Package leaflet: Information for the patient
Fluorouracil 50 mg/ml Solution for Injection or Infusion
fluorouracil

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 or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See Section 4.

What is in this leaflet

1. What Fluorouracil Injection is and what it is used for

The name of your medicine is 'Fluorouracil 50 mg/ml Solution for Injection or Infusion' but in the rest of the leaflet it will be called 'Fluorouracil Injection'.

What Fluorouracil Injection is
Fluorouracil Injection contains the active ingredient Fluorouracil. It is an anti-cancer medication. It is part of chemotherapy.

What Fluorouracil Injection is used for
Fluorouracil Injection is used to treat many common cancers, particularly cancers of the large bowel, oesophagus, pancreas, stomach, head and neck and breast. It may be used in combination with other anti-cancer medicines or radiotherapy.

You must talk to a doctor if you do not feel better or if you feel worse.

2. What you need to know before you use Fluorouracil Injection

Do not use Fluorouracil Injection
- if you are allergic to fluorouracil or any of the other ingredients of this medicine (listed in section 6).
- if you are in a seriously weakened state due to long illness
- if you have a serious infection (e.g. chickenpox or shingles)
- if your cancer is non-malignant
- if your bone marrow has been damaged by other cancer treatments (including radiotherapy)
- if you are taking brivudine, sorivudine or their chemically related analogues (antiviral drugs). Fluorouracil must not be taken within 4 weeks of treatment with brivudine, sorivudine or their chemically related analogues.
- if you are breast feeding
- if you have serious liver disease
- if you are homozygotic for dihydropyrimidine dehydrogenase (DPD) enzyme
- if you have reduced activity/deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD)

Tell your doctor if any of the above applies to you before this medicine is used.

Warnings and precautions
Talk to your doctor or pharmacist or nurse before using Fluorouracil Injection. Take special care with Fluorouracil Injection:
- if your bone marrow is not producing blood cells normally (your doctor will do a blood test to check this)

- if you have any problems with your kidneys
- if you have any problems with your liver including jaundice (yellowing of the skin)
- if you have suffered from angina (chest pain) or have a history of heart disease, as you may be more likely to have an attack of angina or a heart attack, or show signs of heart problems when you take an ECG test
- if you have had high-dose radiation treatment to the pelvis.
- if tumours have spread (metastasised) into your bone marrow
- if you are in generally poor health and have lost a lot of weight
- if you have had surgery within the last 30 days.
- if you have gastrointestinal (GI) side effects (oral ulceration (stomatitis), diarrhoea, bleeding from the G.I. tract) or hemorrhage at any site.
- if you know that you have a partial deficiency in the activity of the enzyme dihydropyrimidine dehydrogenase (DPD)
- if you have problems with your heart. Tell your doctor if you experience any chest pain during treatment.
- if you have a family member who has partial or complete deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD)

DPD deficiency: DPD deficiency is a genetic condition that is not usually associated with health problems unless you receive certain medicines. If you have DPD deficiency and take Fluorouracil Injection, you are at an increased risk of severe side effects (listed under section 4 Possible side effects). It is recommended to test you for DPD deficiency before start of treatment. If you have no activity of the enzyme you should not take Fluorouracil Injection. If you have a reduced enzyme activity (partial deficiency) your doctor might prescribe a reduced dose. If you have negative test results for DPD deficiency, severe and life-threatening side effects may still occur.

Contact your doctor immediately if you are concerned about any of the side effects or if you notice any additional side effects not listed in the leaflet (see section 4 Possible side effects).

Contact your healthcare provider immediately, if you experience the following signs or symptoms: new onset of confusion, disorientation, or otherwise altered mental status, difficulty with balance or coordination, visual disturbances. These could be signs of encephalopathy which can lead to coma and death, if left untreated.

