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 or nurse.
- 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 or nurse. This includes any possible side effects not listed in this leaflet. See Section 4.

What is this leaflet
1. What Fluorouracil Injection is and what it is used for
2. What you need to know before you use Fluorouracil Injection
3. How to use Fluorouracil Injection
4. Possible side effects
5. How to store Fluorouracil Injection
6. Contents of the pack and other information

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.

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 and radiotherapy.

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

Do not use Fluorouracil Injection
- if you are allergic (hypersensitive) to Fluorouracil or any of the other ingredients of Fluorouracil Injection (listed in section 6).
- if you have serious infections (e.g. Herpes zoster, chickenpox)
- if your tumour is non-malignant.
- if you have been very much weakened by long illness.
- if your bone marrow has been damaged by other treatments (including radiotherapy).
- if you are taking brivudin, sorivudin and analogues (an antiviral drug)
- if you are pregnant or breast feeding women
- if you have serious impaired liver function
- if you are homozygotic for dihydropyrimidine dehydrogenase (DPD) enzyme

Warnings and precautions
Talk to your doctor or pharmacist or nurse before using Fluorouracil Injection. Take special care with Fluorouracil Injection:
- if the number of cells in your blood become too low (you will have blood tests to check this)
- if you have oral ulceration, fever or hemorrhage at any site or weakness (these symptoms may be the consequence of the very low number of cells in your blood),
- if you have any problems with your kidneys
• if you have any problems with your liver including jaundice (yellowing of the skin)
• if you problem with your heart. Tell your doctor if you experience any chest pain during treatment.
• if you have reduced activity/deficiency of the enzyme DPD (dihydropyrimidine dehydrogenase).
• If you have had high-dose pelvic radiation.
• if you have gastrointestinal side effects (stomatitis, diarrhoea, bleeding from the G.I. tract) or hemorrhage at any site.

**Other medicines and Fluorouracil Injection**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
• Methotrexate (an anti-cancer medicine)
• Metronidazole (an antibiotic)
• Calcium leucovorin (also called calcium folinate - 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 2a; brivudin, sorivudin and analogues (an antiviral)
• Cisplatin (an anticancer medicine)
• Phenytoin (used to control epilepsy/fits and irregular heart rhythm)
• Vaccines
• Vinorelbine (an anti-cancer medicine)
• Cyclophosphamide (an anti-cancer medicine)
• Levamisol (medicine used to treat worm infection)
• Tamoxifen (an anti-cancer medicine)

The above medicines affect the effect of Fluorouracil.

**Pregnancy, breast-feeding and fertility**
Fluorouracil should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. You must not take this drug if you are pregnant or planning to become pregnant. If you are a women of childbearing potential you must use an effective method of contraception while taking this drug and at least for 6 months afterwards. If pregnancy occurs during your treatment you must inform your doctor and should use genetic counselling.

Since it is not known whether fluorouracil passes into breast milk, breast-feeding must be discontinued if the mother is treated with Fluorouracil Injection.

If you are a man you should avoid father a child during and for up to 6 months following cessation of treatment with Fluorouracil Injection. You are advice to sought conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with Fluorouracil Injection.

Ask your doctor for advice before taking any medicine.

**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/m²). This should be taken into consideration by patients on a controlled sodium diet.

**3. How to use Fluorouracil Injection**
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 liver and kidneys are working. It will also depend on the results of your blood tests. 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. 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 whilst you are in hospital is unlikely that you will be given too little or too much, however, tell your doctor or pharmacist 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.

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
- quickening of your heart rate and breathlessness
- feeling confused or feeling unsteady on your feet, coordination problems in arms and legs, thinking/speech difficulties, vision/memory problems

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

Very common: may affect more than 1 in 10 people
- Ischemic ECG abnormalities (an insufficient supply of blood to an organ, usually due to a blocked artery)
- Anemia (condition in which the circulating red cell mass is insufficient)
- High fever and a sharp drop in circulating granular white blood cells
- Inflammation of the rectum or anus
- Nausea
- Delayed wound healing
- Weakness
- Inflammation of the mucous lining of any of the structures in the mouth
- Increase in uric acid in the blood

