

## **Package leaflet: Information for the user**

### **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, 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 in this leaflet**

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

#### **1. What Fluorouracil is and what it is used for**

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

This medicine 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 taking brivudin, sorivudin and analogues (an antiviral medicine)
- 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 . 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 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 have 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**

Tell your doctor or nurse if you are using, have recently used or might use any other medicines. In particular tell your doctor if you are taking any of the following medicines because they affect how Fluorouracil works:

- 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, sorivudine and analogues (an antiviral)
- Cisplatin (an anti-cancer 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**

You must not take this medicine 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 medicine 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 advised 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 events on your nervous system and visual changes. If you experience any of these effects, do not drive or use any tools or machines, because they may impair your ability to drive or use machines

### **Fluorouracil contains sodium**

This product contains sodium approximately from 0.34 to 0.39mmol/ml (or 7.9–9.0 mg/ml) of solution in the form of Sodium Hydroxide. This information should be taken into consideration in patients with controlled intake of sodium.

## **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 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 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 nurse 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 medicine ask your doctor.

#### **4. Possible side effects**

Like all medicines, this medicine can have 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 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 (decrease in number of red blood cells that can cause tiredness and lack of energy )               | • 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 throat)                |
| • Inflammation of the rectum or anus  | • Loss of appetite  | • Watery diarrhoea  |
| • Nausea  | • Vomiting  | • Hair loss   |

- Delayed wound healing
- Bleeding from the nose
- Hand-foot syndrome (a toxic skin reaction That may cause redness, tenderness, and possibly peeling of the palms and soles)
- General weakness
- Tiredness
- Fatigue
- Inflammation of the mucous lining of the mouth
- Inflammation of the esophagus (the tube that connects your mouth to your stomach)
- Lack of energy
- Increase in uric acid in the blood

**Common** (may affect up to 1 in 10 patients)

- Angina pectoris (severe chest pain )

**Uncommon** (may affect up to 1 in 100 patients)

- Abnormal heart rhythm
- Heart attack
- Myocardial ischemia (lack of oxygen to the heart muscle)
- Myocarditis (inflammatory disease of the heart muscle)
- Heart failure
- 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 sick
- Inflammation of the skin
- Skin alterations such as dry skin, cracks (fissure), loss of skin (erosion), redness , pruritic maculopapular rash (rash that originates on the arms and then moves to the arms, and then chest)
- A skin eruption accompanying certain infectious diseases
- Appearance of itchy, red marks on the skin
- Sensitivity to sun (photosensitivity)
- Darkening of parts of the skin (hyperpigmentation)
- Streaky darkening (hyperpigmentation) or
- Changes in the nails (e.g. blue coloring near the
- Paronychia (Inflammation of the tissue surrounding a

lightenng (depigmentation) near the veins.	surface, darkening (hyperpigmentation); misshapen nails, pain and thickening of the nail bed.	fingernail)
<ul style="list-style-type: none"> <li>• An inflammation of the matrix of the nail with formation of pus and shedding of the nail</li> <li>• Secretion of tears</li> </ul>	<ul style="list-style-type: none"> <li>• Sperm or egg (ovum) production disorder</li> <li>• Blurred vision,</li> </ul>	<ul style="list-style-type: none"> <li>• liver cell damage</li> </ul>
<ul style="list-style-type: none"> <li>• Eye movement disturbance</li> </ul>	<ul style="list-style-type: none"> <li>• Optic neuritis (a vision disorder characterized by inflammation of the optic nerve)</li> </ul>	<ul style="list-style-type: none"> <li>• Inflammation or redness of the lining of the white part of the eye and the underside of the eyelid.</li> <li>• double vision</li> </ul>
<ul style="list-style-type: none"> <li>• decrease in visual sharpness</li> </ul>	<ul style="list-style-type: none"> <li>• excessive sensitivity to light and the aversion to sunlight or well-lit places</li> </ul>	<ul style="list-style-type: none"> <li>• oculardisease characterized by chronic inflammation of the eyelid margins</li> </ul>
<ul style="list-style-type: none"> <li>• lower eyelid turns outwards</li> </ul>	<ul style="list-style-type: none"> <li>• Blocked tear ducts</li> </ul>	<ul style="list-style-type: none"> <li>• A layer or mass of dead tissue separated from surrounding living tissue, as in a wound, a sore, or an inflammation.</li> </ul>