Tell your doctor if any of the above applies to you before this medicine is used.
Fluorouracil can cause sensitivity to sunlight. This may result in increased skin reactions. To prevent this you must try to stay out of direct sunlight as much as possible while using it and must not use a sunlamp or sun bed.

Exposure to UV-radiation (e.g. natural sunlight, tanning salon) should be avoided.

Fluorouracil treatment may increase the likelihood of necrosis (death of tissue or skin) caused by radiation following radiotherapy.

The administration of fluorouracil has been associated with the occurrence of hand-foot syndrome, characterised as a tingling sensation of hands and feet, which may progress over a few days to pain when holding objects or walking. The palms and soles become swollen and tender.

Other medicines and Fluorouracil Injection
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
Special care is needed if you are taking/using other medicines as some could interact with Fluorouracil Injection:
- Methotrexate, cyclophosphamide, cisplatin, vinorelbine (anti-cancer medicines)
- Metronidazole (an antibiotic)
- Folinic acid (also called calcium folinate or calcium leucovorin - used to reduce the harmful effects of anti-cancer medicines)
- Allopurinol (used to treat gout)
- Cimetidine (used to treat stomach ulcers)
- Warfarin (used to treat blood clots)
- Interferon alpha (used in treatment of lymphomas and chronic hepatitis)
- Brivudine, sorivudine or their chemically related analogues (anti-viral drugs)
- Phenytoin (used to control epilepsy/fits and also irregular heart rhythm)
- Live vaccines should be avoided as these could cause serious or fatal infections. Contact should be avoided with people who have recently been treated with polio virus vaccine. Killed or inactivated vaccines may be administered; however, the response may be impaired

- Radiation therapy
- Levamisol (medicine used to treat worm infection)
- Tamoxifen (used in some types of breast cancer)
- Clozapine (used in some psychiatric disorders)

Please tell your doctor or pharmacist if you are taking or have recently taken these or any other medicines, including medicines obtained without a prescription.

Pregnancy, breast-feeding and fertility

Pregnancy

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.

Fluorouracil should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. If pregnancy occurs during your treatment you must inform your doctor and should use genetic counselling.

Women must avoid becoming pregnant and use a highly effective method of contraception during treatment with Fluorouracil and for at least 6 months afterwards.

Breast-feeding

Since it is not known whether fluorouracil passes into breast milk, breast-feeding must be discontinued before treatment with Fluorouracil Injection.

Ask your doctor for advice before taking any medicine.

Fertility

Men treated with Fluorouracil are advised not to father a child during and for up to 3 months following the end of treatment. Men and women should both seek advice on fertility such as conservation of eggs or sperm before treatment because of the possibility of irreversible infertility due to the therapy.

Driving and using machines

Do not drive or use machines because fluorouracil may produce side effects like nausea and vomiting. It can also produce adverse event on your nervous system and visual changes. If you experience any of this effect, do not drive or use any tools or machines, it may impair your ability to drive or use machines.

Fluorouracil Injection contains sodium

Fluorouracil injection contains 7.78 mmol (178.2 mg) of sodium per maximum daily dose (600 mg/m^2). This should be taken into consideration by patients on a controlled sodium diet.

3. How to use Fluorouracil Injection

Recommended Dose

Your doctor will work out the correct dose of Fluorouracil Injection for you and how often it must be given.

The dose of medicine given to you will depend on your medical condition, your body weight, if you have had recent surgery and how well your bone marrow, liver and kidneys are working. Your first course of treatment may be given daily or at weekly intervals. Further courses may be given according to your response to treatment. You may also receive treatment in combination with radiotherapy.

Fluorouracil is not recommended for use in children due to insufficient data on safety and efficacy.

The medicine may be diluted with glucose solution, sodium chloride solution or Water for injections before it is given to you. It will be given into a vein either as a normal injection or a slow injection via a drip (infusion).

If you are given more Fluorouracil Injection than you should

As this medicine will be given to you by a doctor or nurse, it is unlikely that you will be given too little or too much, however, tell your doctor or nurse if you have any concerns.

