Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986
This medicine is dispensed with a doctor's prescription only

Entyvio® S.C.
Solution for subcutaneous injection in a pre-filled pen

Active ingredient and its quantity:
Each pre-filled pen contains 108 mg of vedolizumab in 0.68 ml solution.
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 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?

Entyvio S.C. is used to treat the signs and symptoms in adults of:
- moderately to severely active ulcerative colitis.
- moderately to severely active Crohn's disease.

Ulcerative colitis
Entyvio S.C. is indicated for treatment of adults with moderately to severely active ulcerative colitis who demonstrated inadequate response, stopped responding or exhibited intolerance to the standard of care or to tumor necrosis factor-alpha (TNFα) antagonist.

Crohn's disease
Entyvio S.C. is indicated for treatment of adults with moderately to severely active Crohn's disease who demonstrated inadequate response, stopped responding or exhibited intolerance to the standard of care or to tumor necrosis factor-alpha (TNFα) antagonist.

Therapeutic group: Selective immunosuppressants (monoclonal antibodies - MAbs).

Entyvio contains the active substance vedolizumab. Vedolizumab belongs to a group of biological medicines called monoclonal antibodies (MAbs). Entyvio works by blocking a protein located on the surface of white blood cells that causes inflammation in ulcerative colitis and Crohn's disease. This activity reduces the severity of 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, gastroenteritis manifested by severe diarrhoea and vomiting, nervous system infection, cytomegalovirus (CMV), Listeria bacterial infection and infections such as progressive multifocal leukoencephalopathy (PML).

Special warnings about using this medicine

Talk to your doctor, pharmacist or nurse before treatment with Entyvio.

When you first receive this medicine, **tell your doctor, pharmacist or nurse immediately if the following events occur** during treatment and between medicine doses:

- If you experience blurred vision, loss of or double vision, difficulty speaking, weakness in an arm or a leg, a change in the way you walk or balance problems, persistent numbness, decreased sensation or loss of sensation, memory loss or confusion. All these might be symptoms of a **serious and potentially fatal brain condition** known as progressive multifocal leukoencephalopathy **(PML)**.

- If you have an **infection** or think you have an infection. Signs include chills, shivering, persistent cough or high fever. Some infections may become serious and possibly even life-threatening if left untreated.

- If you experience signs of **an allergic reaction** such as wheezing, difficulty breathing, hives, itching, swelling or dizziness. For more detailed information, see 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 receive Entyvio.

- If you are not feeling any better, as 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 18 years of age) due to the lack of information regarding the use of this medicine in the 0-17 age group.

Drug interactions

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

- Entyvio should not be given together with other biological medicines that suppress your immune system, as 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 you may be pregnant or are planning to have a baby, ask your doctor for advice 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 if the benefit to you clearly outweighs the potential risk to yourself and your baby.

If you are a woman of childbearing potential, you are advised to avoid becoming pregnant while using Entyvio. You should use adequate contraception during treatment and 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 stop breastfeeding or to stop Entyvio therapy, taking into account the benefit of breastfeeding for your child and the benefit of therapy for you.

Fertility
There is no information regarding the effect 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 or use tools or machines.

Important information about some of this medicine's ingredients
Entyvio S.C. contains sodium.
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

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.

You or your caregiver will be given training on how to inject Entyvio under the skin (subcutaneous injection).

How much Entyvio will you receive?

Dosage and frequency
The dosage and treatment regimen will be determined only by your doctor. Treatment with Entyvio S.C. is the same for ulcerative colitis and Crohn's disease. The recommended dosage is usually 108 mg of Entyvio administered by subcutaneous injection once every 2 weeks.

- At the start of treatment, the doctor will give you initial doses of Entyvio through a drip into a vein in your arm (intravenous infusion) over about 30 minutes.
- After administration of at least 2 intravenous infusions, you can start receiving Entyvio by a subcutaneous injection. The first subcutaneous injection is given at the time of the next scheduled intravenous infusion, and every 2 weeks thereafter.

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

Injecting Entyvio
The subcutaneous injection can be given by yourself or a caregiver, after training on how to do it. Instructions for use are provided at the end of this leaflet.

If you forget or miss a dose
If you forget or miss a dose, inject the next dose as soon as possible and then every 2 weeks thereafter.

If you stop using Entyvio
Do not stop using Entyvio without consulting your doctor first.

Do not take medicines in the dark! Check the label and dose every time you take a medicine. Wear glasses if you need them.
If you have any further questions about using this medicine, consult your doctor, nurse or pharmacist.

4. Side effects

Like with all medicines, using 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 effects:

- Allergic reactions (may affect up to 1 in 100 users) - signs may include wheezing or difficulty breathing, hives, itching of the skin, swelling, nausea, redness of skin.
- Infections (may affect up to 1 in 10 users) - signs may include chills or shivering, high fever or rash.