Common: may affect up to 1 in 10 people
- Angina pectoris (Severe pain in the chest associated with an insufficient supply of blood to the heart)

Uncommon: may affect up to 1 in 100 people
- Abnormality in the heart’s rhythm
- Myocarditis (inflammatory disease of the heart muscle)
- Heart attack
- Heart insufficiency
- Myocardial ischemia (a loss of oxygen to the heart muscle)
- Dilative cardiomyopathy (a type of heart disease in which the heart muscle is abnormally enlarged, thickened and/or stiffened)
- Cardiac shock
- Dehydration
- Rhythmic motions of the eyes
- Symptoms of Parkinson's disease (a progressive movement disorder marked by tremors, rigidity, slow movements)
- Inflammation of the skin
- Appearance of itchy weals on the skin
- Streaky hyperpigmentation or depigmentation near the veins.
- An inflammation of the matrix of the nail with formation of pus and shedding of the nail
- Secretion of tears
- Eye movement disturbance
- lower eyelid turns outwards
- Euphoria.

- Low blood pressure
- Bacterial infection in the bloodstream or body tissues
- Headache
- Pyramidal signs
- Skin alterations e.g. dry skin, fissure erosion, Redness of the skin, pruritic maculopapular rash (rash that had originated on the lower extremities and had progressed to the arms, and then to the chest)
- Photosensitivity
- Changes in the nails (e.g. diffuse superficial blue pigmentation, hyperpigmentation; nail dystrophy, pain and thickening of the nail bed.
- Blurred vision,
- Optic neuritis (a vision disorder characterized by inflammation of the optic nerve)
- excessive sensitivity to light and the aversion to sunlight or well-lit places
- Blocked tear ducts
- A layer or mass of dead tissue separated from surrounding living tissue, as in a wound, a sore, or an inflammation.

- Sleepiness
- Gastrointestinal ulceration and bleeding, casting off the skin
- Sensations of imbalance and unsteadiness
- Feeling of being sick
- Skin eruptions accompanying certain infectious diseases
- Hyperpigmentation of the skin
- Paronychia (Inflammation of the tissue surrounding a fingernail)
- liver cell damage
- Inflammation or redness of the lining of the white part of the eye and the underside of the eyelid.
- double vision
- ocular disease characterized by chronic inflammation of the eyelid margins
- A layer or mass of dead tissue separated from surrounding living tissue, as in a wound, a sore, or an inflammation.

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

- Insufficient blood flow in brain, intestine and peripheral organs
- swelling (inflammation) of a vein caused by a blood clot
- systemic vasodilation (widening of blood vessels) which results in low blood pressure
- Sperm or ovum production disorder
- Skew of vision
- Generalized allergic reaction
- Development of a clot within blood vessels, can occur in arteries or veins
- Increase of T4 (total thyroxin), increase of T3 (total triiodothyronine)

**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)
- Acute cerebellar syndrome
- Mental confusion or impaired awareness especially regarding to time, place or identity
- Convulsion or coma in patients
- Difficulty in articulating words
- Partial or total loss of the ability to communicate verbally or using written words.
- kidney failure
- Symptoms of leucoencephalopathy (diseases affecting the white substance of the brain) including ataxia (loss of the ability to coordinate muscular movement)
- Confusion
- Abnormal muscular weakness or fatigue
- Damage of liver cells (cases with
receiving high doses of 5-fluorouracil and in patients with dihydropyrimidine dehydrogenase deficiency (fatal outcome)

- inflammation of the gall bladder
- slow progressive destruction of the small bile ducts
- Disorientation

Not Known: frequency cannot be estimated from the available data

- fever
- numbness or weakness of the arms and legs
- vein discolouration proximal to injection sites
- tachycardia, breathlessness

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

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 container 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 B.P or Water for Injections B.P 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 and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

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 content of the pack

1 ml of solution contains 50 mg of fluorouracil (as sodium salt formed in situ). Fluorouracil solution for Injection or Infusion is a clear, almost colourless solution in a Ph. Eur 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 and Manufacturer
Accord Healthcare Limited
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The leaflet was last revised in 09/2017.
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 antineoplasics, 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, Vinorelbine, 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 vial**
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 B.P or Water for Injections B.P 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 and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.