PACKAGE LEAFLET: INFORMATION FOR THE USER

Fluorouracil 50 mg/ml Injection

Read all of this leaflet carefully before you start taking this medicine.

- 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. Do not pass it on to others. It may harm them, even if their symptoms 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

Fluorouracil Injection is an anti-cancer medicine. Treatment with an anti-cancer medicine is sometimes called cancer chemotherapy.

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

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 (including nutritional) state due to long illness
- if your bone marrow has been damaged by other cancer treatments (including radiotherapy)
- if you know that you do not have any activity of the enzyme dihydropyrimidine dehydrogenase (DPD) (complete DPD deficiency)
- if you have a potentially serious infection
- if your cancer is non-malignant
- if you are breast-feeding
- if you are taking or have taken in the past 4 weeks brivudine, sorivudine and similar drugs (antivirals)

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 before using 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
- if you have problems with your heart. Tell your doctor if you experience any chest pain during treatment
- 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 are elderly
- if you know that you have a partial deficiency in the activity of the enzyme dihydropyrimidine dehydrogenase (DPD)
- if you have a family member who has partial or complete deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD)
- if you require blood testing, because it can interfere with some laboratory tests
- if you are monitoring your blood thyroxine levels

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.

Some patients may experience a sensitivity to light following administration of fluorouracil, it is recommended to avoid prolonged exposure to sunlight (see section 4).

Patients undergoing radiotherapy are at an increased likelihood of necrosis (death of tissue or skin) caused by radiation.

If you have had leukaemia and are in remission do not take live vaccines before 3 months after your last chemotherapy. Also you and people in your direct contact such as family members should not take a polio vaccine.

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

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

Other medicines and Fluorouracil Injection
Special care is needed if you are taking/using other medicines as some could interact with Fluorouracil Injection, for example:

- methotrexate, cisplatin, cytarabine, mitomycin-C, tamoxifen (anti-cancer medicines)
- 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; brivudine, sorivudine and similar drugs (antivirals)
- phenytoin (an anti-epilepsy medicine)
- vaccines

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

You may need to be monitored, and your dose of Fluorouracil Injection may be adjusted when given with leucovorin (also called calcium folinate).

Pregnancy, breast-feeding and fertility
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 you are a woman of childbearing potential you must not become pregnant during treatment and 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 before treatment with Fluorouracil Injection.

If you are a man you should avoid to father a child during and for up to 3 months following end of treatment with Fluorouracil Injection. You are advised to seek conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with Fluorouracil Injection.

Driving and using machines
Do not drive or use machines if you experience any side effect from Fluorouracil, such as nausea and vomiting. Fluorouracil can also produce adverse events on your nervous system and cause visual changes. If you experience any of these effects, do not drive or use any tools or machines, as they may impair your ability to do so.

Fluorouracil Injection contains sodium
The 5 ml vial contains 40.1 mg of sodium (main component of cooking/table salt) in each vial. This is equivalent to 2% of the recommended maximum daily dietary intake of sodium for an adult.

The 10 ml vial contains 80.2 mg of sodium (main component of cooking/table salt) in each vial. This is equivalent to 4% of the recommended maximum daily dietary intake of sodium for an adult.

The 20 ml vial contains 160.4 mg of sodium (main component of cooking/table salt) in each vial. This is equivalent to 8% of the recommended maximum daily dietary intake of sodium for an adult.

The 50 ml vial contains 401 mg of sodium (main component of cooking/table salt) in each vial. This is equivalent to 20% of the recommended maximum daily dietary intake of sodium for an adult.

The 100 ml vial contains 802 mg of sodium (main component of cooking/table salt) in each vial. This is equivalent to 40% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Fluorouracil Injection

This medicine is given into a vein or an artery. If it is given into a vein, it can either be injected (using a syringe) or infused (using a drip). If it is given into an artery, it will be given as an infusion.

If it is to be given as an infusion the medicine will be diluted before use.

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 size, if you have had recent surgery and how well your bone marrow, liver and kidneys are working.

Your doctor will tell how well your bone marrow, liver and kidneys are working using blood tests.

The total daily dose should not exceed 1 gram.

If you are given too much or too little Fluorouracil Injection
This medicine will be given to you by a doctor or nurse. It is unlikely that you will be given too much or too little, however, tell your doctor or nurse if you have any concerns. If you have taken too much, your doctor will monitor you closely for at least 4 weeks.

4. Possible side effects

Like all medicines, fluorouracil 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 (which may be due to heart problems, including having a heart attack)
- shortness of breath
- your bowel motions are bloodstained or black
- your mouth becomes sore or develops ulcers
- symptoms of leucoencephalopathy (disease of brain) – extreme weakness and fatigue, staggering while walking, thinking or speech difficulties, seizures, coma.

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

The frequency of possible side effects listed below is defined using the following convention:

Very common: may affect more than 1 in 10 people
Common: may affect up to 1 in 10 people
Uncommon: may affect up to 1 in 100 people
Rare: may affect up to 1 in 1,000 people
Very rare: may affect up to 1 in 10,000 people
Not known (frequency cannot be estimated from the available data)

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

Very common side effects

- infections
- increased chance of picking up infections and/or delayed wound healing due to low white blood cells
- anaemia (reduction in red blood cells)
- difficulty breathing
- abnormality in the heart's rhythm
- diarrhoea
- feeling or being sick
- anorexia (loss of appetite)
- inflammation of the lining of the mouth, throat, gut, rectum or anus
- hair loss (reversible especially in women)
- reddening, swelling or pain in the palms of the hands and/or the soles of the feet
- tiredness
- feel generally unwell
- weakness

Common side effects

- low white blood cells accompanied by fever
- chest pain

Uncommon side effects

- feeling of intense excitement and happiness
- watering eyes, changes in vision, sensitivity to light, side-to-side movements of the eyes
- headache
- dizziness
- symptoms of Parkinson's disease (e.g. shaking hands)
- numbness, tingling or tremor in the hands or feet
- sleepiness
- irregular heart beat, palpitations
- low blood pressure (you may feel faint)
- skin problems (including dry skin, itchy weals, rash, redness, inflammation)
- skin may appear lighter or darker, may occur in patches
- changes in your nails, such as changes in colour or thickening of the nails
- sensitivity of the skin to light

Rare side effects

- serious allergic reaction causing difficulty breathing or dizziness
- feeling confused
- reduced blood supply to the brain, intestines and extremities (ischaemia)
- discolouration in your fingers and toes (Raynaud's syndrome)
- blood clots (pain, redness or swelling of the part affected)

Very rare side effects

- disorientation
- muscle weakness
- brain disorders have been reported causing uncontrollable movements, difficulty speaking, fits and coma
- kidney failure
- cardiac arrest
- sudden cardiac death

Frequency unknown

- a disorder of the nerves which can cause weakness, tingling or numbness
- hyperammonaemic encephalopathy (brain dysfunction caused by elevated ammonia)
- condition characterised by headache, confusion, seizures and changes in vision (posterior reversible encephalopathy syndrome [PRES])
- heart disease that presents with chest pain, shortness of breath, dizziness, fainting, irregular heartbeat (stress cardiomyopathy)
- faster heart beat
- inflammation of the outer lining of the heart
- breathlessness
- fever
- the vein where fluorouracil is administered may become painful or discoloured, which may be the sign of a blood clot
- inflammation of the skin causing red scaly patches and possibly occurring together with pain in the joints and fever (cutaneous lupus erythematosus [CLE])
- air in the intestinal wall
- serious condition that presents with difficulty breathing, vomiting and abdominal pain with muscle cramps (lactic acidosis)
- serious complication with rapid break down of cancer cells causing high levels of uric acid, potassium and phosphate (tumour lysis syndrome)

Fluorouracil may lead to changes in your blood cells. Your doctor will take blood samples to check for abnormalities (e.g. bone marrow depression which may result in low white cells, low red cells, low platelets, low gamma globulins).

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Fluorouracil Injection

Keep out of the sight and reach of children

Expiry
This medicine must not be used after the expiry date which is stated on the vial label and carton after 'EXP'. Where only a month and year is stated, the expiry date refers to the last day of that month.

Storage
Keep the vials in the outer carton, in order to protect from light and store at or below 25°C. They should not be refrigerated or frozen.

Prepared infusions should be used immediately, however, if this is not possible they can be stored for up to 5 days provided they have been prepared in a way to exclude microbial contamination.

Visible signs of deterioration
Do not use this medicine if you notice it appears brown or dark yellow in colour, or if particles are visible.

Disposal
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. Contents of the pack and other information

What Fluorouracil Injection contains
The active substance is fluorouracil. Each millilitre (ml) of solution contains 50 mg of fluorouracil.

The other ingredients are sodium hydroxide (see section 2 "Fluorouracil Injection contains sodium") and Water for Injections.

What Fluorouracil Injection looks like and contents of the pack
Fluorouracil Injection is clear, colourless or slightly yellow solution for injection without visible particles, which comes in glass containers called vials.

It may be supplied in packs containing:
- 5 x 250 mg/5 ml vials
- 5 x 500 mg/10 ml vials
- 5 x 1 g/20 ml vials
- 1 or 10 x 2.5 g/50 ml vial(s)
- 1 x 5 g/100 ml vial
- 1 x 500 mg/10 ml ONCO-VIAL®
- 1 x 1 g/20 ml ONCO-VIAL®
- 1 x 2.5 g/50 ml ONCO-VIAL®

Not all packs may be marketed.

Marketing Authorisation Holder and Manufacturer
Hospira UK Limited, Horizon, Honey Lane, Hurley, Maidenhead, SL6 6RJ, UK

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Fluorouracil 50 mg/ml Injection

The following information is intended for medical or healthcare professionals only

Further to the information included in section 3, practical information on the preparation/handling of the medicinal product is provided here.

Incompatibilities

Formulated solutions are alkaline and it is recommended that admixture with acidic drugs or preparations should be avoided. Fluorouracil Injection is reported to be incompatible with cytarabine, diazepam, methotrexate, platinum compounds, doxorubicin (and presumably other anthracyclines that are unstable at alkaline pH), and calcium folinate (leucovorin).

Use and handling, and disposal
The pH of Fluorouracil Injection is 8.9 and the drug has maximal stability over the pH range 8.6 to 9.0.

If a precipitate has formed as a result of exposure to low temperatures, re-dissolve 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 colour or if particles are visible.

Fluorouracil Injection may be diluted with Glucose 5% Injection or Sodium Chloride 0.9% Injection or Water for Injections immediately before use.

Fluorouracil injection should not be mixed directly, in the same container, with other chemotherapeutic agents or intravenous additives.

Chemical and physical in-use stability has been demonstrated for 5 days at 20-21°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 normally be longer than 24 hours at 2-8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Cytotoxic Handling Guidelines
Should be administered only by, or under the direct supervision of, a qualified physician who is experienced in the use of cancer chemotherapeutic agents.

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. A bland cream 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.

Please refer to the marketing authorisation holder for COSHH hazard datasheets.

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 under aseptic conditions in a suite or cabinet dedicated for the assembly of cytotoxics.
c) The personnel carrying out these procedures should be adequately protected with clothing, gloves and eye shield.
d) Pregnant personnel are advised not to handle chemotherapeutic agents.

Disposal
Syringes, ONCO-VIAL®s and adaptors containing remaining solution, absorbent materials, and any other contaminated material should be placed in a thick plastic bag or other impervious container and incinerated at 700°C.

Directions for use of the ONCO-VIAL®
ONCO-VIAL® should be used with an appropriate Hospira administration device.