You will need to have blood tests during and after treatment with Fluorouracil Injection to check the levels of cells in your blood. Treatment may have to be stopped if the level of white blood cells drops too low.
Nausea, vomiting, diarrhoea, severe mucositis and gastrointestinal ulceration and bleeding may occur if you have too much fluorouracil. If you have any further question on the use of this product ask your doctor.

If you forget to use Fluorouracil Injection
Do not take a double dose to make up for a forgotten dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
If any of the following happen, tell your doctor immediately:
- severe allergic reaction – you may experience a sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), and you may feel you are going to faint
- chest pains
- your bowel motions are bloodstained or black
- your mouth becomes sore or develops ulcers
- numbness, tingling or tremor in the hands or feet
- heart attack or other heart problems such as quickening of your heart rate and breathlessness
- symptoms of leucoencephalopathy (disease of brain) - weakness, coordination problems in arms and legs, thinking/speech difficulties, vision/memory problems, seizures, headaches
- shortness of breath

These are very serious side effects. You may need urgent medical attention.

If you experience any of the following tell your doctor as soon as possible:

Very common: may affect more than 1 in 10 people
- Sore throat
- Insufficient supply of blood to the heart which shows on the heart trace (ECG)
- Myelosuppression (a disorder in which the bone marrow produces reduced number of all types of blood cells [pancytopenia])
- Neutropenia and leucopenia (an abnormally low level of types of white blood cells in the blood)
- Thrombocytopenia (reduced numbers of platelets in the blood which reduces the ability of your blood to clot)
- A sharp drop in circulating granular white blood cells (agranulocytosis)
- Anaemia (condition in which your red blood cells are reduced)
- Increased risk of infection due to immunosuppression
- Wheezing (bronchospasm)
- Nausea
- Vomiting
- Diarrhoea
- Infections
- Loss of appetite
- Delayed wound healing
- Inflammation of the mucous lining of any of the structures in the mouth, throat and the digestive tract e.g. oesophagus (the gullet), rectum or anus
- Increase in uric acid in the blood
- Bleeding from the nose
- Hair loss
- Hand-foot syndrome (toxic skin reaction with redness and swelling of your hands and feet)
- Fatigue, tiredness and lack of energy
- General weakness

Common: may affect up to 1 in 10 people

- Infection in the blood stream (sepsis)
- Heart attack, angina pectoris (Severe pain in the chest associated with an insufficient supply of blood to the heart)
- Low white blood cells accompanied by fever
- Changes in ECG (electrocardiogram – tests to check heart's rhythm and electrical activity)

Uncommon: may affect up to 1 in 100 people

- Abnormality in the heart's rhythm
- Heart attack
- Heart insufficiency
- Myocardial ischemia (reduced oxygen to the heart)
- Myocarditis (inflammatory disease of the heart muscle)
- Congestive cardiomyopathy (a type of heart disease in which the heart muscle is abnormally enlarged, thickened and/or stiffened)
- Cardiac shock
- Low blood pressure
- Sleepiness
- Dehydration
- Liver cell damage
- Gastrointestinal ulceration and bleeding
- Casting off the skin
- Gastrointestinal haemorrhage
- Rhythmic motions of the eyes (nystagmus)
- Headache
- Dizziness
- Sensations of imbalance and unsteadiness
- Symptoms of Parkinson's disease (a progressive movement disorder marked by tremors, rigidity, slow movements)
- Pyramidal signs
- Infection in the blood stream (sepsis)
- Inflammation of the skin (dermatitis)
- Skin alterations e.g. dry skin, fissure erosion, Redness of the skin, pruritic maculopapular rash (an itchy, red bumpy rash)
- A skin eruption accompanying certain infectious diseases
- Appearance of itchy weals on the skin
- Sensitivity to light (Photosensitivity)
- Increased pigmentation of the skin
    - Hyperpigmentation or depigmentation near the veins.
    - Nail pigmentation, nail bed disorder.
- Paronychia (Inflammation of the tissue surrounding a fingernail)
- An inflammation of the matrix of the nail with formation of pus and shedding of the nail
- Sperm or ovum production disorder
- Increased secretion of tears
- Blurred vision
- Inflammation or redness of the lining of the white part of the eye and the underside of the eyelid.
- Eye movement disturbance
- Red eyes (conjunctivitis)
- Optic neuritis (a vision disorder characterized by inflammation of the optic nerve)
- Double vision
- Decrease in visual sharpness
- Excessive eye sensitivity to light and the aversion to sunlight or well-lit places
- Narrowing of the duct which drains tears away from the eye (dacryostenosis)
- Lower eyelid turns outwards (ectropion)
- Euphoria