**Rare** (may affect up to 1 in 1,000 patients)

<ul style="list-style-type: none"> <li>• Insufficient blood flow in brain, intestine and peripheral organs</li> </ul>	<ul style="list-style-type: none"> <li>• discoloration of the fingers, toes, and occasionally other areas</li> </ul>	<ul style="list-style-type: none"> <li>• Generalized allergic reaction</li> </ul>
<ul style="list-style-type: none"> <li>• swelling (inflammation) of a vein caused by a blood clot</li> </ul>	<ul style="list-style-type: none"> <li>• severe, whole-body allergic reaction (anaphylaxis)</li> </ul>	<ul style="list-style-type: none"> <li>• Development of a clot within blood vessels, can occur in arteries or veins</li> </ul>
<ul style="list-style-type: none"> <li>• systemic vasodilation (widening of blood vessels) which results in low blood pressure</li> </ul>	<ul style="list-style-type: none"> <li>• confusion</li> </ul>	<ul style="list-style-type: none"> <li>• Increase in thyroid hormones- T4 (thyroxine), T3 (trijodthyronin)</li> </ul>

**Very rare** (may affect up to 1 in 10,000 patients)

<ul style="list-style-type: none"> <li>• Cardiac arrest (sudden cessation of heartbeat and cardiac function)</li> </ul>	<ul style="list-style-type: none"> <li>• Sudden cardiac death (unexpected death due to heart problems)</li> </ul>	<ul style="list-style-type: none"> <li>• Symptoms of leucoencephalopathy (diseases affecting the white substance of the brain) including ataxie (loss of the ability to coordinate muscular movement)</li> </ul>
<ul style="list-style-type: none"> <li>• Acute cerebellar syndrome</li> </ul>	<ul style="list-style-type: none"> <li>• Difficulty pronouncing words clearly</li> </ul>	<ul style="list-style-type: none"> <li>• Confusion</li> </ul>
<ul style="list-style-type: none"> <li>• Mental confusion or impaired awareness especially regarding to</li> </ul>	<ul style="list-style-type: none"> <li>• Partial or total loss of the ability to communicate verbally or</li> </ul>	<ul style="list-style-type: none"> <li>• Abnormal muscular weakness or fatigue</li> </ul>

- time, place or identity
- Convulsion or coma in patients receiving high doses of fluorouracil and in patients with dihydropyrimidine dehydrogenase deficiency
- inflammation of the gall bladder
- using written words.
- kidney failure
- slow progressive destruction of the small bile ducts
- Damage of liver cells (cases with fatal outcome)

**Not known** (frequency cannot be estimated from the available data):

- fever
- numbness or weakness of the arms and legs

### **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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: [www.hpra.ie](http://www.hpra.ie); e-mail: [medsafety@hpra.ie](mailto:medsafety@hpra.ie).

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. Single use only. Discard any unused portion.

Storage of the unopened vial: Do not store above 25°C. Do not refrigerate or freeze.

Shelf life after dilution: Chemical and physical in-use stability has been demonstrated for 5 days at 20-21°C and for 24 hours at 2°C to 8°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 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 this medicine if it appears brown or dark yellow in solution.

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

Since this product will be administered by a healthcare professional, the medical staff are responsible for the correct storage of the product both before and during its use, as well as for the correct disposal

## **6. Contents of the pack and other information**

### **What Fluorouracil contains**

- The active substance is fluorouracil. One (1) ml of solution contains 50 mg of fluorouracil.
- The other ingredients are water for injections and sodium hydroxide.

### **What Fluorouracil looks like and content of the pack**

Fluorouracil is clear colourless to yellow solution available in Type I flint moulded vials with a grey rubber closure and grey flip-off aluminium seal.

Each 10 ml vial contains 500 mg of fluorouracil.

Each 20 ml vial contains 1 g of fluorouracil.

Each 50 ml vial contains 2.5g of fluorouracil.

Each 100 ml vial contains 5 g of fluorouracil.

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder and Manufacturer**

Marketing Authorisation Holder

Agila Specialties UK Limited

New Bridge Street House,

30-34 New Bridge Street,

London, EC4V 6BJ,

United Kingdom

Manufacturer

Pharmadox Healthcare Ltd.

