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

Velsipity®

Each film-coated tablet contains:
etrasimod L-arginine equivalent to 2 mg etrasimod

Inactive ingredients and allergens: See section 2 under 'Important information about some of this medicine's ingredients' and section 6 'Further information'.

Read the entire leaflet carefully before 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.

In addition to the patient information leaflet, Velsipity also has a patient/caregiver safety information guide and a pregnancy reminder card. The guide and card contain important safety information that you need to know and that you should follow before starting and during treatment with Velsipity. Carefully read the patient/caregiver safety information guide, pregnancy reminder card and patient information leaflet before using this medicine. Keep the guide and card in case you need to read them again.

1. WHAT IS THIS MEDICINE INTENDED FOR?

Velsipity is used to treat adults and adolescents aged 16 years and older for the treatment of moderately to severely active ulcerative colitis who had an inadequate response, or lost response or were intolerant to either conventional therapy or biological treatment.

Therapeutic group:
Sphingosine-1-phosphate receptor modulators.

Ulcerative colitis
Ulcerative colitis is an inflammatory disease of the large bowel.
If you have ulcerative colitis, you will first be given other medicines. If you do not respond well enough or cannot take these medicines, you may be given Velsipity to reduce the signs and symptoms of the disease.

The active ingredient in Velsipity, etrasimod, prevents lymphocytes (a type of white blood cell) from travelling from the lymph nodes (part of the body's immune system that contains lymphocytes) into the blood. These lymphocytes are involved in the inflammation that is linked to the development of ulcerative colitis (UC). By reducing the number of lymphocytes circulating in the blood surrounding the large bowel, etrasimod helps to reduce bowel inflammation and the symptoms associated with the disease.

2. BEFORE USING THIS MEDICINE

Do not use this medicine if:

- you are sensitive (allergic) to the active ingredient (etrasimod) or to any of the other ingredients in this medicine (listed in section 6).
- your doctor has told you that you have a severely weakened immune system.
- you have had a heart attack, unstable angina pectoris (chest pain caused by interruptions in the heart's blood supply that occur at rest or without an obvious reason), stroke, transient

ischaemic attack (TIA, also known as a mini-stroke) or certain types of severe heart failure in the last 6 months.
- you have certain types of arrhythmia (irregular or abnormal heartbeat) – your doctor will check your heart before starting treatment.
- you have a severe active infection or active chronic infection, such as inflammation of the liver (hepatitis) or tuberculosis.
- you have cancer.
- you have severe liver problems.
- you are pregnant or are of childbearing potential and are not using effective contraception.

Special warnings regarding use of the medicine
Before treatment with Velsipity, tell your doctor if:
- you have a slow heart rate or you are taking or have recently taken medicines that slow your heart rate (such as beta blockers or calcium channel blockers).
- you have ever had a stroke or other diseases related to blood vessels in the brain.
- you have problems with your liver.
- you have an infection.
- you have low levels of lymphocytes (a type of white blood cell).
- you have recently had or are planning to have a vaccination.
- you have or have ever had problems with your vision or other symptoms of build-up of fluid in the back of the eye.
- you have inflammation of the eye.
- you have diabetes (which can cause problems with your eyes).
- you have high blood pressure.
- you have severe lung disease, such as pulmonary fibrosis (lung damage with tissue scarring and thickening), asthma or chronic obstructive pulmonary disease (a type of lung disease marked by permanent damage to lung tissues).

Additional warnings:
Slow heart rate and irregular heart rhythm
Before the treatment with Velsipity, your doctor will check your heart using an electrocardiogram (ECG), a test of the heart's electrical activity. This is because Velsipity can cause a temporary decrease in heart rate and other heart rhythm disorders when starting treatment. When this happens, you may feel dizzy or tired or be aware of your heartbeat, or your blood pressure may drop. If these effects are severe, tell your doctor, because you may need treatment right away. If you restart treatment again after stopping for 7 or more days in a row, your doctor may re-check your heart using an ECG.

If you have certain heart conditions, your doctor will also monitor you for at least the first 4 hours after you receive your first dose. Your doctor will ask you to stay at the hospital or clinic for 4 hours and will measure your pulse and blood pressure every hour after taking the first dose of Velsipity. You should have an ECG performed before the first dose of Velsipity and after the 4-hour monitoring period. If after the 4-hour period you have a very slow or decreasing heart rate, or if your ECG shows an abnormality, you may need to be monitored for a longer period until stabilizing.

High blood pressure
As Velsipity can increase your blood pressure, your doctor may want to check your blood pressure regularly.

Infections
Velsipity lowers the levels of white blood cells in your blood (particularly the lymphocyte count). White blood cells fight infection. While you are taking Velsipity (and for up to about 2 weeks after you stop taking it), you may be more likely to get infections, and any infection that you already have may get worse. Talk to your doctor if you develop an infection.

If you think you have an infection, have a fever, feel like you have the flu, have shingles or have a headache accompanied by a stiff neck, with sensitivity to light, nausea, rash, and/or confusion or seizures (fits) (these may be symptoms of meningitis and/or encephalitis caused by a fungal or herpes viral infection), contact your doctor straight away, because it could be serious and life-threatening.

Cases of progressive multifocal leukoencephalopathy (PML) have been reported with medicines similar to Velsipity. PML is a rare viral brain infection that may lead to severe disability or death. PML symptoms include disturbance of vision, progressive weakness, clumsiness, memory loss or confusion. If you develop any of these symptoms, report to your doctor straight away. Your doctor will consider performing further tests to evaluate this condition and will stop your treatment with Velsipity if you are diagnosed with PML.

Macular oedema
Velsipity can cause a problem with your vision called macular oedema (swelling of the macula, the central part of the retina at the back of the eye). The risk of developing macular oedema is higher if you have diabetes, uveitis (inflammation of the uvea, the layer beneath the white of the eyeball), or certain other eye problems. If you have any of these conditions, your doctor will check your vision before you start taking Velsipity and regularly during treatment. If you do not have these conditions, your doctor will check your vision within 3-4 months after starting treatment. Tell your doctor about any change in your vision during treatment with Velsipity.

Call your doctor straight away if you have any of the following conditions:
- blurriness or shadows in the centre of your vision
- a blind spot in the centre of your vision
- sensitivity to light
- unusually coloured (tinted) vision

Tests and follow-up
Your doctor may want to check your blood pressure regularly.
Before you start treatment, your doctor will check your heart using an electrocardiogram (ECG), a test of the heart's electrical activity.
Before, during and after the treatment, your doctor will refer you for blood tests to monitor your liver function.
Your doctor will check your vision around the time you start taking Velsipity and, if there are risk factors, also regularly during treatment.

Cancer
Velsipity weakens your immune system. This increases your risk of developing cancer, in particular skin cancer. Skin cancers have been reported with use of medicines similar to Velsipity. Report to your doctor straight away if you notice any skin nodules (e.g., shiny pearly nodules), patches or open sores that do not heal within weeks. Symptoms of skin cancer may include abnormal growth or changes of skin tissue (e.g., unusual moles) with a change in colour, shape, or size over time. Since there is a risk for skin cancer, you should limit your exposure to sunlight and ultraviolet (UV) light, including phototherapy or photochemotherapy, by wearing protective clothing and regularly applying sunscreen (with high sun protection factor).

Posterior reversible encephalopathy syndrome (PRES)
Posterior reversible encephalopathy syndrome (PRES) is a condition where the brain swells. PRES symptoms include headaches, changes in vision, reduced awareness, confusion, and seizures (fits). If you develop any of these symptoms, speak to your doctor straight away.

Vaccinations
If you need to receive a vaccine, seek your doctor's advice first. Vaccines may not work as well as they should during your treatment with Velsipity. You are advised to make sure you have received all recommended vaccinations before you start treatment. Live vaccines (vaccines that contain a

weakened live pathogen) may trigger the infection that they are supposed to prevent and should therefore be given at least 4 weeks before you start treatment, or at least 2 weeks after you stop taking Velsipity.

Liver function tests
Velsipity may affect your liver function. Tell your doctor straight away if you develop any of the following symptoms: yellowing of your skin or the whites of your eyes, abnormally dark urine (brown coloured), pain on the right side of your stomach area, tiredness, feeling less hungry than usual or unexplained nausea and vomiting.

Before, during and after the treatment, your doctor will refer you for blood tests to monitor your liver function.

Lung problems
Velsipity may have an effect on the lung function. Patients with severe lung problems have a higher chance of developing this type of side effects.

Other treatments for ulcerative colitis (UC)
Your doctor will usually advise that you stop other treatments for ulcerative colitis with the exception of corticosteroids (like cortisone), and mesalazine. Some medicines for ulcerative colitis may also be used for other conditions. Tell your doctor about all other medicines you take. When switching from the previous treatment, because of the risk of additional immunosuppressive effects, the risk of infection may be increased for some time. Do not take any other immunosuppressive medicines unless your doctor has told you to do so.