Rare: may affect up to 1 in 1,000 people

- Insufficient blood flow in brain, intestine and peripheral organs (limbs)
- Poor blood circulation which makes the fingers and toes numb and pale (Raynaud's syndrome)
- Hypersensitivity
- Swelling (inflammation) of a vein caused by a blood clot
- Severe, whole-body allergic reaction (anaphylaxis)
- Development of a clot within blood vessels, can occur in arteries or veins
- Mental confusion or impaired awareness especially regarding time, place or identity
- Confusion
- Kidney failure
- Thyroid function changes – increase of T4 and T3 (total thyroxine and tri-iodothyronine)

Very rare: may affect up to 1 in 10,000 people

- Cardiac arrest (sudden cessation of heartbeat and cardiac function)
- Sudden cardiac death (unexpected death due to heart problems)
- Symptoms of leucoencephalopathy (diseases affecting the white substance of the brain) including ataxia (loss of the ability to coordinate muscular movement)
- Acute cerebellar syndrome
- Difficulty in articulating words
- Partial or total loss of the ability to communicate verbally or using written words.
- Abnormal muscular weakness or fatigue
- Convulsion or coma in patients receiving high doses of 5-fluorouracil and in patients with dihydropyrimidine dehydrogenase deficiency (DPD deficiency)
- Inflammation of the gall bladder
- Damage of liver cells (cases with fatal outcome)

Not Known: frequency cannot be estimated from the available data

- Blood poisoning (septic shock)
- Neutropenic sepsis (a life-threatening reaction to an infection, which can happen in patients with neutropenia – low levels of a type of white blood cell that work as part of the immune system to fight infection in the blood)
- Lung infection
- Urinary tract infection, bacterial infection of the urinary system
- Bacterial infection of the skin causing redness, swelling and pain in the infected area
- Reduction in number of granulocytes, a type of white blood cell
- Reduced appetite
- Disorientation
- Fever
- Numbness or weakness of the arms and legs
- Fits
- Hyperammonaemic encephalopathy (brain dysfunction caused by elevated ammonia)
- Clots in the heart chambers that could break off and block arteries in the body, which, for example, could cause a stroke or lack of blood supply to a limb
- Inflammation of the heart muscle
- Inflammation of the skin causing red scaly patches and possibly occurring together with pain in the joints and fever (cutaneous lupus erythematosus [CLE])
- Heart disease that presents with chest pain, shortness of breath, dizziness, fainting, irregular heartbeat (stress cardiomyopathy)
- Bleeding
- Dark sticky feces containing partly digested blood
- Chest pain
- Air in the intestinal wall
- Serious condition that presents with difficulty breathing, vomiting and abdominal pain with muscle cramps (lactic acidosis)
- Condition characterised by headache, confusion, seizures and changes in vision (posterior reversible encephalopathy syndrome [PRES])
- Serious complication with rapid break down of cancer cells causing high levels of uric acid, potassium and phosphate (tumour lysis syndrome)

- Injection site discoloration

Reporting of side effects
If you get any side effects, talk to your doctor or 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 Fluorouracil Injection

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.
Store below 25°C. Do not refrigerate or freeze.
Keep vial in the outer carton in order to protect from light.
Single use only. Discard any unused portion.

Shelf Life after dilution
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C with Glucose 5% or Sodium Chloride 0.9% Injection or Water for Injections at concentration 0.98 mg/ml of Fluorouracil. However 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.
Do not use if the product appears brown or dark yellow in solution.
Do not use if you notice that the container is damaged or particles/crystals are visible.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines no longer used. These measures will help to protect the environment.

6. Contents of the pack and other information

What Fluorouracil Injection contains
The active substance in Fluorouracil Injection is fluorouracil.
The other ingredients are water for injections, sodium hydroxide and hydrochloric acid.

What Fluorouracil Injection looks like and contents of the pack
1ml of solution contains 50 mg of fluorouracil (as sodium salt formed *in situ*).
Fluorouracil solution for Injection or Infusion is a clear, colourless to slight yellow solution in a Type I clear glass vial with rubber closure.
Each 5 ml vial contains 250 mg of fluorouracil.
Each 10 ml vial contains 500 mg of fluorouracil.
Each 20 ml vial contains 1000 mg of fluorouracil.
Each 50 ml vial contains 2500 mg of fluorouracil.
Each 100 ml vial contains 5000 mg of fluorouracil.
Not all pack sizes may be marketed.

Marketing Authorization Holder
Accord Healthcare Ireland Limited
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

Manufacturer
Accord Healthcare Polska Sp.z o.o.,
ul. Lutomierska 50,95-200 Pabianice, Poland

This medicine is authorised in the member states of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names.

Name of the Member State	Name of the medicine
Austria	Fluorouracil Accord 50 mg/ml, Lösung zur Injektion oder Infusion
Belgium	Fluorouracil Accord Healthcare 50 mg/ml, solution pour injection ou perfusion/ oplossing voor injectie of infusie/ Lösung zur Injektion oder Infusion
Czech Republic	Fluorouracil Accord 50 mg/ml, injekční/infuzní roztok
Denmark	Fluorouracil Accord, injektions og infusionsvæske, opløsning
Estonia	Fluorouracil Accord 50 mg/ml, süste- või infusioonilahus
Finland	Fluorouracil Accord 50 mg/ml, injektio- tai infuusioneste/ Lösning för injektion och infusion
Ireland	Fluorouracil 50 mg/ml, Solution for Injection or Infusion
Italy	Fluorouracile AHCL 50 mg/ml, Soluzione per iniezione o infusione
Spain	Fluorouracil Accord 50 mg/ml, para inyección o infusión EFG
Sweden	Fluorouracil Accord 50 mg/ml, Lösning för injektion och infusion
Latvia	Fluorouracil Accord 50 mg/ml, šķīdums injekcijām vai infūzijām
Lithuania	Fluorouracil Accord 50 mg/ml, injekcinis/infuzinis tirpalas
Poland	Fluorouracil Accord
Portugal	Fluorouracilo Accord
Slovak Republic	Fluorouracil Accord 50 mg/ml, injekčný alebo infúzny roztok
The Netherlands	Fluorouracil Accord 50 mg/ml, oplossing voor injectie of infusie
United Kingdom (Northern Ireland)	Fluorouracil Accord 50 mg/ml Solution for Injection or Infusion
Bulgaria	Fluorouracil Accord 50 mg/ml Solution for Injection or Infusion
Cyprus	Fluorouracil 50 mg/ml Solution for Injection or Infusion
Germany	Fluorouracil Accord 50 mg/ml Injektionslösung bzw. Infusionslösung
Hungary	Fluorouracil Accord 50 mg/ml oldatos injekció vagy infúzió
Iceland	Flúoróúracíl Accord 50 mg/ml stungulyf, lausn eða innrennsli
Malta	Fluorouracil 50 mg/ml Solution for Injection or Infusion
Norway	Fluorouracil Accord 50 mg/ml konsentrat til infusjonsvæske
Romania	Fluorouracil Accord 50 mg/ml solutie injectabila sau perfuzabila
Slovenia	Fluorouracil Accord 50 mg/ml raztopino za injiciranje ali infundiranje

The leaflet was last revised in 12/2023.

