

Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed with a doctor's prescription only

Fruzaqla™ 1 mg

Fruzaqla™ 5 mg

Hard capsules

Each capsule of Fruzaqla 1 mg contains 1 mg of the active ingredient fruquintinib.

Each capsule of Fruzaqla 5 mg contains 5 mg of the active ingredient fruquintinib.

Inactive ingredients and allergens in this medicine: see section 2 under 'Important information about some of this medicine's ingredients', and section 6 ('Additional information') in this leaflet.

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 this medicine intended for?

Fruzaqla is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with:

- fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy
- an anti-VEGF (vascular endothelial growth factor) therapy
- an anti-EGFR (epidermal growth factor receptor) therapy if RAS wild-type and medically appropriate.

Therapeutic group: Antineoplastic agents, tyrosine kinase inhibitors of vascular endothelial growth factor receptor (VEGFR).

2. Before using this medicine

Do not use this medicine if:

You are sensitive (allergic) to the active ingredient fruquintinib or to any of the other ingredients in this medicine (listed in section 6).

Special warnings about using this medicine

Before treatment with Fruzaqla, tell your doctor about your medical condition, and also if:

- You have high blood pressure.
- You have bleeding problems.
- You have an infection.
- You have liver or kidney problems.
- You plan to have surgery or have had recent surgery. You should stop taking Fruzaqla at least 2 weeks before your planned surgery. Your doctor will tell you when you can start taking Fruzaqla again after the surgery.
- You have recently had a blood clot, stroke, or heart attack.
- You are allergic to tartrazine (FD&C Yellow No. 5) or sunset yellow FCF (FD&C Yellow No. 6).

- You are pregnant or plan to become pregnant – see section ‘Pregnancy, Breastfeeding and Fertility’.
- You are breastfeeding or plan to breastfeed – see section ‘Pregnancy, Breastfeeding and Fertility’.
- You are taking blood thinners (anticoagulants).

Children and adolescents

Fruzaqla is intended for use in adults; it is not known if Fruzaqla is safe and effective in children and adolescents. The safety and efficacy of the medication in patients under the age of 18 have not been studied.

Tests and follow-up

A pregnancy test should be performed before starting treatment with Fruzaqla - see section ‘Pregnancy, Breastfeeding and Fertility’.

The doctor will check your blood pressure before starting treatment with Fruzaqla, once a week during the first month of treatment, and then at least once a month or more frequently if needed during treatment.

Your doctor will conduct blood tests before and during treatment with Fruzaqla to check for liver issues.

Your doctor will check for protein in your urine before starting treatment with Fruzaqla and during the treatment.

Interactions with other medicines

If you are taking, have recently taken or might take other medicines, including nonprescription medicines and dietary supplements, tell your doctor or pharmacist. Particularly if you are taking blood thinners (anticoagulants).

Medicines that greatly accelerate the clearance of Fruzaqla from the body may reduce its effectiveness (e.g. rifampin). Concomitant use should be avoided. If possible, avoid concomitant use of medicines that may also affect the efficacy of Fruzaqla (e.g. efavirenz).

Using this medicine and food

Fruzaqla can be taken with or without food.

Pregnancy, Breastfeeding and Fertility

Pregnancy

Fruzaqla can harm your unborn baby. You should not become pregnant during treatment with Fruzaqla.

Women who can become pregnant:

- A pregnancy test should be performed before starting treatment with Fruzaqla.
- Use effective contraception during treatment and for 2 weeks after your last dose of Fruzaqla.
- Tell your doctor right away if you become pregnant during treatment with Fruzaqla.

Men with female partners who can become pregnant:

- Use effective contraception during treatment and for 2 weeks after your last dose of Fruzaqla.
- Tell your doctor right away if your partner becomes pregnant during your treatment with Fruzaqla.

Breastfeeding

It is not known if Fruzaqla passes into breast milk. Do not breastfeed during treatment and for 2 weeks after your last dose of Fruzaqla.

Fertility

Fruzaqla may cause fertility problems in females, which may affect your ability to have children. Talk to your doctor if you have concerns about fertility.

Driving and using machines

Fruzaqla has a minor effect on your ability to drive and use machines. You may feel tired after taking Fruzaqla. Do not drive or use any tools or machines if you experience symptoms that affect your ability to concentrate and react.

Important information about some of this medicine's ingredients

Fruzaqla 1 mg contains colorants which may cause allergic reactions: tartrazine (FD&C Yellow No. 5/E102) and sunset yellow FCF (FD&C Yellow No. 6/E110) - see also section 'Side effects'.

Fruzaqla 5 mg contains colorants which may cause allergic reactions: allura red AC (FD&C Red 40) - see also section 'Side effects'.

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.

Your doctor may change your dose, temporarily stop, or permanently stop treatment with Fruzaqla if you have certain side effects. **Do not** change your dose or stop taking Fruzaqla unless your doctor tells you to do so.

Only your doctor will determine your dose and how you should take this medicine.

The recommended dosage is usually: Fruzaqla once a day for 21 days (3 weeks) and then a break for 7 days (1 week). This is one treatment cycle. Repeat this cycle for as long as your doctor tells you.

Take Fruzaqla about the same time each day, with or without food, and swallow the capsule whole.

Do not chew, dissolve, or open the capsules, as the potential effects of not taking the capsule whole are not known.

If you have, or think you might have difficulty swallowing capsules whole, talk to your doctor before starting treatment.

Do not exceed the recommended dose.

If you have accidentally taken a higher dose

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 Fruzaqla

If you forget to take a dose of Fruzaqla, you can take the forgotten dose within 12 hours on the same day. If more than 12 hours have passed, take your regularly scheduled dose the next day at the usual time.

Do not take a double dose to make up for the forgotten dose.

Do not take another dose if you vomit after taking Fruzaqla. Take your regularly scheduled dose the next day at the usual time.

Adhere to the treatment as recommended by your doctor.

Even if your health improves, do not stop taking this medicine without consulting your doctor.

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

As with any medicine, using Fruzaqla may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

Fruzaqla may cause serious side effects, including:

- **High blood pressure (hypertension). Very Common side effect (occurs in more than 1 out of 10 users):** Fruzaqla may cause hypertension that may be severe. Your doctor may prescribe medicine to treat your high blood pressure if needed. **Tell your doctor if you get any of the following symptoms** of hypertension during treatment:
 - severe headache
 - lightheadedness or dizziness
 - confusion
 - changes in vision
 - chest pain
 - difficulties breathing
 - nosebleeds
 - vomiting
- **Severe bleeding (hemorrhage). Common side effect (occurs in 1-10 out of 100 users):** Fruzaqla can cause bleeding that may be serious and may lead to death. **Tell your doctor if you experience any of the following symptoms** of bleeding during treatment:
 - unusual, severe bleeding, or bleeding that will not stop
 - bruising
 - lightheadedness
 - vomiting blood or vomit that looks like coffee grinds
 - blood in the stool or black stool that looks like tar
 - blood in the urine or urine that looks red, pink or brown
 - coughing up blood or blood clots
 - menstrual bleeding that is heavier than normal
 - unusual vaginal bleeding
 - nosebleeds that happen often
- **Infections. Very common side effect (occurs in more than 1 out of 10 users):** Fruzaqla can increase the risk of infections, including serious infections that may lead to death. The most common infections with Fruzaqla occurred in the urinary tract, nose or throat, and lungs. **Tell your doctor if you experience any of the following symptoms** of infection during treatment:

- fever
 - severe cough with or without an increase in mucus (sputum) production
 - severe sore throat
 - trouble breathing
 - burning or pain when you urinate
 - redness, swelling or pain in any part of the body
- **A tear in the stomach or intestinal wall (gastrointestinal perforation). Common side effect (occurs in 1-10 out of 100 users):** Fruzaqla can cause gastrointestinal perforation that may be serious and may lead to death. **Tell your doctor right away if you experience any of the following symptoms** of gastrointestinal perforation during treatment:
 - severe abdominal pain or abdominal pain that does not go away
 - vomiting or vomiting blood
 - nausea
 - blood in the stool or black stool that looks like tar
 - fever or chills
- **Intestinal blockage (intestinal obstruction). Common side effect (occurs in 1-10 out of 100 users).**
- **Liver problems. Very common side effect (occurs in more than 1 out of 10 users):** Elevation of liver enzymes in the blood is very common with Fruzaqla and can also be severe and may lead to death. **Tell your doctor if you experience any of the following symptoms** of liver problems during treatment:
 - yellowing of the skin or the white part of the eyes
 - dark colored (tea colored) urine
 - pain in the right upper area of the abdomen(stomach)
 - loss of appetite
 - nausea or vomiting
 - bleeding or bruising
- **Protein in the urine (proteinuria). Very common side effect (occurs in more than 1 out of 10 users):** Protein in the urine is very common with Fruzaqla and can also be severe. **Tell your doctor if** you have to urinate more than usual, or if you experience swelling of your face, hands, arms, legs, or feet during treatment.
- **Hand-foot skin reactions (Palmar-Plantar Erythrodysesthesia [PPE]). Very common side effect (occurs in more than 1 out of 10 users):** Hand-foot skin reactions are very common with Fruzaqla and can also be severe. **Tell your doctor if** you experience a severe rash or redness, pain, blisters, bleeding, or swelling on the palms of your hands or soles of your feet during treatment.
- **Posterior Reversible Encephalopathy Syndrome (PRES). Uncommon side effect (occurs in 1-10 out of 1,000 users):** PRES is a serious condition that can happen in your brain during treatment with Fruzaqla. **Tell your doctor right away if** you experience any of the following symptoms during treatment:

- headache
 - seizures
 - confusion
 - changes in vision
 - thinking problems
- **Wound healing problems. Uncommon side effect (occurs in 1-10 out of 1,000 users):** Wounds may not heal properly during treatment with Fruzaqla. **Tell your doctor if** you plan to have any surgery before starting Fruzaqla or during treatment.
 - You should stop taking Fruzaqla at least 2 weeks before the planned surgery.
 - Your doctor will tell you when you can start taking Fruzaqla again after the surgery.
 - **Blood clots in the blood vessels (arteries). Uncommon side effect (occurs in 1-10 out of 1,000 users):** Fruzaqla may cause blood clots or blockage in the blood vessels that may lead to heart attack, stroke, or death. **Get medical help right away if** you experience any of the following symptoms during treatment:
 - severe chest pain or pressure
 - pain in the arms, legs, back, neck or jaw
 - shortness of breath
 - numbness or weakness of the face, arm or leg, especially on one side of the body
 - feeling lightheaded or faint
 - sweating more than usual
 - sudden confusion, difficulties speaking or understanding things
 - difficulties walking
 - sudden severe headache
 - sudden vision changes in one or both eyes
 - dizziness, or loss of balance or coordination
 - **Multiple organ dysfunction. Uncommon side effect (occurs in 1-10 out of 1,000 users).**
 - **Allergic reactions to FD&C Yellow No. 5 and FD&C Yellow No. 6.** Fruzaqla 1 mg contains the inactive ingredients tartrazine (FD&C Yellow No. 5) and sunset yellow FCF (FD&C Yellow No. 6). Tartrazine may cause allergic reactions (including bronchial asthma) in certain people, especially people who also have an allergy to aspirin. Sunset yellow FCF can also cause allergic reactions. **Tell your doctor if** you experience hives, rash, or difficulties breathing during treatment with Fruzaqla.

Other side effects

Tell your doctor, pharmacist or nurse if you experience any of the following side effects:

- **Very common side effects (occur in more than 1 out of 10 users) of Fruzaqla include:**
 - weakness, lack of strength and energy, and feeling very tired or sleepy (asthenia)
 - voice changes or hoarseness

- painful or dry mouth, mouth sores or ulcers (stomatitis)
- stomach-area (abdominal) pain
- reduced activity of the thyroid gland (hypothyroidism), which may cause tiredness, weight gain and skin and hair changes
- diarrhea
- joint pain (arthralgia), bone and muscle pain
- blood tests showing increased levels of the following: triglycerides, cholesterol, aspartate aminotransferase, alanine aminotransferase (ALT), bilirubin, alkaline phosphatase, Activated Partial Thromboplastin Time (aPTT), creatinine, glucose, uric acid.
- blood tests showing decreased levels of the following: albumin, sodium, magnesium, lymphocytes, platelets, calcium, potassium, hemoglobin.
- **Common side effects (occur in 1-10 out of 100 users) of Fruzaqla include:**
 - anal pain (proctalgia)
 - abnormal connection between two parts of your gastrointestinal tract (fistula)
 - increase in pancreatic enzymes
- **Uncommon side effects (occur in 1-10 out of 1,000 users):**
 - pancreatitis

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 'Reporting Side Effects of Drug Treatment' link on the Ministry of Health home page (www.health.gov.il), which opens an online form for reporting side effects, or 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 your 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 at a temperature below 30°C.

Store in the original package to protect from moisture.

Keep the bottle tightly closed.

Do not remove the desiccant from the bottle.

Safely discard any unused medicine.

6. Additional information

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

microcrystalline cellulose or cellulose, microcrystalline (PH-101); corn starch or maize starch, and talc.

The 1 mg capsule shell contains: Gelatin; Titanium dioxide/E171; Tartrazine - FD&C Yellow 5/E102; Sunset yellow FCF - FD&C Yellow 6/E110

The 5 mg capsule shell contains: gelatin; titanium dioxide/E171; brilliant blue FCF FD&C blue 1/E133, allura red AC-FD&C red 40/E129.

Ink content: shellac/dewaxed shellac/E904; dehydrated alcohol/ethanol anhydrous; isopropyl alcohol; butyl alcohol/butanol; propylene glycol/E1520; purified water; strong ammonia solution/ammonia solution, concentrated; potassium hydroxide; ferrosferric oxide/iron oxide black/E172;

What the medicine looks like and contents of the pack:

Fruzaqla 1 mg – A size 3 hard gelatin capsule with a yellow opaque cap and white opaque body, imprinted with 'HM013' over '1 mg' on the capsule body in black ink.

Fruzaqla 5 mg – A size 1 hard gelatin capsule with a red opaque cap and white opaque body, imprinted with 'HM013' over '5 mg' on the capsule body in black ink.

Each carton package contains 21 hard capsules and a desiccant.

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

Registration numbers of the medicine in the Ministry of Health National Drug Registry:

Fruzaqla 1 mg: 178-41-37922-99

Fruzaqla 5 mg: 178-42-37923-99

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