KW20A Kordin Industrial park, Paola

PLA 3000, Malta



**This medicinal product is authorised in the Member States of the EEA under the following names:**

<b>Member states</b>	<b>Name of Medicinal Product</b>
Austria	Agicil 50 mg/ml Injektionslösung/Infusionslösung
Belgium	Agicil 50 mg/ml solution injectable/infusion
Cyprus	Agicil 50 mg / ml ενέσιμο διάλυμα/έγχυση
Denmark	Agicil 50 mg / ml injektions- /infusionsvæske, opløsning
Finland	Agicil 50 mg/ml injektio/infusioneste, liuos
Germany	Agicil 50 mg/ml Injektionslösung/Infusionslösung
Greece	Agicil 50 mg / ml ενέσιμο διάλυμα/έγχυση
Ireland	Fluorouracil 50 mg/ml Solution for injection or infusion
Italy	Fluorouracil Agila
Luxembourg	Agicil 50 mg/ml solution for injection/infusion
Malta	Agicil 50mg/ml solution for injection/infusion
Netherland	Agicil 50 mg/ml Oplossing voor injectie/infusie
Norway	Agicil 50 mg/ml injeksjons/infusionsvæske, oppløsning
Portugal	Agicil 50 mg/ ml, solução injectável /para perfusão
Spain	Agicil 50 mg/ml solución inyectable/perfusion
Sweden	Agicil 50 mg/ml injektions/infusionsvätska, lösning
United Kingdom	Agicil 50 mg/ml solution for injection/infusion

**The leaflet was last revised in 05/2015.**

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**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.

### **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.

### **Instructions for use**

Fluorouracil injection can be given by intravenous injection or 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.

### **Preparation Instructions**

Fluorouracil injection may be diluted with glucose 5% injection or sodium chloride 0.9% injection or water for injections immediately before parenteral use.

## **Dosage and Administration**

Selection of an appropriate dose and treatment regime depend upon the condition of the patient, the type of carcinoma being treated and whether fluorouracil is to be administered alone or in combination with other therapy. Initial treatment should be given in hospital and the total daily dose should not exceed 1 gram. It is customary to calculate the dose in accordance with patient's actual weight unless there is obesity, oedema or some other form of abnormal fluid retention such as ascites. In this case, ideal weight is used as the basis for calculation.

Reduction of the dose is advisable in patients with any of the following:

1. Cachexia
2. Major surgery within preceding 30 days
3. Reduced bone marrow function
4. Impaired hepatic or renal function

Fluorouracil injection can be given by intravenous injection.

### **ADULT DOSE**

The following regimen have been recommended for use as a single agent.

#### **Initial Treatment:**

This may be in the form of an infusion or an injection, the former usually being preferred because of lesser toxicity.

#### **Intravenous Infusion:**

15 mg/kg bodyweight or 600 mg/m<sup>2</sup> but not more than 1 g per infusion, diluted in 500 ml of 5% glucose or 0.9% NaCl injection and given by intravenous infusion at a rate of 40 drops per minute over 4 hours. Alternatively the daily dose may be infused over 30-60 minutes or may be given as a continuous infusion over 24 hours. The infusion may be repeated daily until there is evidence of toxicity (stomatitis, diarrhea, leucopenia or thrombocytopenia) or a total dose of 12-15 g has been reached.

#### **Intravenous Injection:**

12 mg/kg bodyweight or 480 mg/m<sup>2</sup> may be given daily for 3 days and then, if there is no evidence of toxicity (stomatitis, diarrhea, leucopenia or thrombocytopenia), 6 mg/kg or 240 mg/m<sup>2</sup> on alternate days for 3 further doses (day 5-7-9). An alternative regime is 15 mg/kg as a single intravenous injection once a week throughout the course.

#### **Maintenance Therapy:**

An initial intensive course may be followed by maintenance therapy providing there are no significant toxic effects. In all instances, toxic side effects must disappear before maintenance therapy is started.

Treatment can be continued with intravenous injections of 5 – 10 mg/kg bodyweight or 200-400 mg /m<sup>2</sup> at weekly intervals.

#### **In combination with Irradiation:**

Irradiation combined with 5-FU has been found to be useful in the treatment of certain types of metastatic lesions in the lungs and for the relief of pain caused by recurrent, inoperable growth. The standard dose of 5-FU should be used.

**Combination with other cytostatic agents:**

Fluorouracil can be used with other cytostatic agents. In this case the standard dose is reduced.

**Special populations**

Renal or hepatic impairment.

Caution is advised and the dose might need to be reduced in patients with renal or hepatic impairment.

**CHILDREN**

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

**ELDERLY**

No dosage adjustment necessary.

**Shelf Life and storage**

Shelf-life of unopened vial

10 months. Single use only. Discard any unused portion.

Do not store above 25°C. Do not refrigerate or freeze,

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

Chemical and physical in-use stability with the selected physiological solutions (0.9 % sodium chloride, 5 % dextrose and water for injections) at concentration 2.0 mg/ml has been demonstrated for 120 hours at 20-21°C and for 24 hours at 2°C to 8°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 normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions