**Package leaflet: Information for the patient**

**Pemetrexed EVER Pharma 25 mg/ml concentrate for solution for infusion**
pemetrexed

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Pemetrexed EVER Pharma is and what it is used for

Pemetrexed EVER Pharma is a medicine used in the treatment of cancer. It contains the active substance pemetrexed. Pemetrexed belongs to a group of medicines known as folic acid analogues and disrupts processes that are essential for cells to divide.

Pemetrexed EVER Pharma is given in combination with cisplatin, another anti-cancer medicine, as treatment for malignant pleural mesothelioma, a form of cancer that affects the lining of the lung, to patients who have not received prior chemotherapy.

Pemetrexed EVER Pharma is also given in combination with cisplatin for the initial treatment of patients with advanced stage of lung cancer.

Pemetrexed EVER Pharma can be prescribed to you if you have lung cancer at an advanced stage if your disease has responded to treatment or it remains largely unchanged after initial chemotherapy.

Pemetrexed EVER Pharma is also a treatment for patients with advanced stage of lung cancer whose disease has progressed after other initial chemotherapy has been used.

## 2. What you need to know before you use Pemetrexed EVER Pharma

**Do not use Pemetrexed EVER Pharma**
- if you are allergic to pemetrexed or any of the other ingredients of this medicine (listed in section 6).
- if you are breast-feeding; you must discontinue breast-feeding during treatment with Pemetrexed EVER Pharma.
- if you have recently received or are about to receive a vaccine against yellow fever.

**Warnings and precautions**
Talk to your doctor or hospital pharmacist before receiving Pemetrexed EVER Pharma.

If you currently have or have previously had problems with your kidneys, talk to your doctor or hospital pharmacist as you may not be able to receive Pemetrexed EVER Pharma.
Before each infusion you will have samples of your blood taken to evaluate if you have sufficient kidney and liver function and to check that you have enough blood cells to receive Pemetrexed EVER Pharma. Your doctor may decide to change the dose or delay treating you depending on your general condition and if your blood cell counts are too low.
If you are also receiving cisplatin, your doctor will make sure that you are properly hydrated and receive appropriate treatment before and after receiving cisplatin to prevent vomiting.

If you have had or are going to have radiation therapy, please tell your doctor, as there may be an early or late radiation reaction with Pemetrexed EVER Pharma.

If you have been recently vaccinated, please tell your doctor, as this can possibly cause bad effects with Pemetrexed EVER Pharma.

If you have heart disease or a history of heart disease, please tell your doctor.

If you have an accumulation of fluid around your lungs, your doctor may decide to remove the fluid before giving you Pemetrexed EVER Pharma.

**Children and adolescents**
There is no relevant use of Pemetrexed EVER Pharma in the paediatric population

**Other medicines and Pemetrexed EVER Pharma**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicine for pain or inflammation (swelling), such as medicines called "nonsteroidal anti-inflammatory drugs" (NSAIDs), including medicines purchased without a doctor's prescription (such as ibuprofen). There are many sorts of NSAIDs with different durations of activity. Based on the planned date of your infusion of Pemetrexed EVER Pharma and/or on the status of your kidney function, your doctor needs to advise you on which medicines you can take and when you can take them. If you are unsure, ask your doctor or pharmacist if any of your medicines are NSAIDs.

Like other chemotherapy medicines Pemetrexed EVER Pharma is not recommended with live attenuated vaccines. Inactive vaccines should be used where possible

**Pregnancy**
If you are pregnant, think you may be pregnant or are planning to have a baby, tell your doctor. The use of Pemetrexed EVER Pharma should be avoided during pregnancy. Your doctor will discuss with you the potential risk of taking Pemetrexed EVER Pharma during pregnancy. Women must use effective contraception during treatment with Pemetrexed EVER Pharma and for 6 months after receiving the last dose.

**Breast-feeding**
If you are breast-feeding, tell your doctor. Breast-feeding must be discontinued during Pemetrexed EVER Pharma treatment.

**Fertility**
Men are advised not to father a child during and up to 3 months following treatment with Pemetrexed EVER Pharma and should therefore use effective contraception during treatment with Pemetrexed EVER Pharma and for up to 3 months afterwards. If you would like to father a child during the treatment or in the 3 months following receipt of treatment, seek advice from your doctor or pharmacist. Pemetrexed EVER Pharma can affect your ability to have children. Talk to your doctor to seek advice about sperm storage before starting your therapy.

**Driving and using machines**
Pemetrexed EVER Pharma may make you feel tired. Be careful when driving a car or using machines.