The following information is intended for medical or healthcare professionals only:

INSTRUCTIONS FOR USE/HANDLING, PREPARATION AND DISPOSAL GUIDE FOR USE WITH FLUOROURACIL INJECTION

Cytotoxic Handling Guidelines

Fluorouracil should be administered only by or under the supervision of a qualified physician who is experienced in the use of cancer chemotherapeutic drugs.

Fluorouracil Injection should only be prepared for administration by professionals who have been trained in the safe use of the preparation. Preparation should only be carried out in an aseptic cabinet or suite dedicated for the assembly of cytotoxics.

In the event of spillage, operators should put on gloves, face mask, eye protection and disposable apron and mop up the spilled material with an absorbent material kept in the area for that purpose. The area should then be cleaned and all contaminated material transferred to a cytotoxic spillage bag or bin and sealed for incineration.

Contamination

Fluorouracil is an irritant, contact with skin and mucous membranes should be avoided.

In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline. Hydrocortisone cream 1% may be used to treat the transient stinging of the skin. Medical advice should be sought if the eyes are affected or if the preparation is inhaled or ingested.

First Aid

Eye contact: Irrigate immediately with water and seek medical advice.
Skin contact: Wash thoroughly with soap and water and remove-contaminated clothing.
Inhalation, Ingestion: Seek medical advice.

Disposal

Syringes, containers, absorbent materials, solution and any other contaminated material should be placed in a thick plastic bag or other impervious container, marked as cytotoxic waste and incinerated at a minimum of 700°C.
Chemical inactivation can be achieved by 5% sodium Hypochlorite over 24 hours.

Preparation guidelines:

a) Chemotherapeutic agents should be prepared for administration only by professionals who have been trained in the safe use of the preparation.

b) Operations such as reconstitution of powder and transfer to syringes should be carried out only-in the designated area.

c) The personnel carrying out these procedures should be adequately protected with special clothing, two pairs of gloves one latex, one PVC, (the latex being worn beneath the PVC), this covers differences in permeabilities to the various antineoplastics, and eye shields. Luerlock syringes and fittings should always be used both in the preparation of cytotoxic products and for their administration.

d) Pregnant personnel are advised not to handle chemotherapeutic agents.

(e) Refer to local guidelines before commencing.

Instructions for use

Fluorouracil Injection can be given by intravenous injection as bolus, infusion or continuous infusion.

Incompatibilities

Fluorouracil is incompatible with calcium folinate, Carboplatin, Cisplatin, Cytarabine, Diazepam, Doxorubicin, Droperidol, Filgrastim, Gallium nitrate, Methotrexate, Metoclopramide, Morphine, Ondansetron, parenteral nutrition, Vinorelbin, other Anthracyclines.

Formulated solutions are alkaline and it is recommended that admixture with acidic drugs or preparations should be avoided.
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf Life and storage

Shelf-life of unopened vials
2 years. Single use only. Discard any unused portion.

Store below 25°C. Do not refrigerate or freeze. Keep container in the outer carton in order to protect from light.
If a precipitate has formed as a result of exposure to low temperature, redissolve by heating to 60°C accompanied by vigorous shaking. Allow to cool to body temperature prior to use. The product should be discarded if it appears brown or dark yellow in solution.

Shelf Life after dilution
In use: Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C with Glucose 5% or Sodium Chloride 0.9% Injection or Water for Injections at concentration 0.98 mg/ml of Fluorouracil.

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.