Women of childbearing potential
If Velsipity is used during pregnancy, it can harm the unborn baby. Before you start treatment with Velsipity, your doctor will explain the risk to you and ask you to do a pregnancy test in order to ensure that you are not pregnant. Your doctor will give you a patient card which explains why you should not become pregnant while taking Velsipity. The patient card also explains what you should do to avoid becoming pregnant while you are taking Velsipity. You must use effective contraception during treatment and for at least 14 days after stopping treatment with Velsipity (see ‘Pregnancy, contraception and breast-feeding' in section 2).

If any of these apply to you, talk to your doctor or pharmacist before receiving treatment with Velsipity.

Children and adolescents
This medicine is not intended for use in children and adolescents under the age of 16. This is because the efficacy and safety of Velsipity has not been studied in this age group.

Drug interactions
If you are taking or have recently taken, other medicines, including nonprescription medicines and dietary supplements, tell your doctor or pharmacist. This is because Velsipity can affect the way other medicines work. Also, other medicines can affect the way Velsipity works. In particular, before starting treatment with Velsipity, inform your doctor or pharmacist if you are taking or have previously taken:

- Medicines to control your heart rate and blood pressure (beta blockers and calcium channel blockers). Use of these medicines could strengthen the effect of Velsipity on irregular heartbeat.
- Medicines to control your heart rhythm (antiarrhythmics), or heartbeat.
- Medicines that affect your immune system; use of these medicines with Velsipity could weaken the immune system.
- Vaccines. If you need to receive a vaccine, talk to your doctor. You should not take Velsipity for at least 2 weeks before a vaccination. You should not take Velsipity for at least 4 weeks after receiving a live vaccine.

- Fluconazole (an anti-fungal treatment) and certain other medicines that inhibit the clearance of Velsipity from the body can increase the levels of Velsipity in the blood, which increases the risk of side effects with Velsipity. It is recommended that you do not take these medicines while taking Velsipity. Your doctor will advise you on this.
- Rifampicin, enzalutamide, and certain other medicines that enhance the clearance of Velsipity from the body can decrease the levels of Velsipity in the blood, reducing its effectiveness. It is recommended that you do not take these while also taking Velsipity. Your doctor will advise you on this.
- Velsipity may slightly increase the levels of hormones released from some contraceptive pills. You will still be protected from pregnancy, but your chances of side effects from contraceptive pills may be higher. If you have any side effects, talk to your doctor or pharmacist.

Using this medicine and food
Take this medicine with food for the first 3 days. After this, you can take the medicine each day with or without food.

Pregnancy, contraception and breast-feeding
If you are pregnant or breast-feeding, think you are pregnant or are planning to become pregnant, consult your doctor before taking this medicine.

Pregnancy and contraceptives for women
Do not use this medicine if you are pregnant, are planning to become pregnant, or if you are a woman who could become pregnant, and you are not using effective contraception. If Velsipity is used during pregnancy, there is a risk of harm to the unborn baby.
If you are a woman who could become pregnant, consult your doctor about the risk before treatment with Velsipity. Your doctor may ask you to do a pregnancy test in order to ensure that you are not pregnant. You must use effective contraception during treatment and for at least 14 days after the end of treatment with Velsipity. Consult your doctor about use of contraceptives during this period.

Your doctor will give you a patient card which explains why you should not become pregnant while taking Velsipity.

If you do become pregnant during treatment with Velsipity, inform your doctor straight away. Your doctor will likely stop treatment (see ‘If you stop taking Velsipity' in section 3). Pre-natal checks will be performed to monitor the health of the unborn baby.

Breast-feeding
You should not breast-feed while being treated with this medicine. It is not known whether the medicine passes into breast milk and therefore a risk of side effects for the baby cannot be ruled out.

Driving and using machines
Velsipity has no or negligible influence on the ability to drive and operate machines. If you feel dizzy after taking Velsipity, do not drive or use machines.

Important information about some of this medicine’s ingredients
Velsipity contains a colouring agent, tartrazine (E102), which may cause allergic reactions.
Velsipity contains sodium.
This medicine contains less than 23 mg sodium per dose and is therefore considered ‘sodium free'.

3. HOW TO USE THIS MEDICINE?
Treatment with Velsipity will be started under the supervision of a doctor who is a specialist in treating ulcerative colitis (UC).
Always use this medicine according to your doctor's instructions.
Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the medicine.

The dosage and treatment regimen will be determined by your doctor only. The standard dosage is usually: one 2 mg tablet taken once daily. **Do not exceed the recommended dose.**
How to take: Take the medicine with food for the first 3 days. After this, you can take the medicine each day with or without food.
Swallow the tablet whole with water. There is no information about crushing/splitting/chewing.

If you received a dose of Velsipity that was too high
If you have taken an overdose, or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

If you forget to take Velsipity
If you forget to take a dose of Velsipity, take the next dose at your usual time. Do not take a double dose.

Adhere to the treatment as recommended by your doctor.
Even if your health improves, do not stop taking this medicine without consulting your doctor.

If you stop taking Velsipity
Do not stop the treatment or change your dose without consulting your doctor. If your doctor decides to pause your treatment for 7 days or more in a row, the medicine must be taken with food for the first 3 days after you restart treatment. After that, you can take the medicine with or without food.

If you restart taking Velsipity after stopping your treatment for 7 days or more in a row, the effect on heart rate that may be seen when treatment is first started may re-appear, and you may need to be monitored at the hospital or clinic. Do not restart taking Velsipity after stopping use of the medicine for more than 7 days without seeking advice from your doctor.

Velsipity will stay in your body for up to 14 days after you stop taking it. Your white blood cell count (lymphocyte count) may remain low for up to about 2 weeks, and the side effects described in this leaflet may still appear (see ‘Side effects' in section 4) during this period.

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

4. SIDE EFFECTS
As with any medicine, use of Velsipity 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 – see also the list in section 2 ‘Additional warnings’
Refer to your doctor immediately if you notice any of the following side effects, which could become serious:

Common side effects (may affect up to 1 in 10 people)
- bradycardia (slow heart rate)
- hypertension (high blood pressure)
- urinary tract infection (infection of the parts of the body that collect and pass out urine)
- lower respiratory tract infection (infection of the lower airways or lungs)

Uncommon side effects (may affect up to 1 in 100 people)
- atrioventricular block (a type of heart rhythm disorder)
- macular oedema (swelling in the macula, the central part of the retina at the back of the eye)

Additional side effects – see also the list in section 2 ‘Additional warnings’

Refer to your doctor immediately if you notice any of the following side effects:

Very common side effects (may affect more than 1 in 10 people)
- lymphopenia (low levels of lymphocytes, a type of white blood cell)

Common side effects (may affect up to 1 in 10 people)
- hypercholesterolaemia (high blood cholesterol levels)
- headache
- feeling dizzy
- increased liver enzyme levels in blood tests, which can be a sign of problems with your liver function
- neutropenia (low levels of neutrophils, a type of white blood cell)
- visual impairment

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 or by using the link: https://sideeffects.health.gov.il

5. HOW TO STORE THE MEDICINE?
- Prevent poisoning! This and any other medicine should be kept in a closed place, out of the reach and sight of children and/or infants to avoid poisoning. 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 package. The expiry date refers to the last day of that month.
  Storage conditions:
- Store below 25°C.
- Store in the original package in order to protect from moisture.
- Do not use this medicine if you notice any damage or signs of damage.
- Do not throw away the medicine via wastewater or household waste. Ask the pharmacist how to throw away this medicine. These measures will help protect the environment.

6. FURTHER INFORMATION
In addition to the active ingredient, this medicine also contains:
Tablet core
mannitol (E421), microcrystalline cellulose (E460i), sodium starch glycolate (Type A), magnesium stearate (E470b).
Tablet coating:
poly(vinyl alcohol) (E1203), titanium dioxide (E171), macrogol 4000 (E1521), talc (E553b), indigo carmine aluminium lake (E132), tartrazine aluminium lake (E102) and brilliant blue FCF aluminium lake (E133).

What the medicine looks like and contents of the pack:
Velsipity 2 mg: A green, round, film-coated tablet of approximately 6 mm diameter with "ETR" on one side and "2" on the other side.
The medicine is marketed in a carton containing a blister pack of 28 or 98 film-coated tablets, or a bottle pack containing 30 film-coated tablets. Not all pack types may be marketed.

Registration holder and address: Pfizer Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach 46725.

Registration number of the medicine in the Ministry of Health's National Drug Registry: 177-69-38002

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