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

Zeposia® 0.23 mg
Zeposia® 0.46 mg
Zeposia® 0.92 mg

Active ingredient and its quantity:
Zeposia® 0.23 mg: Each capsule contains 0.23 mg ozanimod (as hydrochloride)
Zeposia® 0.46 mg: Each capsule contains 0.46 mg ozanimod (as hydrochloride)
Zeposia® 0.92 mg: Each capsule contains 0.92 mg ozanimod (as hydrochloride)

Inactive ingredients - see section 6 'Additional information' and section 2 under 'Important information about some of this medicine's ingredients'.

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, ask the doctor or pharmacist.
This medicine has been prescribed to treat 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 leaflet, Zeposia has a **patient/caregiver safety information guide and a pregnancy reminder card**. The guide and card contain important safety information, which you should know, before starting and during the treatment with Zeposia and which you should follow. Carefully read the patient/caregiver safety information guide, the pregnancy reminder card, and patient leaflet before starting treatment with this medicine. Keep the guide and card for further reference if needed.

1. What is this medicine intended for?
- Zeposia is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features.
- Zeposia is indicated for the treatment of moderately to severely active ulcerative colitis (UC) in adults.

Therapeutic group: selective immunosuppressants.

Zeposia contains the active substance ozanimod that belongs to a group of medicines which can reduce the number of white blood cells (lymphocytes) circulating freely round the body.

Multiple sclerosis
- Multiple sclerosis (MS) is a disease in which the immune system (the body's defenses, including white blood cells) wrongly attacks the protective coating around the nerves in the brain and spinal cord. This stops the nerves from working properly and may result in symptoms such as numbness, difficulty in walking, and problems with vision and balance.
- In relapsing remitting multiple sclerosis, attacks on the nerve cells are followed by periods of remission. The symptoms may disappear during the remission periods, but some problems may remain.

Zeposia helps to protect against immune system attacks on the nerve cells by stopping certain white blood cells from reaching the brain and spinal cord, where they could cause inflammation and damage the nerves' protective coating.

Ulcerative colitis
- Ulcerative colitis is an inflammatory disease of the bowel.

Zeposia helps to reduce the inflammation in ulcerative colitis by stopping certain white blood cells from reaching the intestinal lining.

2. Before using this medicine
Do not use this medicine if:
- you are sensitive (allergic) to ozanimod or to any of the other ingredients of this medicine (listed in section 6)
- the doctor has told you that you have a severely weakened immune system
- you have had a heart attack, angina, stroke or mini-stroke (Transient Ischemic Attack - TIA), or certain types of severe heart failure in the last 6 months
- you have or have had certain types of irregular or abnormal heartbeats (arrhythmia) – your doctor will check your heart before starting treatment
- you have severe infection such as liver inflammation (hepatitis) or tuberculosis
- you have cancer
- you have severe liver problems
- you are pregnant or can become pregnant and are not using effective contraception

Special warnings about using this medicine
Before treatment with Zeposia, 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 untreated severe breathing problems when you sleep (severe sleep apnoea);
- you have problems with your liver;
- you have an infection;
- you have low levels of a type of white blood cell called lymphocytes;
- you have never had, or are not sure if you have had chickenpox;
- you have recently had or are planning to have a vaccination;
- you or others notice worsening of your MS symptoms, as well as any new or unfamiliar symptoms. These may be due to a rare infection of the brain called progressive multifocal leukoencephalopathy (PML);
- you have ever had problems with your vision or other symptoms of build-up of fluid in the central area of the retina called the macula (a condition called macular oedema);
- you have inflammation of the eye (uveitis);
- you have diabetes (which can cause problems with your eyes);
- you have severe lung disease (pulmonary fibrosis or chronic obstructive pulmonary disease).

