PACKAGE LEAFLET: INFORMATION FOR THE PATIENT

Fluorouracil 50 mg/ml
Solution for Injection/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 nurse
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See Section 4.

WHAT IS IN THIS LEAFLET

1. WHAT FLUOROURACIL IS AND WHAT IT IS USED FOR

Fluorouracil contains the active ingredient fluorouracil. It is an anti-cancer medication.

Fluorouracil 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

Do not use Fluorouracil :
- if you are allergic to fluorouracil or any of the other ingredients of this medicine (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 being treated now or have been treated in the last 4 weeks with brivudine as part of herpes zoster (chickenpox or shingles) therapy.
- if you are pregnant or breast feeding woman.
- if you have serious impaired liver function.
- if you are homozygotic for dihydropyrimidine dehydrogenase (DPD) enzyme.
- if you know that you do not have any activity of the enzyme dihydropyrimidine dehydrogenase (DPD) (complete DPD deficiency).

Warnings and precautions
Talk to your doctor or nurse before using Fluorouracil

Take special care with Fluorouracil :
- 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 haemorrhage 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 have problems with your heart. Tell your doctor if you experience any chest pain during treatment.
- 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 have had high-dose pelvic radiation.
- if you have gastrointestinal side effects (stomatitis, diarrhoea, bleeding from the G.I. tract) or haemorrhage at any site.

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, 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. 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 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.

Other medicines and Fluorouracil
Before starting treatment, tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is extremely important, as taking more than one medicine at the same time can strengthen or weaken the effect of the medicines.

You must not take brivudine (an anti-viral medicine for the treatment of shingles or chickenpox) at the same time as 5-fluorouracil treatment.
If you have taken brivudine you must wait for at least 4 weeks after stopping brivudine before starting to take 5-fluorouracil. See also section "Do not take Fluorouracil".

The below medicines affect the effect of fluorouracil:
- 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
- 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)

Pregnancy, breast-feeding and fertility
You must not take this drug if you are pregnant or planning to become pregnant.
If you are a woman 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 .

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

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 contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per millilitre, i.e. essentially 'sodium- free'.

3. HOW TO USE FLUOROURACIL

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 water for injection, glucose solution or sodium chloride solution before it is given to you. It is given into a vein or an artery. If it is given into a vein, it can either be given as a normal injection or a slow injection via a drip (infusion). If it is given into an artery, it will be given as an infusion.

If you are given more Fluorouracil 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 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,
- shortness of breath,
- 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
- If severe stomatitis (sores in your mouth and/or throat), mucosal inflammation, diarrhoea, neutropenia (increased risk for infections), or neurotoxicity occurs during the first cycle of treatment a DPD deficiency may be involved (please see Section 2: Warning and precautions).

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

Very common side effects (more than 1 in 10 patients):
- Ischemic ECG abnormalities (an insufficient supply of blood to an organ, usually due to a blocked artery)
- Neutropenia (an abnormally low level of neutrophils in the blood)
- Leucopenia (an abnormally low number of white blood cells in the circulating blood)
- Anemia (condition in which the circulating red cell mass is insufficient)
- Pancytopenia (a disorder in which the bone marrow greatly decreases or stops production of blood cells)
- Decrease in the production of blood cells
- High fever and a sharp drop in circulating granular white blood cells
- The inflammation of the lining of the mouth and digestive tract
- Pharyngitis (inflammation of the mucous membranes lining the pharynx)
- Inflammation of the rectum or anus
- Loss of appetite
- Watery diarrhoea
- Nausea
- Vomiting
- Hair loss
- Hand-foot syndrome is a toxic skin reaction
- Delayed wound healing
- Bleeding from the nose
- Fatigue
- General weakness
- Tiredness
- Lack of energy
- Inflammation of the mucous lining of any of the structures in the mouth
- Inflammation of the oesophagus
- Increase in uric acid in the blood
- Infections

Common side effects (less than 1 in 10 patients):
- Angina pectoris (Severe pain in the chest associated with an insufficient supply of blood to the heart)
- Low white blood cells accompanied by fever

Uncommon side effects (less than 1 in 100 patients):
- Abnormality in the heart's rhythm
- Heart attack
- Myocardial ischemia (a loss of oxygen to the heart muscle)
- Myocarditis (inflammatory disease of the heart muscle)
- Heart insufficiency
- Dilative 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
- Bacterial infection in the bloodstream or body tissues
- Gastrointestinal ulceration and bleeding, casting off the skin
- Rhythmic motions of the eyes
- Headache
- Sensations of imbalance and unsteadiness
- Symptoms of Parkinson's disease (a progressive movement disorder marked by tremors, rigidity, slow movements)
- Pyramidal signs
- Feeling of being sick
- Inflammation of the skin
- 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)
- A skin eruption accompanying certain infectious diseases
- Appearance of itchy weals on the skin
- Photosensitivity
- Hyperpigmentation of the skin
- Streaky hyperpigmentation or depigmentation near the veins.
- Changes in the nails (e.g. diffuse superficial blue pigmentation, hyperpigmentation; nail dystrophy, pain and thickening of the nail bed.
- 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

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The following information is intended for healthcare professionals only:

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

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.

