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Product	Entyvio IV	**Job No.**	230000806
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Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed with a doctor's prescription only

ENTYVIO® I.V.
Powder for concentrate for solution for infusion

Active ingredient
Each vial contains 300 mg of vedolizumab.
Inactive ingredients and allergens: See section 6, "Additional information".

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult with your doctor or pharmacist.
This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar to yours.

1. What is this medicine intended for?

Ulcerative colitis
Entyvio I.V. is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have shown an inadequate response with or lost response to, or were intolerant to either conventional therapy or to a tumor necrosis factor-alpha (TNFα) antagonist.

Crohn's disease
Entyvio I.V. is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have shown an inadequate response with or lost response to or were intolerant to either conventional therapy or to a tumor necrosis factor-alpha (TNFα) antagonist.

Therapeutic group: Selective immunosuppressants.

Entyvio contains the active ingredient vedolizumab. Vedolizumab belongs to a group of biological medicines called monoclonal antibodies (MAbs). Entyvio works by blocking a protein on the surface of white blood cells that cause the inflammation in ulcerative colitis and in Crohn's disease. This reduces the severity of the inflammation.

2. Before using this medicine

Do not use this medicine if:
- You are sensitive (allergic) to vedolizumab or to any of the other ingredients in this medicine (as listed in section 6).

- You have an active severe infection, such as: tuberculosis, blood poisoning, inflammation in your digestive system (gastroenteritis) that is characterized by acute diarrhea and vomiting, nervous system infection, cytomegalovirus (CMV), listeria infection (listeriosis), or infections like progressive multifocal leukoencephalopathy (PML).

Special warnings about using this medicine

Before the treatment with Entyvio, talk with your doctor or nurse.

When you first receive this medicine, during the treatment, and between doses of the medicine, **notify your doctor or nurse immediately in the following instances:**

- if you experience blurred vision, loss of vision or double vision, difficulty speaking, weakness in an arm or leg, a change in the way you walk or problems with your balance, persistent numbness, decreased sensation or loss of sensation, memory loss or confusion. These may all be symptoms of a **serious and potentially fatal brain condition** known as progressive multifocal leukoencephalopathy **(PML)**.
- if you have an **infection**, or think that you have an infection. Signs include: chills, shivering, persistent cough or a high fever. Certain infections may become serious and possibly even life-threatening if left untreated.
- if you experience signs of **an allergic reaction or other reaction to the infusion**, such as wheezing, difficulty breathing, hives, itching, swelling or dizziness. These could occur during or after the infusion. For more detailed information, see ‘infusion and allergic reactions’ in section 4.
- if you are going to receive any **vaccination** or have recently received a vaccination. Entyvio may affect the way you respond to a vaccination.
- if you have cancer, tell your doctor. Your doctor will have to decide if you can still be given Entyvio.
- if you are not feeling any better, since vedolizumab may take up to 14 weeks to work in some patients with very active Crohn’s disease.

Children and adolescents

Entyvio is not recommended for use in children or adolescents (under the age of 18) due to the lack of information regarding the use of this medicine in this age group.

Drug interactions

If you are taking or have recently taken other medicines, including nonprescription medications and dietary supplements, tell your doctor, nurse or pharmacist.

Entyvio should not be given with other biological medicines that suppress the immune system, because the effect of this is not known.

Tell your doctor if you have previously taken:

- natalizumab (a medicine for multiple sclerosis) or
- rituximab (a medicine for certain types of cancer and rheumatoid arthritis). Your doctor will decide if you can be given Entyvio.

Pregnancy, breastfeeding and fertility

If you are pregnant or breastfeeding, think that you may be pregnant or are planning to become pregnant, consult with your doctor before taking this medicine.

Pregnancy

The effects of Entyvio in pregnant women are not known. Therefore, this medicine is not recommended for use during pregnancy. You and your doctor should decide whether the benefit to you clearly outweighs the potential risk to yourself and your baby.