During treatment with Zeposia, if you develop unexplained nausea, vomiting, pain on the right side of the stomach area (abdominal pain), tiredness, loss of appetite, yellowing of your skin or the whites of your eyes (jaundice) and/or dark urine, speak to your doctor straight away. These symptoms may be due to a problem with your liver.
Before, during and after the treatment, your doctor will request blood tests to monitor your liver function. If your test results indicate a problem with your liver, you may have to interrupt treatment with Zeposia.

While you are taking Zeposia (and for up to 3 months after you stop taking it), you may get infections more easily. Any infection that you already have may get worse. Talk to your doctor if you develop an infection.

During treatment with Zeposia, if you develop disturbance of vision, progressive weakness, clumsiness, memory loss or confusion, or if you have multiple sclerosis and you think your disease is getting progressively worse, speak to your doctor straight away. These symptoms may be due to progressive multifocal leukoencephalopathy (PML), a rare brain infection that may lead to severe disability or death.

During treatment with Zeposia, if you develop a severe headache, feel confused, or have seizures (fits) and loss of vision, speak to your doctor straight away. These symptoms may be due to a syndrome called posterior reversible encephalopathy syndrome (PRES).

As Zeposia may increase the risk of skin cancer, you should limit your exposure to sun light and UV (ultraviolet) light, by wearing protective clothing and applying regular sunscreen (with high sun protection factor).

Women of childbearing potential
If used during pregnancy, Zeposia can harm the unborn baby. Before you start treatment with Zeposia, 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/caregiver safety information guide and a pregnancy reminder card which explain why you should avoid pregnancy while taking Zeposia. The guide and card also explain what you should do to avoid becoming pregnant while you are taking Zeposia. You must use effective contraception during treatment and for 3 months after stopping treatment (see the section '*Pregnancy, breast-feeding and fertility'*).

If any of these apply to you, tell your doctor or pharmacist before taking Zeposia.

Tests and follow-up
- Before you start taking Zeposia, the doctor will check your heart using an electrocardiogram (ECG).
  If you have certain heart conditions, the doctor will monitor you for at least the first 6 hours after your first dose of the medicine.
- As Zeposia can increase your blood pressure, your doctor may want to check your blood pressure regularly.
- Before you start taking Zeposia, your doctor will check your liver function. Blood tests to monitor your liver function should be performed in the first, third, sixth, ninth, and twelfth months of taking Zeposia, and periodically thereafter.
- If you have diabetes, inflammation of the eye (uveitis) or have or have ever had a retinal disease, your doctor may refer you for an eye examination either before you start or while you are taking Zeposia.
- Your doctor may order a blood test to check your level of blood cells before you start taking Zeposia and then order periodic tests.

Worsening of MS after stopping Zeposia treatment
Tell your doctor straight away if you think your MS worsens after you have stopped treatment with Zeposia (see '*If you stop taking Zeposia*' in section 3).

Children and adolescents
This medicine is not intended for children and adolescents aged under 18 years. This is because Zeposia has not been studied in children and adolescents.

Drug interactions:
If you are taking, have recently taken, or might take other medicines, including non-prescription medications and dietary supplements, tell your doctor or pharmacist. This is because Zeposia can affect the way other medicines work. Also, other medicines can affect the way Zeposia works.

In particular, before taking Zeposia, tell your doctor or pharmacist if you are taking or have recently taken any of the following medicines:
- medicines which suppress or modulate your immune system (e.g. ciclosporin)
- medicines used to treat MS, such as alemtuzumab, beta interferon, dimethyl fumarate, glatiramer acetate, mitoxantrone, natalizumab or teriflunomide
- medicines used to treat ulcerative colitis, such as azathioprine and 6-mercaptopurine
- gemfibrozil to reduce levels of fats or cholesterol in the blood
- clopidogrel, medicine used to prevent blood clots
- rifampicin, an antibiotic for treating tuberculosis and other serious infections
- medicines called monoamine oxidase inhibitors for treating depression (e.g. phenelzine) or Parkinson's disease (e.g. selegiline)
- medicines that slow your heart rate (such as beta blockers or calcium channel blockers)
- certain types of vaccines. Live attenuated vaccines should be avoided during treatment and for 3 months afterwards.

Using this medicine and food
You can take the capsule either with or without food.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
Pregnancy
Do not use Zeposia during pregnancy, if you are trying to become pregnant or if you are a woman who could become pregnant and you are not using effective contraception. If Zeposia is used during pregnancy, there is a risk of harm to the unborn baby. If you are a woman who could become pregnant, your doctor will inform you about this risk before you start treatment with Zeposia and will ask you to do a pregnancy test in order to ensure that you are not pregnant. You must use effective contraception while taking Zeposia and for at least 3 months after you stop taking it. Ask your doctor about reliable methods of contraception.
Your doctor will give you a patient/caregiver safety information guide and a pregnancy reminder card which explain why you should avoid pregnancy while taking Zeposia.

If you do become pregnant while taking Zeposia, tell your doctor straight away. The doctor will decide to stop treatment (see '*If you stop taking Zeposia*' in section 3). Specialised pre-natal monitoring will be performed.

Breast-feeding
You must not breast-feed while you are taking Zeposia. Zeposia can pass into breast milk and there is a risk of serious side effects for the baby.

Fertility
There is no information about the effect of this medicine on human fertility.

Driving and using machines
Zeposia has no or negligible influence on your ability to drive and operate machines.

Important information about some of this medicine's ingredients
Sodium content
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 the doctor or pharmacist if you are not sure about your dose or about how to take this medicine.
Only your doctor will determine your dose and how you should take this medicine.

The recommended dosage is usually:
When you first start taking Zeposia, you need to take it at a low dose and gradually build up, to reduce any effect of slowing your heart rate.
- You will be given a 'treatment initiation pack' to help you start treatment in this way. It contains:
  - 4 light-grey capsules, containing 0.23 mg ozanimod. One capsule should be taken once a day, on days 1 to 4.
  - 3 light-grey and orange capsules, containing 0.46 mg ozanimod. One capsule should be taken once a day, on days 5, 6 and 7.
- On day 8 and thereafter, once you have completed the 'treatment initiation pack', you will move on to a 'maintenance treatment pack' with orange capsules, each containing the recommended dose of 0.92 mg ozanimod. You will continue regular treatment with one 0.92 mg capsule, once a day.
  If you have mild or moderate chronic liver problems, your doctor may need to reduce your 'maintenance' dose to one 0.92 mg capsule every other day.

Do not exceed the recommended dose.

How to take Zeposia
- Zeposia is for oral use.
- Swallow the capsule whole. There is no information about opening a capsule and releasing its content.
- You can take the capsule either with or without food.

If you have accidentally taken a higher dose, or if a child has accidentally swallowed some of this medicine, talk to a doctor or go to a hospital straight away. Take the medicine pack and this leaflet with you.

If you forget to take the medicine, take it as soon as you remember. However, if you forget the dose for the whole day, skip the forgotten dose and take the next dose at your usual time.
Do not take a double dose to make up for a forgotten dose.
- If you forget one or more doses during the first 14 days of starting treatment with Zeposia, talk to your doctor about how to re-start your treatment.

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

If you stop taking Zeposia
- Do not stop taking Zeposia without talking to your doctor first.
- Talk to your doctor about how to re-start your treatment if you have stopped taking Zeposia:
  - for 1 day or more during the first 14 days of treatment
  - for more than 7 consecutive days between day 15 and day 28 of treatment
  - for more than 14 consecutive days after day 28 of treatment.

You will need to start the 'treatment initiation pack' again.

Zeposia will stay in your body for up to 3 months after you stop taking it. Your white blood cell count (lymphocyte count) may also remain low during this time and the side effects described in this leaflet may still occur (see '*Side effects*' in section 4).

Tell your doctor straight away if you think your MS worsens after you have stopped treatment with Zeposia.

Do not take medicines in the dark! Check the label and dose every time 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
Like with all medicines, using the medicine Zeposia 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 or pharmacist immediately if you notice any of the serious side effects listed below:
- **Common side effects (affect 1-10 in 100 users):**
  - slow heart rate
  - urinary tract infection
  - increase in blood pressure
- **Uncommon side effects (affect 1-10 in 1,000 users):**
  - allergic reaction – the signs may include a rash
- **Rare side effects (affect 1-10 in 10,000 users):**
  - brain infection called progressive multifocal leukoencephalopathy (PML) (see section 2)

Other side effects
Tell your doctor or pharmacist if you notice any of the following side effects:
- **Very common side effects (affect more than 1 in 10 users):**
  - infections of the nose or nostrils, nasal cavity, mouth, throat (pharynx), or voice box (larynx) caused by viruses
  - low level of a type of white blood cell called lymphocytes
- **Common side effects (affect 1-10 in 100 users):**
  - inflammation of the throat (pharyngitis)
  - respiratory infection (sign of lung infection)
  - herpes zoster (shingles)
  - herpes simplex or cold sores (oral herpes)
  - headache
  - drop in blood pressure
  - swelling especially of the ankles and feet, due to fluid retention (peripheral oedema)
  - increased liver enzyme levels in blood tests (a sign of liver problems) or yellow pigmentation of the skin, mucus membranes or eyes (jaundice)
  - lung abnormalities which can cause breathlessness
- **Uncommon side effects (affect 1-10 in 1,000 users):**
  - blurred vision (macular oedema)

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.
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. date) which appears on the blister tray and carton. The expiry date refers to the last day of that month.
- Do not store above 25°C.
- Do not use this medicine if you notice any damage or signs of tampering with the pack.
- 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:
- *Capsule content:*
  Microcrystalline cellulose 112 or XLM 90, microcrystalline cellulose 105, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate.
- *Capsule shell:*
  - Each 0.23 mg capsule contains:
    Gelatine, titanium dioxide (E171), black iron oxide (E172), yellow iron oxide (E172), red iron oxide (E172).
  - Each 0.46 mg capsule contains:
    Gelatine, titanium dioxide (E171), yellow iron oxide (E172), black iron oxide (E172), red iron oxide (E172).
  - Each 0.92 mg capsule contains:
    Gelatine, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172).
- *Printing ink:*
  Shellac, dehydrated alcohol, black iron oxide, purified water, propylene glycol, strong ammonia solution, isopropyl alcohol, butyl alcohol, potassium hydroxide.

What the medicine looks like and contents of the pack
- The Zeposia 0.23 mg hard capsule has a light grey opaque cap and body imprinted in black ink with "OZA" on the cap and "0.23 mg" on the body.
- The Zeposia 0.46 mg hard capsule has an orange opaque cap and light-grey opaque body imprinted in black ink with "OZA" on the cap and "0.46 mg" on the body.
- The Zeposia 0.92 mg hard capsule has an orange opaque cap and body imprinted in black ink with "OZA" on the cap and "0.92 mg" on the body.

Pack sizes
- Treatment initiation pack is a 'wallet pack' containing 7 capsules: 4 capsules of 0.23 mg and 3 capsules of 0.46 mg.
- Maintenance pack containing 28 capsules of 0.92 mg.

Registration holder's name and address
Bristol-Myers Squibb (Israel) Ltd.,
18 Aharon Bart St., P.O Box 3361,
Kiryat Arye,
Petach Tikva

Manufacturer's name and address
Celgene Corporation
86 Morris Ave,
Summit, NJ, 07901, USA

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Registration number of the medicine in the Ministry of Health's National Drug Registry:
Zeposia® 0.23 mg: 167-33-36599
Zeposia® 0.46 mg: 167-34-36600
Zeposia® 0.92 mg: 167-35-36601