

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fluorouracil Injection 25 mg/ml, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of Fluorouracil Injection contains:
2500 mg fluorouracil in 100 ml solution (25 mg/ml)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Fluorouracil Injection 25 mg/ml, solution for injection, is a clear, colourless or almost colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluorouracil Injection 25 mg/ml, solution for 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, either as single agent or in combination with other cytotoxic agents.

4.2 Posology and method of administration

Routes of administration:

Fluorouracil Injection can be given by intravenous injection or intravenous or intra-arterial infusion.

Adults:

Selection of an appropriate dose and treatment regime depends 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 0.8 – 1 gram. It is customary to calculate the dose in accordance with the patient's actual bodyweight 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.

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 but not more than 1 g per infusion, diluted in 300 – 500 ml of 5 % glucose or 0.9 % NaCl injection and given 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 or a total dose of 12 – 15 g has been reached.

Intravenous Injection:

12 mg/kg bodyweight may be given daily for 3 days and then, if there is no evidence of toxicity, 6 mg/kg on alternate days for three further doses. 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 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.

The initial course of fluorouracil can be repeated after an interval of 4 – 6 weeks from the last dose or, alternatively, treatment can be continued with intravenous injections of 5 – 15 mg/kg bodyweight at weekly intervals.

This sequence constitutes a course of therapy. Some patients have received up to 30 g at a maximum rate of 1 g daily. A more recent alternative method is to give 15 mg/kg IV once a week throughout the course of treatment. This obviates the need for an initial period of daily administration.

In combination with Irradiation:

Irradiation combined with fluorouracil 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 fluorouracil should be used.

CHILDREN:

No recommendations are made regarding the use of fluorouracil in children.

ELDERLY:

Fluorouracil should be used in the elderly with similar considerations as with normal adult doses.

4.3 Contraindications

Fluorouracil is contraindicated in seriously debilitated patients or those with bone marrow depression after radiotherapy or treatment with other antineoplastic agents.

Fluorouracil is strictly contraindicated in pregnant or breast feeding women.

Fluorouracil should not be used in the management of non-malignant disease.

Fluorouracil is contraindicated in patients who have had a serious hypersensitivity reaction to previous doses of fluorouracil or any of its constituents.

Fluorouracil must not be taken or used concomitantly with brivudin, sorivudine and analogues. Brivudin, sorivudine and analogues are potent inhibitors of the enzyme dihydropyrimidine dehydrogenase (DPD) which degrades fluorouracil (see also sections 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.

All patients should be admitted to hospital for initial treatment.

Adequate treatment with fluorouracil is usually followed by leukopenia, the lowest white blood cell (WBC) 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 WBC count is recommended and treatment should be stopped if platelets fall below 100,000 per mm³ or the WBC count falls below 3,500 per mm³. If the total count is less than 2,000 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 GI 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. Caution should therefore be exercised in treating patients who experience chest pain during courses of treatment, or patients with a history of heart disease.

There have been reports of increased toxicity in patients who have reduced activity/deficiency of the enzyme dihydropyrimidine dehydrogenase.

The enzyme dihydropyrimidine dehydrogenase (DPD) plays an important role in the degradation of fluorouracil. The nucleoside analogues, such as brivudin and sorivudine, can cause a sharp rise in the plasma concentration of 5-fluorouracil or other fluoropyrimidines, with accompanying toxic reactions. For this reason, a period of at least 4 weeks should elapse between taking or using fluorouracil and taking or using brivudin, sorivudine and analogues.

Where applicable, determination of DPD enzyme activity is indicated before starting treatment with 5-fluoropyrimidines. In the event of accidental administration of brivudin to patients being treated with fluorouracil, effective measures should be taken to reduce the toxicity of fluorouracil. Immediate admission to hospital is recommended. All measures should be initiated to prevent systemic infections and dehydration.

Patients taking phenytoin concomitantly with fluorouracil should undergo regular testing because of the possibility of an elevated plasma level of phenytoin.

4.5 Interaction with other medicinal products and other forms of interaction

Various agents have been reported to biochemically modulate the antitumour efficacy or toxicity of fluorouracil, common drugs include methotrexate, metronidazole, leucovorin as well as allopurinol and cimetidine which can affect the availability of the active drug.

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

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Where phenytoin and fluorouracil have been administered concomitantly, there have been reports of elevated plasma levels of phenytoin, resulting in symptoms of phenytoin intoxication (see 4.4).

Fluorouracil should be avoided in combination with clozapine due to the increased risk of agranulocytosis.

4.6 Pregnancy and lactation

Fluorouracil is strictly contraindicated in pregnant and breast feeding women.

4.7 Effects on ability to drive and use machines

Fluorouracil may induce side effects such as nausea and vomiting which could interfere with driving or the use of heavy machinery.

4.8 Undesirable effects

The most commonly reported undesirable effects are diarrhoea, nausea. Leukopenia is also very common and the precautions described above should be followed.

