Clinical Remission* at Week 6</td>
<td>7% (10/148)</td>
<td>15% (32/220)</td>
<td>0.041†</td>
<td>8% (1%, 14%)</td>
</tr>
<tr>
<td>CD Trial II: Clinical Remission* at Week 6</td>
<td>12% (19/157)</td>
<td>15% (24/158)</td>
<td>NS§</td>
<td>3% (-5%, 11%)</td>
</tr>
</tbody>
</table>

* Clinical Remission: CDAI ≤150.
† p-value adjusted for multiple comparisons of two primary endpoints.
§ NS: Not significant (Secondary endpoints including assessments at Week 10 were not tested because the CD Trial II primary endpoint was not statistically significant).

### CD Trial III - Intravenous

In order to be randomized to treatment in CD Trial III, patients had to have received intravenous ENTYVIO and be in clinical response (defined as a ≥70-point decrease in CDAI score from baseline) at Week 6. Patients could have come from either CD Trial I or from a group who received intravenous ENTYVIO open-label.

In CD Trial III, 461 patients were randomized in a double-blind fashion (1:1:1) to one of the following regimens beginning at Week 6: intravenous ENTYVIO 300 mg every four weeks, intravenous ENTYVIO 300 mg every four weeks or placebo every four weeks.

Efficacy assessments were at Week 52. Concomitant aminosalicylates and corticosteroids were permitted through Week 52. Concomitant immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) were permitted outside the U.S. but were not permitted beyond Week 6 in the U.S.

At Week 6, patients were receiving corticosteroids (59%), immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) (31%), and aminosalicylates (41%). Fifty-five percent of patients had an inadequate response, loss of response, or intolerance to one or more TNF blockers (76% of the overall population).

Starting at Week 6, the median CDAI score was 322 in the intravenous ENTYVIO every eight week group, 316 in the intravenous ENTYVIO every four week group, and 315 in the placebo group. Patients who had achieved clinical response (≥70 decrease in CDAI score from baseline) by Week 6 and were receiving corticosteroids were required to begin a corticosteroid-tapering regimen at Week 6.

In CD Trial III a greater percentage of patients in groups treated with intravenous ENTYVIO as compared to placebo were in clinical remission (defined as CDAI ≤150) at Week 52. A greater percentage of patients in groups treated with intravenous ENTYVIO as compared to placebo had a clinical response (defined as ≥100 decrease in CDAI score from baseline) at Week 52 (Table 8). In the subgroup of patients who were receiving corticosteroids at baseline and who were in clinical response at Week 6 (defined as ≥70 decrease in CDAI score from baseline), a greater proportion of patients in groups treated with intravenous ENTYVIO as compared to placebo discontinued corticosteroids by Week 52 and were in clinical remission (defined as a ≥70-point decrease in CDAI score from baseline) at Week 6 and were receiving corticosteroids were required to begin a corticosteroid-tapering regimen at Week 6.

The ENTYVIO every four week dosing regimen did not demonstrate additional clinical benefit over the every eight dosing week regimen. The every four week dosing regimen is not the recommended dosing regimen [see Dosage and Administration (2.2)].

### Table 8. Proportion of Patients Meeting Efficacy Endpoints at Week 52* (CD Trial III)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>ENTYVIO Every 8 Weeks</th>
<th>p-value</th>
<th>Treatment Difference and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Remission at Week 52</td>
<td>22%</td>
<td>39%</td>
<td>0.001</td>
<td>17% (7%, 28%)</td>
</tr>
<tr>
<td>Clinical Response at Week 52</td>
<td>30%</td>
<td>44%</td>
<td>0.013</td>
<td>13% (3%, 24%)</td>
</tr>
<tr>
<td>Corticosteroid-free Clinical Remission at Week 52</td>
<td>16%†</td>
<td>32%‡</td>
<td>0.015</td>
<td>16% (3%, 29%)</td>
</tr>
</tbody>
</table>

* Clinical Remission: CDAI ≤150.
† p-value adjusted for multiple comparisons of two primary endpoints.
‡ Corticosteroid-free clinical remission: Assessed in the subgroup of patients who were receiving corticosteroids at baseline and who were in clinical response (defined as ≥70 decrease in CDAI score from baseline) at Week 6 and were receiving corticosteroids at Week 6 and were receiving corticosteroids were required to begin a corticosteroid-tapering regimen at Week 6.

### Table 9. Proportion of Patients in Clinical Remission at Week 52* (SC CD Trial)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>ENTYVIO SC 108 mg Every 2 Weeks</th>
<th>Estimate† of Treatment Difference (95% CI) Vedorizumab SC vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Population</td>
<td>N=134</td>
<td>N=275</td>
<td>14 (4, 24)†</td>
</tr>
<tr>
<td>Prior TNF blocker failure/exposure</td>
<td>N=71</td>
<td>N=168</td>
<td>27% (48%)</td>
</tr>
<tr>
<td>Without prior TNF blocker failure/exposure</td>
<td>N=63</td>
<td>N=107</td>
<td>43% (49%)</td>
</tr>
</tbody>
</table>

* Patients must have achieved clinical response at Week 6 to continue into SC CD Trial.
† Estimate of treatment difference and the p-value are based on the Cochran-Mantel-Haenszel method.
‡ Clinical remission: CDAI score ≤150. at Week 52.

Among patients using oral corticosteroids at baseline (Week 0) and achieving clinical response at Week 6, 45% (43/95) treated with subcutaneous ENTYVIO compared to 18% (8/44) treated with placebo discontinued corticosteroids and were in clinical remission at Week 52. This result was not statistically significant under the prespecified multiple testing procedure.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### Subcutaneous Injection

ENTYVIO (vedolizumab) injection for subcutaneous use is available in a prefilled syringe or a prefilled pen as a clear to moderately opalescent and colorless to slightly yellow solution. The single-dose, disposable ENTYVIO prefilled syringe and single-dose, disposable ENTYVIO prefilled pen (ENTYVIO PEN) are comprised of a 1 mL long glass syringe with a fixed 27 gauge thin wall, ½ inch needle. The syringe has a rubber needle cover encased in a plastic treatment cap. It is a prefilled pen as a clear to moderately opalescent and colorless to slightly yellow solution. The ENTYVIO prefilled syringe and prefilled pen are single-use devices and not to be re-filled.

#### Subcutaneous Administration

**SC CD Trial - Subcutaneous**

The safety and efficacy of subcutaneous ENTYVIO was evaluated in a randomized, double-blind, placebo-controlled trial (SC CD Trial; NCT02611817) in adult patients with moderately to severely active Crohn’s disease defined as CDAI score of 220 to 450. At baseline, the median CDAI score was 316 (range: 198 to 559).

The trial 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 TNF blockers (including primary non-responders). Patients were permitted to use concomitant stable doses of oral aminosalicylates, oral corticosteroids (prednisone ≤50 mg/day, budesonide ≤9 mg/day, or equivalent steroid), immunomodulators, probiotics, anti-diarrheals, and/or antibiotics. Concomitant biologic therapies, rectal treatment with 5-aminosalicylic acid or corticosteroid enemas/suppositories were prohibited.

All patients received open-label intravenous ENTYVIO 300 mg at Week 0 and Week 2. In order to be randomized to treatment in SC CD Trial, patients had to be in clinical response (defined as a ≥70-point decrease in the CDAI score from baseline) at Week 6. A total of 409 patients were randomized at Week 6 in a double-blind fashion (2:1) to ENTYVIO 108 mg administered by subcutaneous injection or placebo every 2 weeks. Efficacy assessments were at Week 52.

Beginning at Week 6, patients who were receiving corticosteroids were required to begin a corticosteroid-tapering regimen.

At the time of randomization into the double-blind phase (Week 6), patients were receiving corticosteroids (45%), immunomodulators (32%), and aminosalicylates (45%). Fifty-one percent of patients had an inadequate response, loss of response, or intolerance to a TNF blocker therapy prior to enrollment.

Patients in the double-blind phase had a mean age of 38 years (range 18 to 76 years); 55% were male; 91% identified as White, 6% as Asian, and 3% identified as another racial group. The primary endpoint was the proportion of patients with clinical remission (CDAI score ≤150) at Week 52 (see Table 9).

- **Clinical Remission:** CDAI ≤150.
- **Clinical Response:** ≥100 decrease in CDAI from baseline.
- **Corticosteroid-free clinical remission:** Assessed in the subgroup of patients who were receiving corticosteroids at baseline and who were in clinical response (defined as ≥70 decrease in CDAI score from baseline) at Week 6 and were receiving corticosteroids were required to begin a corticosteroid-tapering regimen at Week 6.
PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Infusion-Related and Hypersensitivity Reactions
Instruct patients to report immediately if they experience symptoms consistent with a hypersensitivity reaction during or following an infusion of ENTYVIO [see Warnings and Precautions (5.1)].

Infections
Inform patients that they may be more likely to develop infections when taking ENTYVIO. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of an infection [see Warnings and Precautions (5.2)].

Progressive Multifocal Leukoencephalopathy
Inform patients that progressive multifocal leukoencephalopathy (PML) has occurred in patients who received some integrin receptor antagonist and systemic immunosuppressant products. Instruct patients to report if they experience any new onset or worsening of neurological signs and symptoms immediately, as these could be indicative of PML [see Warnings and Precautions (5.3)].

Liver Injury
Inform patients that elevated transaminase levels with or without elevated bilirubin has occurred in patients who received ENTYVIO. Instruct patients to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice [see Warnings and Precautions (5.4)].

Subcutaneous Dosing Technique
Provide guidance to patients and caregivers on proper subcutaneous administration technique, and how to use the ENTYVIO single-dose prefilled syringe, or ENTYVIO single-dose prefilled pen correctly [see Instructions for Use].

Manufactured by:
Takeda Pharmaceuticals U.S.A., Inc.
Lexington, MA 02421
U.S. License No. 1898

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

ENTYVIO may cause serious side effects, including:

- **Infusion-related and serious allergic reactions.** These reactions can happen while you are receiving ENTYVIO or several hours after treatment. You may need treatment if you have an allergic reaction. Tell your healthcare provider or get medical help right away if you get any of these symptoms during or after an infusion of ENTYVIO: rash, itching, swelling of your lips, tongue, throat or face, shortness of breath or trouble breathing, wheezing, dizziness, feeling hot, or palpitations (feel like your heart is racing).

- **Infections.** ENTYVIO may increase your risk of getting a serious infection. Before receiving ENTYVIO and during treatment with ENTYVIO, tell your healthcare provider if you think you have an infection or have symptoms of an infection such as fever, chills, muscle aches, cough, shortness of breath, runny nose, sore throat, red or painful skin or sores on your body, tiredness, or pain during urination.

- **Progressive Multifocal Leukoencephalopathy (PML).** People with weakened immune systems can get progressive multifocal leukoencephalopathy (PML) (a rare, serious brain infection caused by a virus). Although unlikely while receiving ENTYVIO, a risk of PML cannot be ruled out. PML can result in death or severe disability. There is no known treatment, prevention, or cure for PML. Tell your healthcare provider right away if you have any of the following symptoms: confusion or problems thinking, loss of balance, change in the way you walk or talk, decreased strength or weakness on one side of the body, blurred vision, or loss of vision.

- **Liver Problems.** Liver problems can happen in people who receive ENTYVIO. Tell your healthcare provider right away if you have any of the following symptoms: tiredness, loss of appetite, pain on the right side of your stomach (abdomen), dark urine, or yellowing of the skin and eyes (jaundice).

See “What are the possible side effects of ENTYVIO?” for more information about side effects.

What is ENTYVIO?

ENTYVIO is a prescription medicine used in adults for the treatment of:

- moderately to severely active ulcerative colitis (UC).
- moderately to severely active Crohn’s disease (CD).

It is not known if ENTYVIO is safe and effective in children under 18 years of age.

Who should not receive ENTYVIO?

Do not receive ENTYVIO if you have had an allergic reaction to ENTYVIO or any of the ingredients in ENTYVIO. See the end of this Medication Guide for a complete list of ingredients in ENTYVIO.

Before receiving ENTYVIO, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection, think you may have an infection or have infections that keep coming back (see “What is the most important information I should know about ENTYVIO?”).

- have liver problems.

- have tuberculosis (TB) or have been in close contact with someone with TB.

- have recently received or are scheduled to receive a vaccine. Talk to your healthcare provider about bringing your vaccines up-to-date before starting treatment with ENTYVIO.

- are pregnant or plan to become pregnant. It is not known if ENTYVIO will harm your unborn baby. Tell your healthcare provider right away if you become pregnant while receiving ENTYVIO.

- are breastfeeding or plan to breastfeed. ENTYVIO can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take ENTYVIO.

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

Especially tell your healthcare provider if you take or have recently taken Tysabri (natalizumab), Tyruko (natalizumab-sztn), a Tumor Necrosis Factor (TNF) blocker medicine, a medicine that weakens your immune system (immunosuppressant), or corticosteroid medicine.

How should I use ENTYVIO?

When given in a vein (intravenously):

- You may receive ENTYVIO through a needle placed in a vein (intravenous infusion) in your arm.
  - ENTYVIO is given to you over a period of about 30 minutes.
  - Your healthcare provider will monitor you during and after the ENTYVIO infusion for side effects to see if you have a reaction to the treatment.

When given under the skin (subcutaneously):

- You may receive ENTYVIO as an injection under your skin (subcutaneous) every 2 weeks. You may receive your first subcutaneous injection after at least 2 intravenous infusions in place of the next scheduled intravenous infusion.
  - See the detailed Instructions for Use that comes with ENTYVIO about the right way to prepare and give ENTYVIO.
  - ENTYVIO is provided as single-dose prefilled syringe or single-dose prefilled pen (ENTYVIO PEN) for subcutaneous use. Your healthcare provider will prescribe the type that is best for you.
  - If your healthcare provider decides that you or your caregiver can give your injections of ENTYVIO at home, you or your caregiver should be shown the right way to prepare and inject ENTYVIO.
Do not inject ENTYVIO until you or your caregiver have been shown the right way by your healthcare provider.

Always check the label of your prefilled syringe or prefilled pen to make sure you have the correct medicine before each injection.

Do not shake ENTYVIO.

ENTYVIO is injected under your skin (subcutaneously) 1 time every 2 weeks.

Inject ENTYVIO under the skin (subcutaneous injection) in your upper legs (thighs) or stomach area (abdomen). The upper arms may also be used if a caregiver gives the injection.

Use a different injection site each time you use ENTYVIO.

Do not give an injection into moles, scars, bruises, or skin that is tender, hard, red, or damaged.

If you are not able to inject ENTYVIO at your regular scheduled time or you miss a dose of ENTYVIO, inject the dose as soon as possible. Then, inject your next dose every 2 weeks thereafter. If you are not sure when to inject ENTYVIO, call your healthcare provider.

If you take more ENTYVIO than you were told to take, call your healthcare provider.

What are the possible side effects of ENTYVIO?
ENTYVIO may cause serious side effects, see “What is the most important information I should know about ENTYVIO?”

The most common side effects of ENTYVIO include: common cold, headache, joint pain, nausea, fever, infections of the nose and throat, tiredness, cough, bronchitis, flu, back pain, rash, itching, sinus infection, throat pain, pain in extremities, and with injections under the skin: pain, swelling, itching, hives, bruising, rash, or redness at the injection site.

These are not all of the possible side effects of ENTYVIO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ENTYVIO?
- Store ENTYVIO in a refrigerator between 36°F to 46°F (2°C to 8°C).
- If needed, the prefilled syringe or prefilled pen can be left out of the refrigerator in its box at room temperature up to 77°F (25°C) for up to 7 days (for example, when traveling). Do not use the prefilled syringe or prefilled pen if left out of the refrigerator for more than 7 days or left in direct sunlight.
- Do not freeze ENTYVIO. Do not use ENTYVIO if it has been frozen.
- Keep ENTYVIO in the original package to protect from light until the time of use.
- ENTYVIO prefilled syringe or prefilled pen is not made with natural rubber latex.

Keep ENTYVIO and all medicines out of the reach of children.

General information about the safe and effective use of ENTYVIO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ENTYVIO for a condition for which it was not prescribed. Do not give ENTYVIO to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about ENTYVIO that is written for health professionals.

What are the ingredients in ENTYVIO?

Active ingredient: vedolizumab

Inactive ingredients in vial for intravenous infusion: arginine hydrochloride, histidine, histidine monohydrochloride, polysorbate 80 and sucrose

Inactive ingredients in prefilled syringe or prefilled pen for subcutaneous injection: arginine hydrochloride, citric acid monohydrate, histidine, histidine monohydrochloride, polysorbate 80, sodium citrate dihydrate, and Sterile Water for Injection

Manufactured by: Takeda Pharmaceuticals U.S.A., Inc.
Lexington, MA 02421
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For more information, go to www.ENTYVIO.com or call 1-877-TAKEDA7 (1-877-825-3327).

This Medication Guide has been approved by the U.S. Food and Drug Administration

VMB245 R10

Revised: 4/2024
INSTRUCTIONS FOR USE
ENTYVIO® (en ti’ ve oh) PEN
(vedolizumab)
Injection, for subcutaneous use
Single-dose prefilled pen

This Instructions for Use contains information on how to inject ENTYVIO.

Your ENTYVIO single-dose prefilled pen

Important information you need to know before injecting ENTYVIO:
- Read and follow this Instructions for Use before you inject ENTYVIO.
- Your healthcare provider should show you how to use the ENTYVIO PEN before you use it for the first time.
- ENTYVIO PEN is for subcutaneous injection only (inject directly into fatty layer under the skin).
- Do not shake the prefilled pen.
- Do not remove the purple cap from the prefilled pen until you are ready to inject.
- Do not put or press your thumb, fingers, or hand over the yellow needle shield. The yellow needle shield is visible when the purple cap is removed.
- Do not use the prefilled pen if it is dropped or damaged.

Storing ENTYVIO
- Store your prefilled pen in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Your prefilled pen can be left in its box at room temperature up to 77°F (25°C) for up to 7 days (for example, when traveling). Do not use the prefilled pen if it is left out of the refrigerator for more than 7 days.
- Do not freeze the prefilled pen.
- Do not leave the prefilled pen in direct sunlight.
- Throw away the prefilled pen in a FDA-cleared sharps disposal container if it has been left out of the refrigerator for more than 7 days, frozen, or left in direct sunlight. See Step 14 for instructions on how to throw away (dispose of) the prefilled pen.
- Always keep ENTYVIO PENs, the sharps disposal container, and all medicines out of the reach of children.

Getting Your Supplies Ready
Step 1. Remove the ENTYVIO PEN box from the refrigerator
Take 1 prefilled pen box from the refrigerator and check the expiration date on the box (see Figure A).
- Do not use the prefilled pen if any of the seals on the box are broken.
- Do not use the prefilled pen if the expiration date on the box has passed.

Step 2. Wait 30 minutes
Wait 30 minutes and let the prefilled pen come to room temperature (see Figure B).
- Do not warm the prefilled pen any other way.
- Do not let the prefilled pen sit in direct sunlight.
- Do not take the prefilled pen out of its tray until you are ready to inject.

Step 3. Gather supplies
Find a clean, flat surface like a table. Gather supplies that are not in the prefilled pen box (see Figure C).
- Alcohol pad
- Cotton ball or gauze
- Sharps disposal container (see Step 14 “Throw away (dispose of) the prefilled pen”)

Preparing to Inject ENTYVIO
Step 4. Wash hands
Wash your hands with soap and clean water (see Figure D).

Step 5. Remove the prefilled pen from the tray
Peel off the paper on the tray and lift the prefilled pen straight out (see Figure E).
- Do not shake the prefilled pen.
- Do not remove the purple cap from the prefilled pen until Step 9.

Step 6. Inspect the prefilled pen
Check the expiration date (EXP) printed on the prefilled pen and the medicine in the prefilled pen viewing window (see Figure F). The medicine should be colorless to pale yellow. It is normal to see air bubbles. Inspect the prefilled pen for any damage.
- Do not use the prefilled pen if the expiration date on the prefilled pen has passed.
- Do not use the prefilled pen if the medicine is cloudy or has particles floating in it.
- Do not use the prefilled pen if any part of it is damaged.

Step 7. Choose injection site
Choose an injection site on your bare skin from one of the following (see Figure G):
- front of the thighs
- stomach area (avoid the area 2 inches around the belly button)
For caregivers only: back of the upper arms may also be used.
- Do not inject into the same spot you used for your last injection.
- Do not inject into moles, scars, bruises, or skin that is tender, hard, red, or damaged.

Step 8. Clean the injection site
Clean the injection site with an alcohol pad (see Figure H). Let your skin dry.
- Do not touch or blow on the cleaned injection site before you inject.

Continue to Step 9

Injecting ENTYVIO
Step 9. Remove the purple cap and throw it away
When you are ready to inject, pull the purple cap straight off and throw it right away in the sharps disposal container (see Figure I).
- The needle is inside the yellow needle shield (under purple cap).
- Do not put or press your thumb, fingers, or hand over the yellow needle shield.
- Do not put the purple cap back on. This could accidentally start the injection.
**How Supplied**

- 100 decrease in CDAI score from baseline at Week 52
- 100 decrease in CDAI from baseline
- ≥0.015
- 16%

**General information about the safe and effective use of ENTYVIO.**

ENTYVIO may cause serious side effects, including:

- Medical conditions, including if you:
  - Have liver problems
  - Have weakened immune system
  - Have received a transplant (organ or bone marrow)
  - Have cancer
  - Are pregnant or planning to become pregnant
  - Are breastfeeding or plan to breastfeed
  - Have or had another blood disorder

- Infections
- Life-threatening allergic reactions
- Cancer
- Skin reaction
- Liver problems
- Severe skin reactions
- Severe gastrointestinal disorders

**What is ENTYVIO?**

ENTYVIO is a medicine that is used to treat the symptoms of ulcerative colitis (inflammation of the lining of the large intestine) when surgery is not needed, and for the treatment of Crohn’s disease (inflammation of the intestines), when other medicines have not worked, or when surgery is not needed.

**Who should not take ENTYVIO?**

- Patients who are allergic to vedolizumab or any of the other ingredients in ENTYVIO
- Patients who are pregnant or breastfeeding
- Patients who have infections

**How should I use ENTYVIO?**

- **Subcutaneous Use:** ENTYVIO is injected under your skin (subcutaneously) 1 time every 2 weeks.
- **Intravenous Use:** ENTYVIO is administered by a healthcare provider intravenously.
- **Injection Schedule:**
  - Intravenous use: every 4 weeks
  - Subcutaneous use: every 2 weeks

**Important information you need to know before injecting ENTYVIO:**

- Read and follow this Instructions for Use before you inject ENTYVIO.
- Your healthcare provider should show you how to use the ENTYVIO prefilled syringe before you use it for the first time.
- ENTYVIO prefilled syringe is for subcutaneous injection only (inject directly into fatty layer under the skin).
- Do not shake the prefilled syringe.
- Do not remove the needle cap from the prefilled syringe until you are ready to inject.
- Do not use the prefilled syringe if it is dropped or damaged.
- Each prefilled syringe has a needle guard. It will automatically cover the needle after the injection is completed to reduce the risk of accidental needle sticks.

**Storing ENTYVIO**

- Store your prefilled syringe in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Your prefilled syringe can be left in its box at room temperature up to 77°F (25°C) for up to 7 days (for example, when traveling). Do not use the prefilled syringe if it is left out of the refrigerator for more than 7 days.
- Do not freeze the prefilled syringe.
- Do not leave the prefilled syringe in direct sunlight.
- Throw away the prefilled syringe in a FDA-cleared sharps disposal container if it has been left out of the refrigerator for more than 7 days, frozen, or left in direct sunlight. See Step 14 for instructions on how to throw away (dispose of) the prefilled syringe.
- Always keep ENTYVIO prefilled syringes, the sharps disposal container, and all medicines out of the reach of children.

**Getting Your Supplies Ready**

**Step 1. Remove the ENTYVIO prefilled syringe box from the refrigerator**

Take 1 prefilled syringe box from the refrigerator and check the expiration date on the box (see Figure A).
- Do not use the prefilled syringe if any of the seals on the box are broken.
- Do not use the prefilled syringe if the expiration date on the box has passed.
Step 2. Wait 30 minutes
Wait 30 minutes and let the prefilled syringe come to room temperature (see Figure B).
- Do not warm the prefilled syringe any other way.
- Do not let the prefilled syringe sit in direct sunlight.
- Do not take the prefilled syringe out of its tray until you are ready to inject.

Step 3. Gather supplies
Find a clean, flat surface like a table. Gather supplies that are not in the prefilled syringe box (see Figure C).
- Alcohol pad
- Cotton ball or gauze
- Sharps disposal container (see Step 14 “Throw away (dispose of) the prefilled syringe”)

Preparing to Inject ENTYVIO

Step 4. Wash hands
Wash your hands with soap and clean water (see Figure D).

Step 5. Remove the prefilled syringe from the tray
Peel off the paper on the tray and lift the prefilled syringe straight out (see Figure E).
- Do not lift from the purple plunger.
- Do not shake the prefilled syringe.
- Do not remove the needle cap from the prefilled syringe until Step 9.

Step 6. Inspect the prefilled syringe
Check the expiration date (EXP) printed on the prefilled syringe and the medicine in the prefilled syringe (see Figure F). The medicine should be colorless to pale yellow. It is normal to see air bubbles. Inspect the prefilled syringe for any damage.
- Do not use the prefilled syringe if the expiration date on the prefilled syringe has passed.
- Do not use the prefilled syringe if the medicine is cloudy or has particles floating in it.
- Do not use the prefilled syringe if any part of it is damaged.
- Do not try to remove air bubbles from the prefilled syringe.

Step 7. Choose injection site
Choose an injection site on your bare skin from one of the following (see Figure G):
- front of the thighs
- stomach area (avoid the area 2 inches around the belly button)

For caregivers only: back of the upper arms may also be used.
- Do not inject into the same spot you used for your last injection.
- Do not inject into moles, scars, bruises, or skin that is tender, hard, red, or damaged.

Step 8. Clean the injection site
Clean the injection site with an alcohol pad (see Figure H). Let your skin dry.
- Do not touch or blow on the cleaned injection site before you inject.

Continue to Step 9 ➔

Injecting ENTYVIO

Step 9. Remove the needle cap and throw it away
When you are ready to inject, pull the needle cap straight off and throw it right away in the sharps disposal container (see Figure I). You may see a drop of liquid at the end of the needle. This is normal.
- Do not touch or pull back the purple plunger.
- Do not touch or re-cap the needle.
- Do not use a prefilled syringe with a bent or broken needle.

Step 10. Pinch the skin
With the needle cap off, hold the prefilled syringe with one hand and pinch the skin around the injection site with your other hand (see Figure J).
- Hold the pinch until the injection is completed.

Step 11. Insert the prefilled syringe at 45-degree angle
Insert the needle at about a 45-degree angle all the way into the pinched skin (see Figure K).
- Avoid touching the plunger until the needle is inserted.

Step 12. Push down on the plunger
Push the plunger all the way down until all the medicine is injected (see Figure L).
- Keep pressure on the plunger and take the needle out of the skin.
- If you are not able to start or cannot complete the injection by pushing the plunger all the way down, you may not have received your full dose. Call your pharmacy or healthcare provider.

Step 13. Take your thumb off the plunger
Take your thumb off the plunger to allow the needle guard to cover the needle (see Figure M).
- You may see a small amount of blood at the injection site. If you do, press on your skin with a cotton ball or gauze.

Step 14. Throw away (dispose of) the prefilled syringe
Throw away (dispose of) the used prefilled syringe in a FDA-cleared sharps disposal container right away after use (see Figure N). Do not recycle or throw away the prefilled syringe in your household trash.
- Throw away the remaining supplies in your household trash or sharps disposal container.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be local or state laws about how you should throw away needles and syringes.
- For more information about safe sharps disposal, and for specific information about sharps disposal in the state you live in, go to the FDA’s website at: http://www.fda.gov/safesharpsdisposal.

If you have questions or concerns about your ENTYVIO prefilled syringe, please call your healthcare provider. You can also call 877-825-3327 or visit www.ENTYVIO.com for more information.

Manufactured by:
Takeda Pharmaceuticals U.S.A., Inc.
Lexington, MA 02421

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This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Approved: 9/2023

SPI-0503