

Public Assessment Report
Decentralised Procedure

**FLUOROURACIL 50MG/ML SOLUTION FOR
INJECTION OR INFUSION**

UK/H/1185/001/DC
UK Licence No: PL 20075/0078

ACCORD HEALTHCARE LIMITED

LAY SUMMARY

On 10th June 2009, the UK granted Accord Healthcare Limited a Marketing Authorisation (licence) for the medicine Fluorouracil 50mg/ml Solution for Injection or Infusion.

Fluorouracil Injection contains the active ingredient Fluorouracil. It is an anti-cancer medication. 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 and radiotherapy.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Fluorouracil 50mg/ml Solution for Injection or Infusion outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Fluorouracil 50mg/ml Solution for Injection or Infusion
Type of Application	Generic, Article 10.1
Active Substance	Fluorouracil
Form	Solution for Injection or Infusion
Strength	50mg/ml
MA Holder	Accord Healthcare Limited, Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF
Reference Member State (RMS)	UK
CMS	Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, Ireland, Italy, Latvia, Lithuania, The Netherlands, Poland, Portugal, Slovakia, Spain and Sweden
Procedure Number	UK/H/1185/001/DC
End of Procedure	Day 210 – 28 th April 2009

Module 2

Summary of Product Characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fluorouracil 50 mg/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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 1 g of fluorouracil.

Each 100 ml vial contains 5 g of fluorouracil.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection or Infusion.

A clear colourless solution with a pH in the range of 8.5 to 9.1.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluorouracil Injection may be used alone or in combination, for its palliative action in the management of common malignancies particularly cancer of the colon, and breast.

4.2 Posology and method of 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 1gram. 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 or, intravenous or intra-arterial infusion.

ADULT DOSE

The following regimens 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 /m² 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, diarrhoea, leucopenia or thrombocytopenia) or a total dose of 12-15 g has been reached.

Intravenous Injection:

12 mg/kg bodyweight or 480 mg/m² may be given daily for 3 days and then, if there is no evidence of toxicity (stomatitis, diarrhoea, leucopenia or thrombocytopenia), 6 mg/kg or 240 mg/m² 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.

Intra-arterial Infusion:

5/7.5 mg/kg bodyweight or 200-300 mg/m² daily may be given by 24 hour continuous intra-arterial infusion.

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/m² 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.

4.3 Contraindications

Hypersensitivity to the Fluorouracil or to any of the excipients.

Fluorouracil is contraindicated in the following

- Serious infections (e.g. Herpes zoster, chickenpox).
- Seriously debilitated patients.
- Bone marrow depression after radiotherapy or treatment with other antineoplastic agents.
- Management of non-malignant disease

5-Fluorouracil (5-FU) must not be given in combination with brivudin, sorivudin and analogues. Brivudin, sorivudin und analogues are potent inhibitors of the 5-FU-metabolising enzyme dihydropyrimidine dehydrogenase (DPD) (see section 4.4 and 4.5).

4.4 Special warnings and precautions for use

It is recommended that Fluorouracil should only be given by, or under the strict supervision of, a qualified physician who is conversant with the use of potent antimetabolites and has the facilities for regular monitoring of clinical, biochemical and haematological effects during and after administration. All patients should be admitted to hospital for initial treatment.

Adequate treatment with Fluorouracil is usually followed by leucopenia, the lowest white blood cell (W.B.C.) count commonly being observed between the 7th and 14th day of the first course, but occasionally being delayed for as long as 20 days. The count usually returns to normal by the 30th day. Daily monitoring of platelet and W.B.C. count is recommended and treatment should be stopped if platelets fall below 100,000 per mm³ or the W.B.C. count falls below 3,500 per mm³. If the total count is less than 2000 per mm³, and especially if there is granulocytopenia, it is recommended that the patient be placed in protective isolation in the hospital and treated with appropriate measures to prevent systemic infection.

Treatment should also be stopped at the first sign of oral ulceration or if there is evidence of gastrointestinal side effects such as stomatitis, diarrhoea, bleeding from the G.I. tract or haemorrhage at any site. The ratio between effective and toxic dose is small and therapeutic response is unlikely without some degree of toxicity. Care must be taken therefore, in the selection of patients and adjustment of dosage.