**Pemetrexed EVER Pharma contains sodium**
This medicine contains 96.6 mg sodium (main component of cooking/table salt) in each dose (500 mg pemetrexed for every square meter of your body's surface area). This is equivalent to 4.8 % of the recommended maximum daily dietary intake of sodium for an adult.

## 3. How to use Pemetrexed EVER Pharma

Pemetrexed EVER Pharma 25 mg/ml concentrate for solution for infusion will always be given to you by a healthcare professional. The dose of Pemetrexed EVER Pharma is 500 milligrams for every square metre of your body's surface area. Your height and weight are measured to work out the surface area of your body. Your doctor will use this body surface area to work out the right dose for you. This dose may be adjusted, or treatment may be delayed depending on your blood cell counts and on your general condition. A hospital pharmacist, nurse or doctor will have mixed the Pemetrexed EVER Pharma concentrate with 9 mg/ml (0.9 %) sodium chloride or 5 % glucose solution for injection before it is given to you.

You will always receive Pemetrexed EVER Pharma by infusion into one of your veins. The infusion will last approximately 10 minutes.

When using Pemetrexed EVER Pharma in combination with cisplatin:
The doctor or hospital pharmacist will work out the dose you need based on your height and weight. Cisplatin is also given by infusion into one of your veins and is given approximately 30 minutes after the infusion of Pemetrexed EVER Pharma has finished. The infusion of cisplatin will last approximately 2 hours.

You should usually receive your infusion once every 3 weeks.

Additional medicines:
Corticosteroids: your doctor will prescribe you steroid tablets (equivalent to 4 milligrams of dexamethasone twice a day) that you will need to take on the day before, on the day of, and the day after Pemetrexed EVER Pharma treatment. This medicine is given to you to reduce the frequency and severity of skin reactions that you may experience during your anticancer treatment.

Vitamin supplementation: your doctor will prescribe you oral folic acid (vitamin) or a multivitamin containing folic acid (350 to 1000 micrograms) that you must take once a day while you are receiving Pemetrexed EVER Pharma. You must take at least 5 doses during the seven days before the first dose of Pemetrexed EVER Pharma. You must continue taking the folic acid for 21 days after the last dose of Pemetrexed EVER Pharma. You will also receive an injection of vitamin B12 (1000 micrograms) in the week before administration of Pemetrexed EVER Pharma and then approximately every 9 weeks (corresponding to 3 courses of Pemetrexed EVER Pharma treatment). Vitamin B12 and folic acid are given to you to reduce the possible toxic effects of the anticancer treatment.

Your condition will be closely monitored during treatment. This routinely involves blood tests, including checks on your liver and kidney function. Your dose may be changed, or treatment delayed depending on results from these tests.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You must contact your doctor immediately if you notice any of the following:

- Fever or infection (common): if you have a temperature of 38°C or greater, sweating or other signs of infection (since you might have less white blood cells than normal which is very common). Infection (sepsis) may be severe and could lead to death

- If you start feeling chest pain (common) or having a fast heart rate (uncommon)

- If you have pain, redness, swelling or sores in your mouth (very common)

- Allergic reaction: if you develop skin rash (very common) / burning or prickling sensation (common), or fever (common). Rarely, skin reactions may be severe and could lead to death. Contact your doctor if you get a severe rash, or itching, or blistering (Stevens-Johnson Syndrome or Toxic epidermal necrolysis)

- If you experience tiredness, feeling faint, becoming easily breathless or if you look pale (since you might have less haemoglobin than normal which is very common)

- If you experience bleeding from the gums, nose or mouth or any bleeding that would not stop, reddish or pinkish urine, unexpected bruising (since you might have less platelets than normal which is very common)

- If you experience sudden breathlessness, intense chest pain or cough with bloody sputum (uncommon) (may indicate a blood clot in the blood vessels of the lungs)

Side effects with Pemetrexed EVER Pharma may include:

*Very common (may affect more than 1 in 10 people)*
- Infection
- Pharyngitis (a sore throat)
- Low number of neutrophil granulocytes (a type of white blood cell)
- Low white blood cells
- Low haemoglobin level
- Pain, redness, swelling or sores in your mouth
- Loss of appetite
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- Vomiting
- Diarrhoea
- Nausea
- Skin rash
- Flaking skin
- Abnormal blood test showing reduced functionality of kidneys
- Fatigue (tiredness)

*Common (may affect up to 1 in 10 people)*
- Blood infection
- Fever with low number of neutrophil granulocytes (a type of white blood cell)
- Low platelet count
- Allergic reaction
- Loss of body fluids
- Taste change
- Damage to the motor nerves which may cause muscle weakness and atrophy (wasting) primary in the arms and legs
- Damage to the sensory nerves that may cause loss of sensation, burning pain and unsteady gait
- Dizziness
- Inflammation or swelling of the conjunctiva (the membrane that lines the eyelids and covers the white of the eye)
- Dry eye

- Watery eyes
- Dryness of the conjunctiva (the membrane that lines the eyelids and covers the white of the eye) and cornea (the clear layer in front of the iris and pupil).
- Swelling of the eyelids
- Eye disorder with dryness, tearing, irritation, and/or pain
- Cardiac Failure (Condition that affects the pumping power of your heart muscles)
- Irregular heart rhythm
- Indigestion
- Constipation
- Abdominal pain
- Liver: increases in the chemicals in the blood made by the liver
- Increased skin pigmentation
- Itchy skin
- Rash on the body where each mark resembles a bullseye
- Hair loss
- Hives
- Kidney stop working
- Reduced functionality of kidney
- Fever
- Pain
- Excess fluid in body tissue, causing swelling
- Chest pain
- Inflammation and ulceration of the mucous membranes lining the digestive tract

*Uncommon (may affect up to 1 in 100 people)*
- Reduction in the number of red, white blood cells and platelets
- Stroke
- Type of stroke when an artery to the brain is blocked
- Bleeding inside the skull
- Angina (Chest pain caused by reduced blood flow to the heart)
- Heart attack
- Narrowing or blockage of the coronary arteries
- Abnormal heart rhythm
- Deficient blood distribution to the limbs
- Blockage in one of the pulmonary arteries in your lungs
- Inflammation and scarring of the lining of the lungs with breathing problems
- Passage of bright red blood from the anus
- Bleeding in the gastrointestinal tract
- Ruptured bowel
- Inflammation of the lining of the oesophagus
- Inflammation of the lining of the large bowel, which may be accompanied by intestinal or rectal bleeding (seen only in combination with cisplatin)
- Inflammation, oedema, erythema, and erosion of the mucosal surface of the oesophagus caused by radiation therapy
- Inflammation of the lung caused by radiation therapy

*Rare (may affect up to 1 in 1,000 people)*
- Destruction of red blood cells
- Anaphylactic shock (severe allergic reaction)
- Inflammatory condition of the liver
- Redness of the skin
- Skin rash that develops throughout a previously irradiated area

*Very rare (affect up to 1 of 10 000 people)*
- Infections of skin and soft tissues

- Stevens-Johnson syndrome (a type of severe skin and mucous membranes reaction that may be life threatening)
- Toxic epidermal necrolysis (a type of severe skin reaction that may be life threatening)
- Autoimmune disorder that results in skin rashes and blistering on the legs, arms, and abdomen
- Inflammation of the skin characterized by the presence of bullae which are filled with fluid
- Skin fragility, blisters and erosions and skin scarring
- Redness, pain and swelling mainly of the lower limbs
- Inflammation of the skin and fat beneath the skin (pseudocellulitis)
- Inflammation of the skin (dermatitis)
- Skin to become inflamed, itchy, red, cracked, and rough
- Intensely itchy spots

*Not known (frequency cannot be estimated from the available data)*
- Form of diabetes primarily due to pathology of the kidney
- Disorder of the kidneys involving the death of tubular epithelial cells that form the renal tubules

You might have any of these symptoms and/or conditions. You must tell your doctor as soon as possible when you start experiencing any of these side effects.

If you are concerned about any side effects, talk to your doctor.

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Website: www.hpra.ie
By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Pemetrexed EVER Pharma

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after 'EXP'. The expiry date refers to the last day of that month.

Do not freeze.

*Infusion Solution:* Chemical and physical in-use stability of infusion solution of pemetrexed was demonstrated for 28 days at refrigerated temperature (2 °C to 8 °C) and for 7 days at 20 °C to 30 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.
Pemetrexed EVER Pharma should not be used if there are any signs of particles.

This medicine is for single use only; any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 6. Contents of the pack and other information

**What Pemetrexed EVER Pharma contains**
The active substance is pemetrexed.

One ml of concentrate contains 25 mg pemetrexed (as pemetrexed disodium).

One vial of 4 ml concentrate contains 100 mg pemetrexed (as pemetrexed disodium)
One vial of 20 ml concentrate contains 500 mg pemetrexed (as pemetrexed disodium)
One vial of 40 ml concentrate contains 1000 mg pemetrexed (as pemetrexed disodium)

The other ingredients are trometamol, monothioglycerol, citric acid, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) and water for injections.

Further dilution by a healthcare provider is required prior to administration.

**What Pemetrexed EVER Pharma looks like and contents of the pack**
Pemetrexed EVER Pharma concentrate for solution for infusion is an aqueous, clear, slightly yellowish or yellow-greenish solution.

Pemetrexed EVER Pharma is provided in a colourless glass vial with rubber stopper and an aluminium cap with plastic flip-off. Vials may or may not be sheathed in a protective sleeve.

Each pack of Pemetrexed EVER Pharma contains one vial.

Pack sizes
1 x 4 ml vial (100 mg/4 ml)
1 x 20 ml vial (500 mg/20 ml)
1 x 40 ml vial (1000 mg/40 ml)

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
EVER Valinject GmbH
Oberburgau 3
4866 Unterach am Attersee
Austria

**Manufacturer**
EVER Pharma Jena GmbH
Otto Schott Str. 15
07745 Jena
Germany

EVER Pharma Jena GmbH
Brüsseler Str. 18
07747 Jena
Germany

This medicinal product is authorised in the Member States of the EEA under the following names:

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| AT | Pemetrexed EVER Pharma 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung |
| BE | Pemetrexed EVER Pharma 25 mg/ml concentraat voor oplossing voor infusie / solution à diluer pour perfusion / Konzentrat zur Herstellung einer Infusionslösung |
| CZ | Pemetrexed EVER Pharma 25 mg/ml koncentrát pro infuzní roztok |
| DE | Pemetrexed EVER Pharma 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung |
| DK | Pemetrexed EVER Pharma 25 mg/ml koncentrat til infusionsvæske, opløsning |
| ES | Pemetrexed EVER Pharma 25 mg/ml concentrado para solución para perfusión |
| FI | Pemetrexed EVER Pharma 25 mg/ml infuusiokonsentraatti, liuosta varten |

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| FR | Pemetrexed EVER Pharma 25 mg/ml, solution à diluer pour perfusion |
| HR | Pemetrexed EVER Pharma 25 mg/ml koncentrat za otopinu za infuziju |
| HU | Pemetrexed EVER Pharma 25 mg/ml koncentrátum oldatos infúzióhoz |
| IE | Pemetrexed EVER Pharma 25 mg/ml concentrate for solution for infusion |
| IT | Pemetrexed EVER Pharma 25 mg/ml concentrato per soluzione per infusione |
| NL | Pemetrexed EVER Pharma 25 mg/ml concentraat voor oplossing voor infusie |
| NO | Pemetrexed EVER Pharma 25 mg/ml konsentrat til infusjonsvæske, oppløsning |
| PL | Pemetrexed EVER Pharma 25 mg/ml koncentrat do sporządzania roztworu do infuzji |
| PT | Pemetrexed EVER Pharma 25 mg/ml **Concentrado para solução para perfusão** |
| RO | Pemetrexed EVER Pharma 25 mg/ml concentrat pentru soluţie perfuzabilă |
| SE | Pemetrexed EVER Pharma 25 mg/ml koncentrat till infusionsvätska, lösning |
| SI | Pemetreksed EVER Pharma 25 mg/ml koncentrat za raztopino za infundiranje |
| SK | Pemetrexed EVER Pharma 25 mg/ml infúzny koncentrát |

**This leaflet was last revised in 07/2023**.

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The following information is intended for medical and healthcare professionals only:
Please refer to SmPC for full information.
Pregnant personnel should not handle this medicine.

Instructions for use, handling and disposal
1. Use aseptic techniques during dilution of pemetrexed for intravenous infusion administration.

2. Calculate the dose and the number of Pemetrexed EVER Pharma vials needed.

3. The appropriate volume of Pemetrexed EVER Pharma must be further diluted to 100 ml with 9 mg/ml (0.9 %) sodium chloride or 5 % glucose solution for injection, without preservative, and administered as an intravenous infusion over 10 minutes.

4. Pemetrexed infusion solutions prepared as directed above are compatible with polyvinyl chloride and polyolefin lined administration sets and infusion bags. Pemetrexed is incompatible with diluents containing calcium, including lactated Ringer's Injection and Ringer's Injection.
Pemetrexed EVER Pharma contains trometamol as an excipient. Trometamol is incompatible with cisplatin resulting in degradation of cisplatin. This medicinal product must not be mixed with other medicinal products. Intravenous lines should be flushed after administration of Pemetrexed EVER Pharma.

5. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.

6. Pemetrexed solutions are for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

Preparation and administration precautions
As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of pemetrexed infusion solutions. The use of gloves is recommended. If a pemetrexed solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If

pemetrexed solutions contact the mucous membranes, flush thoroughly with water. Pemetrexed is not a vesicant. There is not a specific antidote for extravasation of pemetrexed. There have been a few reported cases of pemetrexed extravasation, which were not assessed as serious by the investigator. Extravasation should be managed by local standard practice as with other non-vesicants.