If you are a woman of childbearing age, you are advised to avoid becoming pregnant while using Entyvio. You should use adequate means of contraception during the treatment and should continue to use contraception for at least 4.5 months after the last treatment.

Breastfeeding

Tell your doctor if you are breastfeeding or planning to breastfeed. Entyvio passes into breast milk. There is not enough information on what effect this may have on your baby and on milk production. A decision must be made whether to discontinue breastfeeding or to discontinue the Entyvio therapy, while taking into account the benefit of breastfeeding for your child and the benefit of the therapy for you.

Fertility

There are no data about the effects of Entyvio on human fertility.

Driving and using machines

This medicine has a minor effect on your ability to drive or use tools or machines. A small number of patients have felt dizzy after receiving Entyvio. If you feel dizzy, do not drive and do not use tools or machines.

3. How to use this medicine?

Always use this medicine according to your doctor's instructions.
Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine.

How much Entyvio will you receive?

Only your doctor will determine your dose and how you should take this medicine. The treatment with **Entyvio I.V.** is the same for ulcerative colitis and for Crohn's disease. The recommended dose is usually 300 mg of Entyvio I.V. administered as follows (see table below):

Treatment (infusion) number	Timing of the treatment (infusion)
Treatment 1	0 weeks
Treatment 2	2 weeks after treatment 1
Treatment 3	6 weeks after treatment 1
Subsequent treatments	Every 8 weeks

Your doctor may decide to alter this treatment program depending upon your response to Entyvio and how suitable it is for you.

- The infusion will be given to you by a doctor or nurse, through a drip in one of the veins in your arm (intravenous infusion), lasting about 30 minutes.
- For the first two infusions, your doctor or nurse will monitor you closely during the infusion and for approximately 2 hours after you have completed the infusion. For all subsequent infusions (after the first two), you will be monitored during the infusion and for approximately 1 hour after you have completed the infusion.

Do not exceed the recommended dose.
Adhere to the treatment as recommended by your doctor.

If you forget or miss your appointment for an Entyvio infusion

If you forget or miss your appointment to receive an infusion, schedule another appointment as soon as possible.

If you stop using Entyvio

Do not stop using Entyvio without first consulting with your doctor.

Do not take medicines in the dark! Check the label and dose <u>every time</u> you take medicine. Wear glasses if you need them.

If you have any further questions about using this medicine, consult with your doctor, nurse or pharmacist.

4. <u>Possible side effects</u>

Like with all medicines, the use of Entyvio may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

Serious side effects

Tell your doctor immediately if you notice any of the following symptoms:

- allergic reactions (may affect up to 1 in 100 users) – signs may include: wheezing or difficulty breathing, hives, itching of your skin, swelling, nausea, pain or irritation at the infusion site, redness of skin.
- infections (may affect up to 1 in 10 users) – signs may include: chills or shivers, high fever or rash.

Other side effects

If you notice any of the following effects, tell your doctor **as soon as possible**:

Very common side effects (may affect more than 1 in 10 users):
Common cold, joint pain, headache.

Common side effects (may affect 1 in 10 users):
Pneumonia, infection of the large intestine due to Clostridium difficile bacteria, fever, chest infection, bronchitis, tiredness, nausea, indigestion, cough, flu (influenza), back pain, throat pain, throat infection (pharyngitis), sinusitis, itchiness, rash and redness, limb pain, muscle cramps, muscle weakness, upper respiratory tract infection, gastrointestinal inflammation – stomach and bowel , anal infection, anal sore, hard feces, constipation, abdominal bloating , passing gas, high blood pressure, tingling or prickling, heartburn, hemorrhoids, nasal congestion, eczema, night sweats, acne (pimples), shingles (herpes zoster),injection site reactions (including pain, swelling, redness or itching).

Uncommon side effects (may affect 1 in 100 users):
Infection in the respiratory tract, redness or tenderness or inflammation of hair follicles, fungal infection in the throat and mouth, vaginal infection (fungal or other), blurred vision (loss of sharpness of eyesight), chills, sensation of coldness.

Very rare side effects (may affect 1 in 10,000 users):
Sudden severe allergic reaction that may cause breathing difficulty, swelling, fast heartbeat, sweating, drop in blood pressure, dizziness, loss of consciousness and collapse (anaphylactic reaction and anaphylactic shock).

Side effects of unknown frequency (frequency cannot be estimated from available information):
A lung disease that causes shortness of breath (interstitial lung disease)

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult with your doctor.

Reporting side effects
You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health's home page (www.health.gov.il), which links to an online form for reporting side effects. You can also use this link: https://sideeffects.health.gov.il

5. How to store the medicine?

- Prevent poisoning! To prevent poisoning, keep this, and all other medicines, in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by a doctor.
- Do not use the medicine after the expiry date (exp. date) which is stated on the

carton/bottle. The expiry date refers to the last day of that month.

- Entyvio I.V. is given by a doctor or nurse, and patients are not supposed to prepare Entyvio I.V. for administration.

Storage conditions

- Entyvio I.V. is intended for single-use only.
- **Unopened vial:** Store in a refrigerator (2°C-8°C). Keep the vial in the original carton in order to protect from light.

Reconstituted and diluted solutions: Use immediately. If this is not possible, reconstituted solution in the vial can be stored for up to 8 hours at 2°C-8°C. After dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, the solution can be stored in the infusion bag for up to 12 hours at a temperature of 20°C-25°C, or for up to 24 hours in a refrigerator (2°C-8°C). The combined stability of Entyvio I.V. in the vial and in the infusion bag, after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection is maintained for 12 hours at a temperature of 20°C-25°C or for 24 hours in a refrigerator (2°C-8°C). A 24-hour period may include up to 8 hours at a temperature of 2°C-8°C for reconstituted solution in the vial, and up to 12 hours at a temperature of 20°C-25°C for diluted solution in the infusion bag, but the infusion bag must be stored in the refrigerator (2°C-8°C) for the rest of the 24-hour period. Any time that the reconstituted solution was stored in the vial should be subtracted from the time that the solution may be stored in the infusion bag.
Do not freeze the reconstituted solution in the vial or the diluted solution in the infusion bag.

	Storage conditions	
	Refrigerator (2°C-8°C)	20°C-25°C
Reconstituted solution in the vial	8 hours	Do not store[1]
Diluted solution in sodium chloride (0.9%) solution for injection	24 hours[2,3]	12 hours[2]

[1] Up to 30 minutes are allowed for reconstitution.

[2] This timeframe is based on the assumption that the reconstituted solution is immediately diluted in the sodium chloride (0.9%) solution for injection and is being stored only in the infusion bag. Any time that the reconstituted solution was stored in the vial should be subtracted from the time the solution may be stored in the infusion bag.

[3] This timeframe may include up to 12 hours at a temperature of 20°C-25°C.

Do not use this medicine if you notice particles in the liquid or discoloration (solution should be clear or opalescent, colorless to light yellow) prior to administration.

Do not throw away the medicines via wastewater or household waste. Ask your pharmacist how to throw away the medicine. This will help protect the environment.

6. Additional information

In addition to the active ingredient, the medicine also contains:

Sucrose, L-arginine hydrochloride, L-histidine, L-histidine monohydrochloride, polysorbate 80.

What the medicine looks like and contents of the pack:

Entyvio I.V. is a white to off-white powder for concentrate for solution for infusion. The powder is provided in a glass vial with a rubber stopper and a plastic cap.

Each pack of Entyvio I.V. contains one vial.

Registration holder's and importer's name and address: Takeda Israel Ltd., 25 Efal St., POB 4140, Petach-Tikva 4951125, Israel.

Registration number of the medicine in the Ministry of Health's National Drug Registry: 153-58-34277-00

This leaflet was revised in August 2023 according to MOH guidelines.

This leaflet is based on the European leaflet approved in July 2023.