Fluorouracil should be used with caution in patients with reduced renal or liver function or jaundice. Isolated cases of angina, ECG abnormalities and rarely, myocardial infarction have been reported following administration of Fluorouracil. Care should therefore be exercised in treating patients who experience chest pain during courses of treatment, or patients with a history of heart disease. Dihydropyrimidine dehydrogenase (DPD) plays an important role in the metabolism of fluorouracil. There have been reports of increased fluorouracil toxicity in patients who have reduced activity/deficiency of DPD. If applicable, determination of DPD enzyme activity is indicated prior to the treatment with 5-fluoropyrimidines.

Nucleoside analogues, e.g. brivudin and sorivudin, which affect DPD activity may cause increased plasma concentrations and increased toxicity of fluoropyrimidines (see section 4.5). Therefore, an interval of at least 4 weeks between administration of fluorouracil and brivudin, sorivudin or analogues should be kept. In the case of accidental administration of nucleoside analogues to patients treated with fluorouracil, effective measures should be taken to reduce fluorouracil toxicity. Immediate hospitalisation is recommended. Any measure to prevent systemic infections and dehydration should be commenced.

Vaccination with a live vaccine should be avoided in patients receiving 5-fluorouracil due to the potential for serious or fatal infections. Contact should be avoided with people who have recently been treated with polio virus vaccine.

It is not advisable to prolonged exposure to sunlight because of the risk of photosensitivity.

Use with caution in patients who have had high-dose pelvic radiation.

Women of childbearing potential and men have to use effective contraception during and up to 6 months after treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Various agents have been reported to biochemically modulate the anti tumour efficacy or toxicity of Fluorouracil. Common drugs include methotrexate, metronidazole, leucovorin interferon alfa and allopurinol.

Fluorouracil should be avoided in combination with clozapine due to increased risk of agranulocytosis. Increased incidence of cerebral infarction has been reported in oropharyngeal cancer patients treated with 5-Fluorouracil and cisplatin.

Marked elevations of prothrombin time and INR have been reported in a few patients stabilised on warfarin therapy following initiation of Fluorouracil regimes.

The enzyme dihydropyrimidinehydrogenase (DPD) plays an important role in the metabolism of Fluorouracil. Medicinal products that affect DPD activity, such as the nucleoside analogues brivudin, sorivudin and chemically related analogues, may cause marked increases in fluorouracil plasma concentrations and thereby increase toxicity. A time interval of minimum 4 weeks between the intake of fluorouracil and brivudin, sorivudin and analogues is recommended (see section 4.4). Cimetidine has been reported to increase plasma concentrations of Fluorouracil, possibly by reduced hepatic metabolism.

In patients receiving phenytoin and 5-Fluorouracil concomitantly, an increase of phenytoin plasma concentration has been reported resulting in symptoms of phenytoin toxicity.

Fluorouracil enhances the action of other cytostatic drugs and irradiation therapy (see section 4.2).

Vaccination with live vaccines should be avoided in immunocompromised patients.

4.6 Pregnancy and lactation

Women of childbearing potential should be advised to avoid becoming pregnant and use an effective method of contraception during treatment with Fluorouracil and up to 6 months afterwards (see section 4.4). If the drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be fully informed of the potential hazard to the foetus and genetic counselling is recommended. Fluorouracil should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

There are no adequate and well-controlled studies in pregnant women, however, fatal defects and miscarriages have been reported.

Men treated with Fluorouracil are advised not to father a child during and for up to 6 months following cessation of treatment (see section 4.4). Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with Fluorouracil.

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machinery have been performed. Fluorouracil may induce side effects such as nausea and vomiting. It can also produce adverse event on nervous system and visual changes which could interfere driving or the usage of heavy machinery.

4.8 Undesirable effects

Frequencies are defined using the following convention:

Very common ($\geq 1/10$),

Common ($\geq 1/100$ to $< 1/10$),

Uncommon ($\geq 1/1000$ to $< 1/100$),

Rare ($\geq 1/10000$ to $< 1/1000$),

Very rare ($< 1/10000$),

Not known (cannot be estimated from the available data).

Cardiac disorders:Very common

Ischemic ECG abnormalities.

Common

Angina pectoris-like chest pain.

Uncommon

Arrhythmia, myocardial infarction, myocardial ischemia myocarditis, heart insufficiency, dilative cardiomyopathy, cardiac shock.

Very rare

Cardiac arrest, sudden cardiac death

Cardio toxic adverse events mostly occur during or within hours following the first treatment cycle.

There is an increased risk of cardio toxicity in patients with previous coronary heart disease or cardiomyopathy.

Blood and lymphatic system disorders:Very common

Myelosuppression (Onset: 7-10 days, Nadir: 9-14 days, Recovery: 21-28 days), neutropenia, thrombocytopenia, leucopenia, thrombocytopenia, agranulocytosis, anaemia and pancytopenia.

Nervous system disorders:Uncommon

Nystagmus, headache, dizziness, symptoms of Parkinson's disease, pyramidal signs, euphoria, somnolence

Very rare

Symptoms of leucoencephalopathy including ataxie, Acute cerebellar syndrome, nystagmus dysarthie, confusion, disorientation, amyasthenia, aphasia, convulsion or coma in patients receiving high doses of 5-fluorouracil and in patients with dihydropyrimidine dehydrogenase deficiency, kidney failure.

Eye disorders:Uncommon

Excessive lacrimation, blurred vision, eye movement disturbance, optic neuritis, diplopia, decrease in visual acuity, photophobia, conjunctivitis, blepharitis, ectropion, dacryostenosis

Gastrointestinal disorders:Very common

Gastrointestinal adverse events are very common and may be life-threatening. Mucositis (stomatitis, oesophagitis, pharyngitis, proctitis), anorexia, watery diarrhoea, nausea, vomiting.

Uncommon

Dehydration, sepsis, gastrointestinal ulceration and bleeding, sloughing

Skin and subcutaneous tissue disorders:Very common

Alopecia.

Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome) has been noted with protracted and high dose continuous infusion.

The syndrome begins with dysaesthesia of the palms and soles that progress to pain and tenderness. There is associated symmetrical swelling and erythema of the hand and foot.

Uncommon

Dermatitis, skin alterations (e.g. dry skin, fissure erosion, erythema, pruritic maculopapular rash), exanthema, urticaria, 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) and onycholysis..

Metabolism and nutrition disorders:

Very common

Hyperuricaemia.

Vascular disorders:

Rare

Cerebral, intestinal and peripheral ischemia, Raynaud's syndrome, thromboembolism, thrombophlebitis,

Uncommon

Hypotension

General disorders and administration site conditions:

Very common

Delayed wound healing, epistaxis, fatigue, general weakness, tiredness, lack of energy and generalized allergic reaction.

Immune system disorders:

Very common

Bronchospasm, immunosuppression with an increased risk of infection.

Rare

Generalized allergic reactions, anaphylaxis, anaphylactic shock.

Hepatobiliary disorders:

Uncommon

liver cell damage

Very rare

Liver necrosis (cases with fatal outcome), Biliary sclerosis, Cholecystitis

Reproductive system and breast disorder:

Uncommon

Spermatogenesis and ovulation disorder

4.9 Overdose

The symptoms and signs of overdosage are qualitatively similar to the adverse reactions but commonly are more pronounced particularly, the following adverse reactions might occur:

Nausea, vomiting, diarrhoea, gastrointestinal ulceration and bleeding, bone marrow depression (including thrombocytopenia, leukopenia, agranulocytosis).

Treatment consists of drug discontinuation and supportive measures (see section 4.4).

No specific antidotal therapy exists.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pyrimidine analogues

ATC code: L01BC02.

Fluorouracil is an analogue of uracil, a component of ribonucleic acid. The drug is believed to function as an antimetabolite. After intracellular conversion to the active deoxynucleotide, it interferes with the synthesis of DNA by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase. Fluorouracil may also interfere with RNA synthesis.

5.2 Pharmacokinetic properties

After intravenous administration, Fluorouracil is distributed through the body water and disappears from the blood within 3 hours. It is preferentially taken up by actively dividing tissues and tumours after conversion to its nucleotide. Fluorouracil readily enters the C.S.F. and brain tissue.

Following IV administration, the plasma elimination half-life averages about 16 minutes and is dose dependant. Following a single IV dose of Fluorouracil approximately 15 % of the dose is excreted

unchanged in the urine within 6 hours; over 90% of this is excreted in the first hour. The remainder is mostly metabolised in the liver to inactive metabolites by the usual body mechanisms for uracil. Hepatic impairment may result in slower metabolism of Fluorouracil and may require dose adjustment

5.3 Preclinical safety data

Preclinical information has not been included, as the clinical toxicity profile of fluorouracil has been established after many years of clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (For pH adjustment)
Hydrochloric acid (For pH adjustment)
Water for Injections

6.2 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.

6.3 Shelf life

Shelf life of unopened vial:

2 years.

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.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate or freeze.
Keep container in the outer carton in order to protect from light.
For storage condition of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Fluorouracil Injection 50 mg/ml, 5 ml is filled in 5 ml Ph.Eur Type I clear glass vials with rubber closure.

Fluorouracil Injection 50 mg/ml, 10 ml is filled in 10 ml Ph.Eur Type I clear glass vials with rubber closure.

Fluorouracil Injection 50 mg/ml, 20 ml is filled in 20 ml Ph.Eur Type I clear glass vials with rubber closure.

Fluorouracil Injection 50 mg/ml, 100ml is filled in 100 ml Ph.Eur Type I clear glass vials with rubber closure.

Pack sizes:

Pack of 1X 5 ml vial

Pack of 1X 10 ml vial

Pack of 1X 20 ml vial

Pack of 1X 100 ml vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The pH of Fluorouracil Injection is 8.9 and the drug has maximal stability over the pH range 8.5 and 9.1.

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

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.

Administration

For instruction on administration, see section 4.2.

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**Diluents**

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.

The product should be discarded if it appears brown or dark yellow in solution.

The remainder of solutions should be discarded after use: do not make up into multidose preparations.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited,
319, Pinner Road,
North Harrow,
Middlesex, HA1 4HF,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0078

- 9** **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY**
10/06/2009
- 10** **DATE OF REVISION OF THE TEXT**
10/06/2009



**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 given this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor nurse
- 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 any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

In this leaflet:

1. What Fluorouracil Injection is and what it is used for
2. Before you use Fluorouracil Injection
3. How Fluorouracil Injection is given
4. Possible side effects
5. How to store Fluorouracil Injection
6. Further 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 and breast. It may be used in combination with other anti-cancer medicines and radiotherapy.

2. 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.
- if you have serious infections (e.g. Herpes zoster, chickenpox)

Module 3

- 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)

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 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.

Taking other medicines:

Please tell your doctor if you are taking any of the following medicines or have recently taken any other medicines including medicines obtained without a prescription

- 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 anticancer medicine)
- Phenytoin (used to control epilepsy/fits and irregular heart rhythm)
- Vaccines

The above medicines affect the effect of Fluorouracil.

Pregnancy and breast-feeding:

If you are a women of childbearing potential you must use an effective method of contraception while taking this drug and atleast 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 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.

3. How Fluorouracil Injection is 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 liver and kidneys are working. It will also depend on the results of your blood tests. The dose should not be more than 1 g per day. 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 either 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 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, Fluorouracil can have side effects, although not everybody gets them.

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
- Secretion of tears
- Blurred vision
- Eye movement disturbance
- Optic neuritis (a vision disorder characterized by inflammation of the optic nerve)

- Inflammation or redness of the lining of the white part of the eye and the underside of the eyelid.
- 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

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)

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
- Sperm or ovum production disorder
- Generalized allergic reaction

Rare side effects (more than 1 in 10,000 but less than 1 in 1,000 patients):

- 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
- Sperm or ovum production disorder

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)
- Loss of the ability to coordinate muscular movement
- Difficulty in articulating words
- Confusion
- Mental confusion or impaired awareness
- Especially regarding place
- Abnormal muscular weakness or fatigue
- Rhythmic, oscillating motions of the eyes
- Acute cerebellar syndrome
- Partial or total loss of the ability to communicate verbally or using written words.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist

5. How to store Fluorouracil Injection

- Keep out of the reach and sight of children.
- Do not use Fluorouracil Injection 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.

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.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further 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:

1ml 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 1 g of Fluorouracil

Each 100 ml vial contains 5 g of Fluorouracil

Not all pack sizes may be marketed

Marketing Authorization Holder and Manufacturer:

Accord Healthcare Limited
Sage House,
319, Pinner Road,
North Harrow,
Middlesex, HA1 4HF,
United Kingdom

The leaflet was last approved in 05/2009.

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.

Instructions for use

Fluorouracil Injection can be given by intravenous injection, or intravenous or intra-arterial 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 vials

2 years. Single use only. Discard any unused portion.

Store below 25°C. Do not refrigerate or freeze. Keep container in the

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.

outer carton in order to protect from light.

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.

- 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.

Module 4 Labelling



**Fluorouracil 50 mg/ml Solution
for Injection or Infusion**

Fluorouracil
For intravenous use and intra-arterial use.
Read the package leaflet before use.

250 mg/5 ml PL 20075/0078
PA 1390/015/001

accord
Code: Guj/Drugs/1025

1 x 5 ml Vial

Varnish Free Area

EXP
Lot

**Fluorouracil 50 mg/ml Solution
for Injection or Infusion**

Fluorouracil
For intravenous use and intra-arterial use.
Read the package leaflet before use.

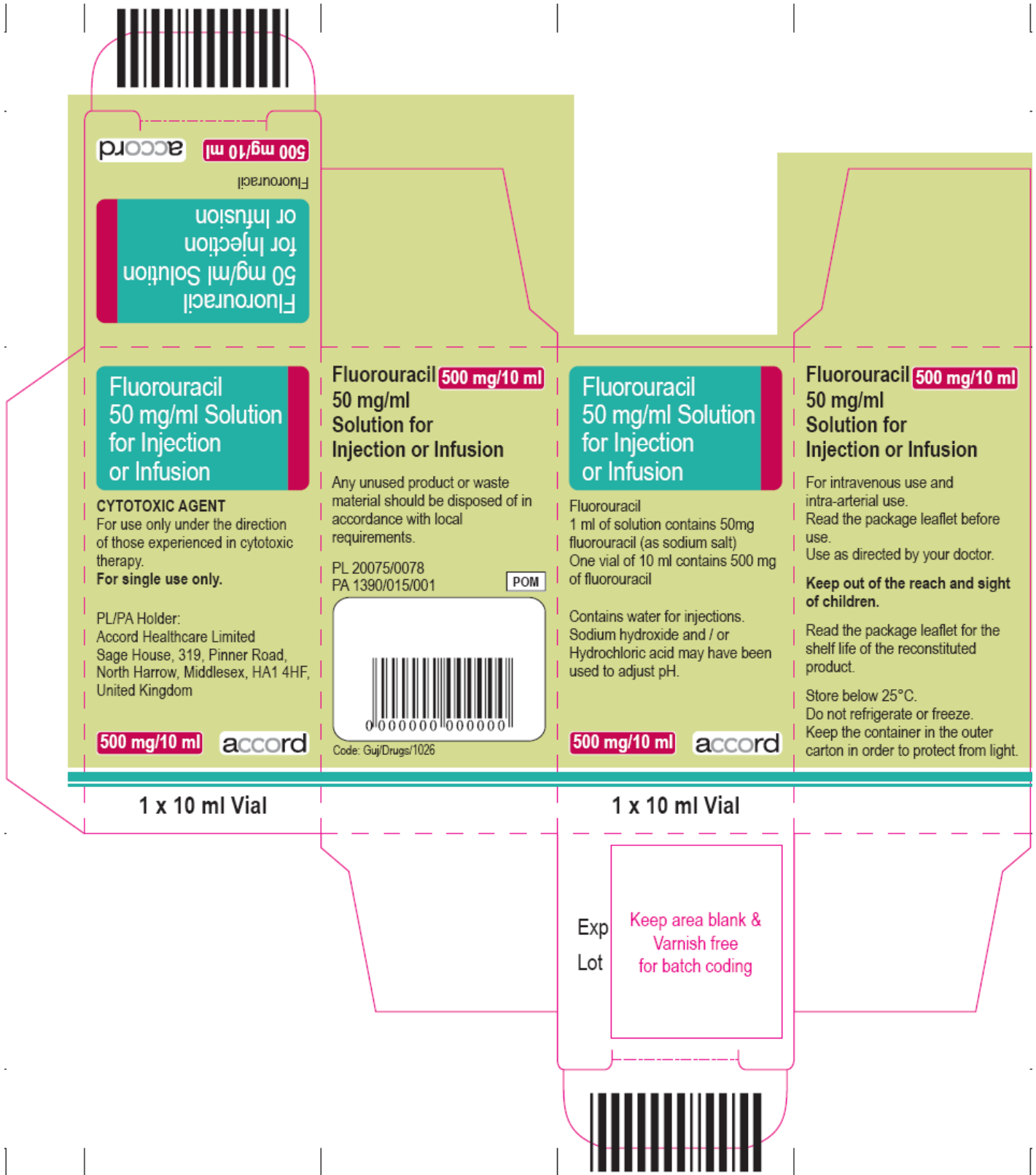
250 mg/5 ml PL 20075/0078
PA 1390/015/001

accord
Code: Guj/Drugs/1026

1 x 5 ml Vial

Varnish Free Area

EXP
Lot



**Fluorouracil 50 mg/ml Solution
for Injection or Infusion**

Fluorouracil
For intravenous use and intra-arterial use.
Read the package leaflet before use.

500 mg/10 ml PL 20075/0078
PA 1390/015/001

accord
Code: Guj/Drugs/1026

1 x 10 ml Vial

Varnish Free Area

EXP
Lot

**Fluorouracil 50 mg/ml Solution
for Injection or Infusion**

Fluorouracil
For intravenous use and intra-arterial use.
Read the package leaflet before use.

500 mg/10 ml PL 20075/0078
PA 1390/015/001

accord
Code: Guj/Drugs/1026

1 x 10 ml Vial

Varnish Free Area

EXP
Lot



1 g/20 ml accord

Fluorouracil

Fluorouracil 50 mg/ml Solution for Injection or Infusion

Fluorouracil 50 mg/ml Solution for Injection or Infusion

CYTOTOXIC AGENT
For use only under the direction of those experienced in cytotoxic therapy.
For single use only.

PL/PA Holder:
Accord Healthcare Limited
Sage House, 319,
Pinner Road, North Harrow,
Middlesex, HA1 4HF,
United Kingdom

1 g/20 ml accord

Fluorouracil 50 mg/ml Solution for Injection or Infusion

Any unused product or waste material should be disposed of in accordance with local requirements.

PL 20075/0078
PA 1390/015/001

POM



Code: Guj/Drugs/1026

Fluorouracil 50 mg/ml Solution for Injection or Infusion

Fluorouracil
1 ml of solution contains 50mg fluorouracil (as sodium salt)
One vial of 20 ml contains 1 g of fluorouracil

Contains water for injections. Sodium hydroxide and / or Hydrochloric acid may have been used to adjust pH.

1 g/20 ml accord

Fluorouracil 50 mg/ml Solution for Injection or Infusion

For intravenous use and intra-arterial use.
Read the package leaflet before use.
Use as directed by your doctor.

Keep out of the reach and sight of children.

Read the package leaflet for the shelf life of the reconstituted product.

Store below 25°C.
Do not refrigerate or freeze.
Keep the container in the outer carton in order to protect from light.

1 x 20 ml Vial

1 x 20 ml Vial

Exp
Lot

Keep area blank & Varnish free for batch coding



**Fluorouracil 50 mg/ml
Solution for Injection
or Infusion**

Fluorouracil
**For intravenous use and intra-arterial
use.**
Read the package leaflet before use.

1 g/20 ml PL 20075/0078
PA 1390/015/001 **accord**
Code: Guj/Drugs/1026

1 x 20 ml Vial

Varnish Free Area

EXP
Lot

**Fluorouracil 50 mg/ml
Solution for Injection
or Infusion**


Fluorouracil
**For intravenous use and intra-arterial
use.**
Read the package leaflet before use.

1 g/20 ml PL 20075/0078
PA 1390/015/001 **accord**
Code: Guj/Drugs/1026

1 x 20 ml Vial

Varnish Free Area

EXP
Lot



Keep area blank &
Varnish free
for batch coding

Exp
Lot

Fluorouracil 50 mg/ml
Solution for Injection
or Infusion

Fluorouracil 5 g/100 ml

50 mg/ml
Solution for Injection or
Infusion

Any unused product or waste material should be disposed of in accordance with local requirements.

PL 20075/0078
PA 1390/015/001

POM

Fluorouracil 50 mg/ml
Solution for Injection
or Infusion

Fluorouracil 5 g/100 ml

50 mg/ml
Solution for Injection or
Infusion

Fluorouracil
1 ml of solution contains 50mg
fluorouracil (as sodium salt)
One vial of 100 ml contains 5 g of
fluorouracil

Contains water for injections.
Sodium hydroxide and / or Hydrochloric
acid may have been used to adjust pH.