Preparation (guidelines):
Contamination
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.

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.
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.

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.

Instruction for Use
Fluorouracil can be given by intravenous injection, or intravenous or intra-arterial infusion.

Incompatibilities
Fluorouracil is incompatible with folinic acid, carboplatin, cisplatin, cytarabine, diazepam, doxorubicin, droperidol, filgrastim, gallium nitrate, methotrexate, metoclopramide, morphine, ondansetrone, parenteral nutrition, vinorelbin, and 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.

- Sperm or ovum production disorder
- 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
- Optic neuritis (a vision disorder characterized by inflammation of the optic nerve)
- Double vision
- Decrease in visual sharpness
- Excessive sensitivity to light and the aversion to sunlight or well-lit places
- Ocular disease characterized by chronic inflammation of the eyelid margins
- Lower eyelid turns outwards
- Blocked tear ducts
- A layer or mass of dead tissue separated from surrounding living tissue, as in a wound, a sore, or an inflammation.
- Liver cell damage

Rare side effects (less than 1 in 1,000 patients):
- Generalized allergic reaction
- Insufficient blood flow in brain, intestine and peripheral organs
- Discoloration of the fingers, toes, and occasionally other areas
- Development of a clot within blood vessels, can occur in arteries or veins
- Swelling (inflammation) of a vein caused by a blood clot
- Severe, whole-body allergic reaction (anaphylaxis)
- Systemic vasodilation (widening of blood vessels) which results in low blood pressure
- Confusion
- Increase of T4 (total thyroxin), increase of T3 (total trijodthyronin)

Very rare side effects (less than 1 in 10,000 patients):
- 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)
- Difficulty in articulating words
- Confusion
- Mental confusion or impaired awareness especially regarding to time, place or identity
- Abnormal muscular weakness or fatigue
- Acute cerebellar syndrome
- Partial or total loss of the ability to communicate verbally or using written words.
- Convulsion or coma in patients receiving high doses of 5-fluorouracil and in patients with dihydropyrimidine dehydrogenase deficiency
- Kidney failure
- Damage of liver cells (cases with fatal outcome)
- Inflammation of the gall bladder
- Slow progressive destruction of the small bile ducts

Not Known (Frequency cannot be estimated from the available data):
- Fever
- Numbness or weakness of the arms and legs
- Hyperammonaemic encephalopathy (brain dysfunction caused by elevated ammonia)
- 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)
- 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)

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via: 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

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.

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.

Do not use if the product appears brown or dark yellow in solution.

Do not use this medicine if you notice that the container is damaged or particles/crystals are visible.

Do not throw away any medicines via wastewater. 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 contains
- The active substance is fluorouracil.
- The other ingredients are trometamol, sodium hydroxide and water for injections.

What Fluorouracil looks like and contents of the pack
Fluorouracil 50 mg/ml, Solution for injection or Infusion is a clear, colourless to almost colourless solution in a type I clear glass vial with rubber closure.

1 ml of solution contains 50 mg of fluorouracil (as sodium salt formed in situ).
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 100 ml vial contains 5000 mg of fluorouracil.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Hikma Farmacêutica (Portugal), S.A.
Estrada do Rio da Mó, 8, 8A e 8B – Fervença
2705-906 Terrugem SNT
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Manufacturer
Thymoorgan Pharmazie GmbH
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Shelf life and storage
Shelf life of unopened vial:
Presentation 250 mg/5 ml – 18 months
Presentation 500 mg/10 ml – 2 years
Presentation 1000 mg/20 ml – 2 years
Presentation 5000 mg/100 ml – 2 years

Shelf Life after dilution
In use: Chemical and physical in-use stability has been demonstrated for 5 days at 20º - 25ºC and 2º - 8ºC with Water for Injection, Glucose 5% and Sodium Chloride 0.9% solutions at concentrations 0.5 mg/ml, 2.0 mg/ml and 4.0 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.