Other side effects
Tell your doctor **as soon as possible** if you notice any of the following effects:

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):
Fever, pulmonary infection, bronchitis, tiredness, nausea, cough, influenza, back pain, pain in the throat and ears, inflammation of the throat, inflammation of the sinuses (infectious or other), sensation disorders, itching, rash and redness, pain in the limbs, muscle cramps, muscle weakness, upper respiratory tract infection, gastrointestinal inflammation – stomach and bowel (viral or other), anal infection, anal sore, anal fissure, hard faeces, constipation, abdominal bloating, passing gas, high blood pressure, prickling or tingling, heartburn, haemorrhoids, nasal congestion, eczema, night sweats, acne (pimples), injection site reactions (including pain, swelling, redness or itching).

Uncommon side effects (may affect 1 in 100 users):
Redness or tenderness of hair follicles, throat and mouth yeast infection, vaginal infection (fungal or other), shingles (herpes zoster), respiratory tract infection, chills, sensation of coldness.

Very rare side effects (may affect 1 in 10,000 users):
Pneumonia, blurred vision (loss of visual acuity), sudden, severe allergic reaction which may cause breathing difficulties, swelling, fast heartbeat, sweating, drop in blood pressure, lightheadedness, loss of consciousness and collapse (anaphylactic reaction and anaphylactic shock)

Side effects of unknown frequency (the frequency cannot be estimated from the available data):
A lung disease causing 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 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 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) which is stated on the package. The expiry date refers to the last day of that month.

Storage conditions

- Store in a refrigerator (2°C-8°C). Keep the pre-filled pen in the original package in order to protect from light. If needed, the pre-filled pen can be left out of the refrigerator in its original package at room temperature (up to 25°C) for up to 7 days. Do not use the pre-filled pen if it has been left out of the refrigerator for more than 7 days.
- Do not freeze. Do not leave in direct sunlight.
- Entyvio is intended for single use only.

- Do not use this medicine if you notice any particles in the liquid or discolouration (the solution should be colourless to yellow) prior to administration.
- Do not throw away the medicine via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Additional information

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

L-arginine hydrochloride, sodium citrate dihydrate, L-histidine, L-histidine monohydrochloride, polysorbate 80, citric acid monohydrate and water for injection.

What the medicine looks like and contents of the pack:

Entyvio is a colourless to yellow solution for injection provided in a glass pre-filled pen, equipped with a safety mechanism locking the needle once the pen is removed from the injection site.

The product is registered as a pack containing 1, 2 or 6 pre-filled pens. **Not all pack sizes may be marketed.**

Registration holder's name and address: Takeda Israel Ltd., 25 Efal St., P.O.B 4140, Petach Tikva 4951125, Israel.

Manufacturer's name and address:
Takeda Pharma A/S, Delta Park 45, 2665 Vallensbaek Strand, Denmark.

Registration number of the medicine in the National Drug Registry of the Ministry of Health:
170-22-36542-00

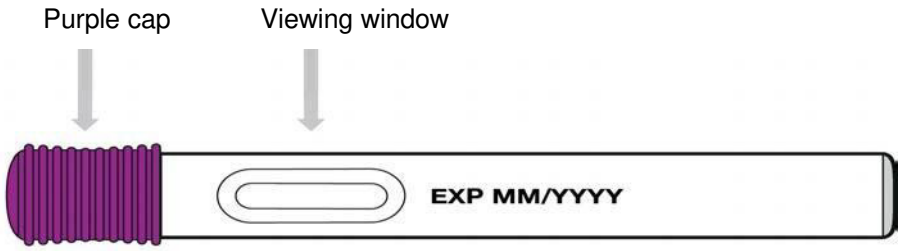
The leaflet was approved in February 2022 according to MOH guidelines.

Instructions for use of Entyvio S.C.
Solution for subcutaneous injection in a pre-filled pen

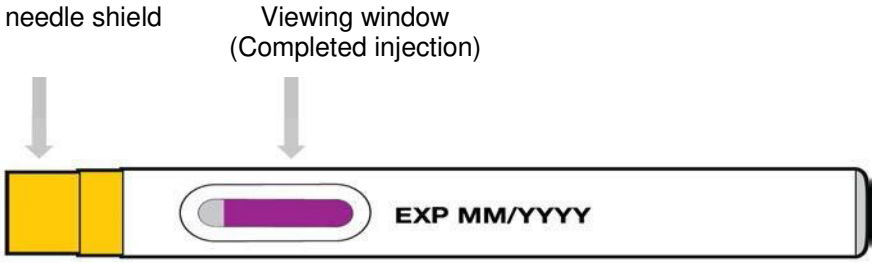
Read and follow the following instructions before you inject the medicine. Your doctor, nurse or pharmacist should instruct you how to use the Entyvio pre-filled pen before you use it for the first time.

Entyvio single-dose pre-filled pen

Before use



After use



1) Place the items you need for the injection on a clean and flat surface

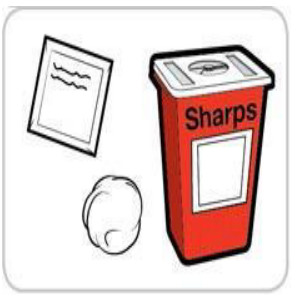
- Take a single pre-filled pen pack out of the refrigerator.
  - **Do not** use the pre-filled pen if any of the seals on the pack are broken or missing.
  - Check the expiry date (EXP) on the pack. **Do not** use the medicine if the expiry date on the pack has passed.

- Wait **30 minutes** until the pre-filled pen reaches room temperature.

  - **Do not** warm the pre-filled pen in any other way.
  - **Do not** place it in direct sunlight.
  - **Do not** take the pre-filled pen out of its tray until you are ready to inject.

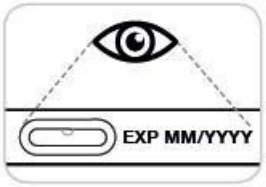
Wait 30 minutes

- You will also need the following items:
  - Alcohol pad
  - Cotton ball or gauze
  - Sharps disposal container



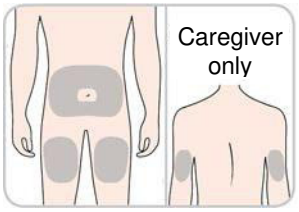
2) Open and check the pre-filled pen

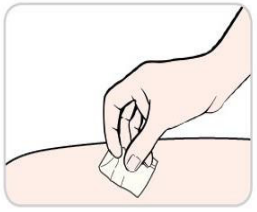
- Wash your hands.
- Peel back the paper on the tray and take the pre-filled pen out.
- Visually inspect the pre-filled pen for damage.
  - **Do not** use the pre-filled pen if any part of it is damaged.
- Check the expiry date on the pre-filled pen.
  - **Do not** use the pre-filled pen if the expiry date on it has passed.
- Visually inspect the medicine solution. It should be colourless to yellow.
  - **Do not** use the pre-filled pen if the medicine solution is cloudy or contains particles floating in it.
- You may see air bubbles in the pre-filled pen. This is normal.
  - **Do not** shake.

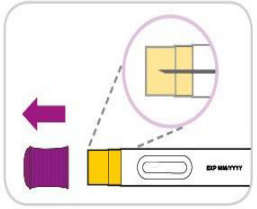


3) Prepare the injection site

- **Choose an injection site** on your bare skin from any of the following sites:
  - Front of the thighs, or
  - Abdominal area, except for the area of 5 cm around the navel, or
  - Back of the upper arm (only if a caregiver injects the medicine to you).
- Use a new injection site or a different area within the same injection site for each injection.
  - Do not inject into moles, scars, bruises, or areas in which the skin is tender, hard, red or damaged.
- Wipe the chosen site with an alcohol pad. Let your skin dry.
  - **Do not** touch this area again before the injection.
- Pull the purple cap straight off and throw it away.
  - **Do not** put or press thumb, fingers or hand over the yellow needle shield.
  - **Do not** re-cap the pre-filled pen.
  - **Do not** use a dropped pre-filled pen.



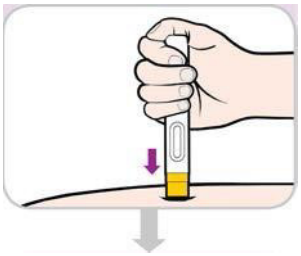




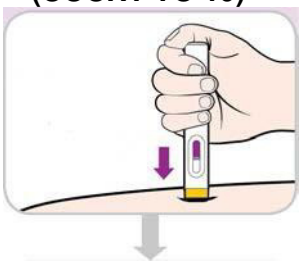
4) Inject the medicine

- Hold the pre-filled pen so you can see the viewing window.
- Place the pre-filled pen at **90 degrees** to the injection site.
  - Make sure **that the yellow end is directed toward the injection site.**
  - **Do not** push down until you are ready to inject.
- **Push down on the pre-filled pen as far as it will go** to begin the injection.
- **Hold and count to 10** while pushing down with constant pressure. This will allow all of the medicine to be injected.
  - You may hear 2 clicks, one at the start and one near the end of the injection.
- **Verify that the viewing window is filled with purple** before you stop pushing.
  - You will see a small amount of grey in the window. This is normal.
- Lift the pre-filled pen from the injection site.
  - The yellow needle shield will drop down and lock over the needle.
  - If the viewing window did not fill completely, call your doctor, nurse or pharmacist. You may not have received your full dose of medicine.
- 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.

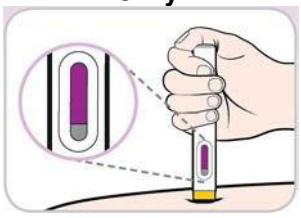
Push



Hold (COUNT TO 10)



Verify



5) Throw away used materials

- Put the used pre-filled pen in a puncture-resistant container, like a sharps container, immediately after use.
  - Dispose of the sharps container according to the local regulations.
- The rest of the materials can be thrown away in the household waste.