Fluorouracil 50 mg/ml
Solution for Injection
or Infusion

Fluorouracil 5 g/100 ml

50 mg/ml
Solution for Injection or
Infusion

For intravenous use and intra-arterial use.
Read the package leaflet before use.
Use as directed by your doctor.


Keep out of the reach and sight of
children.

Read the package leaflet for the shelf
life of the reconstituted product.

Store below 25°C.
Do not refrigerate or freeze.
Keep the container in the outer carton in
order to protect from light.

5 g/100 ml

accord



Code: Guj/Drugs/1026

5 g/100 ml

accord

1 x 100 ml Vial

1 x 100 ml Vial

Fluorouracil 50 mg/ml Solution for Injection or Infusion

Fluorouracil
 1 ml of solution contains 50mg fluorouracil (as sodium salt)
 One vial of 100 ml contains 5 g of fluorouracil
 Contains water for injections.
 Sodium hydroxide and / or Hydrochloric acid may have been used to adjust pH.
 For intravenous use and intra-arterial use. Read the package leaflet before use.
 Use as directed by your doctor.
Keep out of the reach and sight of children.
 Read the package leaflet for the shelf life of the reconstituted product.
 Store below 25°C. Do not refrigerate or freeze.
 Keep the container in the outer carton in order to protect from light.

CYTOTOXIC AGENT
 For use only under the direction of those experienced in cytotoxic therapy.
For single use only.

PL/PA Holder:
 Accord Healthcare Limited
 Sage House, 319, Pinner Road,
 North Harrow, Middlesex,
 HA1 4HF,
 United Kingdom

PL 20075/0078
 PA 1390/015/001

5 g/100 ml

POM

Any unused product or waste material should be disposed of in accordance with local requirements.



Code: Guj/Drugs/1008

1 X 100 ml Vial

Varnish Free Area

EXP

Lot

Fluorouracil 50 mg/ml Solution for Injection or Infusion

Fluorouracil
 1 ml of solution contains 50mg fluorouracil (as sodium salt)
 One vial of 100 ml contains 5 g of fluorouracil
 Contains water for injections.
 Sodium hydroxide and / or Hydrochloric acid may have been used to adjust pH.
 For intravenous use and intra-arterial use. Read the package leaflet before use.
 Use as directed by your doctor.
Keep out of the reach and sight of children.
 Read the package leaflet for the shelf life of the reconstituted product.
 Store below 25°C. Do not refrigerate or freeze.
 Keep the container in the outer carton in order to protect from light.

CYTOTOXIC AGENT
 For use only under the direction of those experienced in cytotoxic therapy.
For single use only.


PL/PA Holder:
 Accord Healthcare Limited
 Sage House, 319, Pinner Road,
 North Harrow, Middlesex,
 HA1 4HF,
 United Kingdom

PL 20075/0078
 PA 1390/015/001

5 g/100 ml

POM

Any unused product or waste material should be disposed of in accordance with local requirements.



Code: Guj/Drugs/1026

1 X 100 ml Vial

Varnish Free Area

EXP

Lot

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, Ireland, Italy, Latvia, Lithuania, The Netherlands, Poland, Portugal, Slovakia, Spain, Sweden and the UK considered that the application for Fluorouracil 50mg/ml Solution for Injection or Infusion could be approved. The product is a prescription only medicine (POM) which may be used alone or in combination for its palliative action in the management of common malignancies particularly cancer of the colon, and breast

This application for Fluorouracil 50mg/ml Solution for Injection or Infusion is submitted as an abridged standard application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product to Cinkef-U 50mg/ml Solução injetável, first authorised in the European Economic Area (EEA) to Mayne Pharma since August 1997.

The product contains the active substance fluorouracil, an anti-neoplastic agent that is used for the palliative treatment of a number of malignancies, both as a single agent and in combination with other agents.

No new preclinical studies were conducted, which is acceptable given that the product contains a widely-used, well-known active substance. No clinical studies have been performed and none are required for this application as the pharmacology of fluorouracil is well-established. No clinical pharmacology data is required for this generic solution for injection or infusion.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Fluorouracil 50mg/ml Solution for Injection or Infusion
Name(s) of the active substance(s) (INN)	Fluorouracil
Pharmacotherapeutic classification (ATC code)	Pyrimidine analogues (L01BC02)
Pharmaceutical form and strength(s)	50mg/ml Solution for Injection or Infusion
Reference numbers for the Decentralised Procedure	UK/H/1185/001/DC
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, Ireland, Italy, Latvia, Lithuania, The Netherlands, Poland, Portugal, Slovakia, Spain and Sweden
Marketing Authorisation Number(s)	PL 20075/0078
Name and address of the authorisation holder	Accord Healthcare Limited, Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF

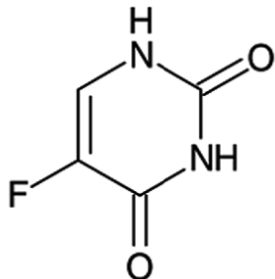
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Fluorouracil
Chemical name: 5-Fluoro-1H, 3H-pyrimidine-2,4-dione
5-Fluoro-2,4(1H, 3H) pyrimidinedione
2,4-dioxo-5-fluoro pyrimidine

Structural formula:



Molecular formula: $C_4H_3FN_2O_2$

Appearance: White or almost white crystalline powder.
Solubility: Sparingly soluble in water, slightly soluble in alcohol and practically insoluble in chloroform and ether.
Molecular weight: 130.1
Chirality: This does not have a chiral centre.

Fluorouracil is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture of the active substance fluorouracil from its starting materials are controlled by a Certificate of Suitability.

An appropriate retest period has been proposed based on stability data submitted for the active substance fluorouracil.

An appropriate specification is provided for the active substance, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specification.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients sodium hydroxide, hydrochloric acid and water for injections.

All excipients comply with their European Pharmacopoeia monograph.

None of the excipients contain materials of animal or human origin. No genetically modified

organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development

The objective of the development programme was to produce a product that could be considered a generic medicinal product of Cinkef-U 50mg/ml Solução injectável (Mayne Pharma, August 1997).

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished product versus the reference product Cinkef-U 50mg/ml Solução injectável (Mayne Pharma).

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. The applicant has committed to perform process validation with the three commercial scale batches of the drug product.

Finished Product Specification

The finished product specification proposed for the product is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container-Closure System

The product is packaged in type I glass vials with rubber closure. Specifications and certificates of analysis for the packaging used have been provided. The product is packaged in sizes of 5ml, 10ml, 20ml and 100ml vials.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the European Pharmacopoeia Type I and relevant regulations regarding use of materials in contact with food.

Stability of the product

Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of two years for an unopened product with storage conditions “Store below 25°C” and “Do not refrigerate or freeze” and “Keep container in the outer carton in order to protect from the light”.

Shelf life of the product after dilution, in use has been demonstrated for 24 hours at 25°C. However, after dilution, the product should be used almost immediately, with storage conditions “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.”

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels

The SPC, PIL and labelling are pharmaceutically acceptable.

User testing results have been submitted for a typical PIL for this product. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms

The MAA form is pharmaceutically satisfactory.

Expert report

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion

The grant of a marketing authorisation is recommended.

III.2 PRE-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of fluorouracil are well-known. As fluorouracil is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required.

The pre-clinical expert report is based on literature sources and has been written by an appropriately qualified person.

III.3 CLINICAL ASPECTS

1. Introduction

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. For more details, the reader should refer to the company's clinical overview and summary and to the clinical file.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

2. Clinical study reports

No bioequivalence studies have been performed and none are required for this application, as the applicant's product is similar to the reference product in terms of qualitative and quantitative composition and is expected to perform identically *in vivo*. A human bioavailability study is not relevant to this application as the compound is intended for injection or infusion.

3. Post marketing experience

Fluorouracil has a well-recognised efficacy and an acceptable level of safety in the indications approved for Fluorouracil 50mg/ml Solution for Injection or Infusion, and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the marketing authorisation is supported.

4. Benefit-Risk assessment

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with fluorouracil is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

5. Conclusions

The grant of a marketing authorisation for Fluorouracil 50mg/ml Solution for Injection or Infusion is recommended from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY

The important quality characteristics of Fluorouracil 50mg/ml Solution for Injection or Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

CLINICAL

No bioequivalence studies have been performed and none are required for this application, given the composition of the product and its intended route of administration.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with fluorouracil is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome