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

Pemazyre 4.5 mg tablets
Pemazyre 9 mg tablets
Pemazyre 13.5 mg tablets

Active ingredient and its quantity:

Each tablet of Pemazyre 4.5 mg contains 4.5 mg of pemigatinib.

Each tablet of Pemazyre 9 mg contains 9 mg of pemigatinib.

Each tablet of Pemazyre 13.5 mg contains 13.5 mg of pemigatinib.

For inactive and allergenic ingredients in the preparation – 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 to treat your illness. Do not pass it on to others. It may harm them, even if it seems to you that their illness is similar to yours.

1. What is the medicine intended for?

Pemazyre is indicated to treat adults with bile duct cancer that has spread to other parts of the body or cannot be removed by surgery and after treatment with other medicine
Pemazyre can only be used if a test has shown that cancer cells have an abnormal form of the FGFR2 protein.
Therapeutic group: Antineoplastic agents, tyrosine kinase inhibitors
Pemazyre contains the active substance pemigatinib, which belongs to a group of cancer drugs called tyrosine kinase inhibitors. It blocks the action of proteins in the cell called fibroblast growth factor receptor types 1,2 and 3 (FGFR1, FGFR2, and FGFR3) which help regulate cell growth. Cancer cells may have an abnormal form of this protein. By blocking FGFR, pemigatinib can prevent the growth of such cancer cells.

2. Before using the medicine

Do not use this medicine if:

- You are sensitive (allergic) to the active substance (pemigatinib) or to any of the other ingredients in this medicine (see section 6 "Additional information").
- You are using St John's wort (Hypericum), a medicine to treat depression

Special warnings about using this medicine

Before taking Pemazyre talk to your doctor if:

- You have been told that you have an increase or decrease of a mineral in your blood called phosphorus
- You have vision or eye problems
- You have severely reduced liver function. Your treatment may need to be adjusted
- You have severely reduced kidney function. Your treatment may need to be adjusted
- You have cancer cells that have spread into the brain or spinal cord

Pemazyre may harm the unborn baby. An effective contraception must be used during treatment and for at least 1 week after the last dose of Pemazyre in women of childbearing age and in men with women partners of childbearing age.

Children and adolescents

This medicine is not intended for children and adolescents under 18 years.

There is no information on the safety and efficacy of this medicine in children and adolescents under 18 years old.

Tests and follow-up

Eye examinations are recommended:

- before starting treatment with Pemazyre
- every 2 months for the first 6 months of treatment
- every 3 months thereafter or immediately if any visual symptoms occur, including flashes of light, visual disturbances or dark spots.

Tell your doctor straight away if you get any symptoms with your vision.

You should also use lubricating or hydrating eye drops or gels to help prevent or treat dry eyes.

Your healthcare professional will do blood tests to check levels of phosphate in your blood. If your levels are too high or too low, you may need to:

- change the amount of phosphate you eat in your diet
- change your dose of Pemazyre, or
- start or stop taking other medications that affect the amount of phosphate in your blood.

Interactions/Drug interactions

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines, including non-prescription medications and nutritional supplements.

Especially inform the doctor or pharmacist if you are taking the following medicines:

- St John's wort - a medicine to treat depression. You must not take St John's wort during treatment with Pemazyre.
- medicines with active substance names ending with "prazole" that are used to reduce the release of stomach acid. Avoid using these medicines during treatment with Pemazyre
- itraconazole - a medicine to treat fungal infections
- rifampicin - a medicine to treat tuberculosis or certain other infections
- carbamazepine, phenytoin, phenobarbital, primidone- medicines to treat epilepsy
- efavirenz - medicine to treat HIV infection
- ifosfamide or cyclophosphamide - other medicines to treat cancer
- methadone - a medicine to treat severe pain or for managing addiction

- digoxin - a medicine to treat heart disease
- dabigatran - a medicine to prevent blood clots
- colchicine - a medicine to treat gout attacks

Pemazyre with food and drink

Avoid eating grapefruit or drinking grapefruit juice while using this medication

Pregnancy, breastfeeding, and fertility

If you are pregnant, breast-feeding, think you may be pregnant or are planning to have a baby, tell your doctor before taking this medicine.

Pregnancy

Based on the findings from animal studies and mechanism of action of the medicine Pemazyre may cause harm to the fetus when given to a pregnant woman. There is no information available regarding pregnant women and the risk related to the medicine

Women who can get pregnant need:

- Perform a pregnancy test before initiating treatment
- Use effective contraception during treatment and for at least 1 week after the last dose of Pemazyre.
- Talk to your doctor about the most suitable contraception for you.
- Tell your doctor immediately if you become pregnant during Pemazyre treatment.

In male patients whose partner may become pregnant, effective contraception should be used during treatment with pemigatinib and for at least 1 week after the last dose of Pemazyre.

Breastfeeding

It is not known whether Pemazyre or its metabolites pass into breast milk. It is also unclear whether it effects the breastfeeding baby, or it affects breast milk production. There is a risk of severe side effects to the breastfeeding baby. Consequently, breastfeeding should be discontinued while taking the medicine, nor for at least one week after taking the last dose of the medicine.

Driving and using machines

Pemazyre has moderate influence on the ability to drive and use machines. Adverse reactions such as fatigue and visual disturbances have been associated with Pemazyre, therefore, care must be taken when driving and using machines. Do not drive or using machines if you feel tired or have visual disturbances.

3. How to use this medicine?

Always use the preparation according to your doctor's instructions.
Check with your doctor or pharmacist if you are not sure about the dosage or treatment regimen of the preparation.
The dosage and treatment regimen will be determined by the doctor only.

Pemazyre treatment should be started by a doctor who is experienced in the diagnosis and treatment of bile duct cancer.
The recommended dose is:
1 tablet of 13.5 mg taken once daily for 14 days, followed by 7 days without taking Pemazyre.
Treatment is continued with the same pattern of 14 days of Pemazyre once daily, followed by 7 days off therapy. Do not take Pemazyre during the 7 days off therapy. Your doctor will adjust the dose or stop treatment if needed.

Do not exceed the recommended dose.

Treatment duration:
Take Pemazyre for as long as it is prescribed by the attending doctor.

Method of administration:

Swallow the tablet whole with one glass of water at the same time every day. Pemazyre may be taken with food or between meals.
Do not crush, chew, split or dissolve the tablets.

If you have accidentally taken a higher dose or if a child has accidentally swallowed the medicine, proceed immediately to a doctor or a hospital emergency room and bring the package of the medicine with you.

If you forget to take this medicine at the scheduled time
If you miss a dose of Pemazyre by 4 hours or more, or if you vomit after taking Pemazyre, do not take another tablet to make up for the missed dose. Take your next dose of Pemazyre at the scheduled time.

Treatment should be continued as recommended by your doctor**.**
Even if there is an improvement in your health, do not stop treatment with the medicine without consulting with your doctor, this could reduce the success of therapy.

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

If you have any further questions regarding the use of the medicine, consult a doctor or pharmacist.

4. <u>Side effects</u>

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

Seek medical attention immediately if you have any of the serious side effects below that could appear with the following frequency:

Very common side effects (<u>occur in more than one in ten users</u>):

- low sodium in blood- symptoms include decreased concentration, headache, nausea, poor balance, confusion, seizures, coma.
- blood tests showing increase of creatinine, which can suggest kidney problems. Usually raised creatinine does not cause symptoms, but symptoms of kidney problems may include nausea and changes in urination.

Other side effects could appear with the following frequency:

Very common side effects (occur in more than one in ten users):

- high or low phosphate levels seen in blood tests
- taste disturbance
- dry eye
- nausea
- inflammation of the inner lining of the mouth
- diarrhoea
- constipation
- dry mouth
- skin reactions with redness, swelling and pain on palms of the hands and soles of the feet, called hand-foot syndrome
- nail toxicity, including nails separating from the nail bed, nail pain, nail bleeding, breaking of the nails, colour or texture changes in your nails, infected skin around the nail
- hair loss
- dry skin
- joint pain
- fatigue

Common side effects (occur in 1-10 in 100 users):

- fluid build-up under the retina (the light-sensitive layer at the back of the eye)
- inflammation of the cornea (the clear outer layer of the eye)
- reduced vision
- eyelash changes including abnormally long eyelashes, ingrown eyelashes
- abnormal hair growth

Uncommon (occur in up to 1 in 100 users)

- deposition of calcium salts that appears as hard papules, nodules, or plaques in or under the skin in any area of the body and can cause pain and ulcers.

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 the following link:
https://sideeffects.health.gov.il

5. How to store the medicine?

- Avoid poisoning! This medicine and any other medicine should be kept in a closed place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting without explicit instructions from the 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 30°C.

Do not throw away any medicines 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:
Microcrystalline cellulose, sodium starch glycolate, magnesium stearate.

What the medicine looks like and contents of the pack:

Pemazyre 4.5 mg tablets are round, white to off-white, debossed on one side with “I” and “4.5” on the reverse.

Pemazyre 9 mg tablets are oval, white to off-white, debossed on one side with “I” and “9” on the reverse.
Pemazyre 13.5 mg tablets are round, white to off-white, debossed on one side with “I” and “13.5” on the reverse.

The tablets are provided in blisters containing 14 tablets.
The carton contains 14 tablets.

Registration holder’s name and address:
Medison Pharma Ltd., 10 Hashiloach St., Petach Tikva.

Manufacturer’s name and address:
Incyte Biosciences International Sàrl.
Rue Docteur – Yersin 12, 1110 Morges, Switzerland

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Registration number of the medicine in the Ministry of Health’s National Drug Registry:

169-74-36995-99, 169-75-36996-99, 169-76-36997-99