Frequency assessment:

Very common ($\geq 1/10$)

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

Uncommon ($\geq 1/1,000, < 1/100$)

Rare ($\geq 1/10,000, < 1/1,000$)

Very rare ($< 1/10,000$)

Not known (cannot be estimated from the available data)

Infections and infestations	<u>Very common</u> Infections <u>Uncommon</u> Sepsis
Blood and lymphatic system disorders	<u>Very common</u> Leukopenia, myelosuppression, neutropenia, granulocytopenia, thrombocytopenia, anemia, pancytopenia <u>Rare</u> Agranulocytosis
Immune system disorders	<u>Very common</u> Immunosuppression <u>Very rare</u> Anaphylactic reaction, anaphylactic shock
Endocrine disorders	<u>Rare</u> Increase of T4 (total thyroxin), increase of T3 (total triiodthyronin)
Metabolism and nutrition disorders	<u>Uncommon</u> Hyperuricemia
Psychiatric disorders	<u>Rare</u> Confusion
Nervous system disorders	<u>Rare</u> Ataxia, extrapyramidal motoric disturbances, cerebellar disturbances, cortical disturbances, nystagmus, headache, vertigo, parkinson-like symptoms, pyramid signs, euphoria, leuko-encephalopathy, speech disorders, aphasia, convulsions, coma, opticus neuritis, peripheral neuropathy
Eye disorders	<u>Common</u> Conjunctivitis

	<u>Uncommon</u> Excessive lacrimation, dacryostenosis, visual changes, photophobia, diplopia, decreased visus, blepharitis, ectropion
Cardiac disorders	<u>Common</u> Chest pain, tachycardia, ECG-changes, angina pectoris <u>Rare</u> Arrhythmia, myocardial infarction, myocarditis, heart failure, dilatative cardiomyopathy, cardiac shock, heart arrest, sudden cardiac death
Vascular disorders	<u>Rare</u> Vasculitis, Raynaud's phenomenon <u>Not known</u> Cerebral ischaemia, intestinal ischaemia, peripheral ischaemia, thromboembolism
Respiratory, thoracic and mediastinal disorders	<u>Uncommon</u> Epistaxis, dyspnea, bronchospasmus
Gastrointestinal disorders	<u>Very common</u> Diarrhoea, nausea, vomiting, mucositis, stomatitis <u>Uncommon</u> Gastrointestinal ulceration, gastrointestinal hemorrhage
Hepatobiliary disorders	<u>Uncommon</u> Liver cell damage <u>Rare</u> Liver necrosis
Skin and subcutaneous tissue disorders	<u>Very common</u> Alopecia, palmar-plantar erythrodysesthesia <u>Uncommon</u> Dermatitis, hyperpigmentation, hypopigmentation, nail discoloration, nail hyperpigmentation, nail dystrophy, nailbed pain, nailbed inflammation, onycholysis, exanthema, dry skin, urticaria, photosensitivity, recall phenomenon
General disorders and administration site conditions	<u>Very common</u> Fever, fatigue <u>Uncommon</u> Thrombophlebitis, vein tracking, dehydration

4.9 Overdose

Manifestations of overdose of fluorouracil can be nausea, vomiting, diarrhoea, gastrointestinal ulceration and bleeding, bone marrow depression (including thrombocytopenia, leukopenia and agranulocytosis). No specific antidotal therapy exists. Patients who have been exposed to an overdose of fluorouracil should be monitored haematologically for at least four weeks. Should abnormalities appear, appropriate therapy should be utilised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

Pharmacotherapeutic group: Antimetabolite

ATC code: L01BC02

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 CSF 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 by the usual body mechanisms for uracil.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide, 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, vinorelbin, other anthracyclines.

Formulated solutions are alkaline and it is recommended that admixture with acidic drug preparations should be avoided.

6.3 Shelf life

2 years

Fluorouracil Injection 25 mg/ml, solution for injection, is intended for single use only.

The chemical and physical in-use stability of the solution diluted with glucose or sodium chloride injection has been demonstrated for 24 hours at a temperature not exceeding 25 °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.

6.4 Special precautions for storage

Do not store Fluorouracil Injection 25 mg/ml, solution for injection, above 25 °C.

Do not refrigerate or freeze.

Keep the container in the outer carton.

If a precipitate has formed as a result of exposure to low temperatures, redissolve by heating to 40 °C accompanied by vigorous shaking. Allow to cool to body temperature prior to use.

6.5 Nature and contents of container

Type I conventional clear glass vials, rubber closures. The rubber stopper is protected by a flanged aluminium cap with a flip-off top.

2500 mg/100 ml: Pack Size: Singles, 10

6.6 Special precautions for disposal and other handling

Fluorouracil Injection 25 mg/ml, solution for injection, should only be opened by trained staff and as with all cytotoxic agents, precautions should be taken to avoid exposing staff during pregnancy. Preparation of solution for administration should be carried out in a designated handling area and working over a washable tray or disposable plastic-backed absorbent paper. Suitable eye protection, disposable gloves, face mask and disposable apron should be worn. Syringes and infusion sets should be assembled carefully to avoid leakage (use of Luer lock fittings is recommended).

On completion, any exposed surface should be thoroughly cleaned and hands and face washed. Fluorouracil is an irritant, contact with skin and mucous membranes should be avoided.

In the event of spillage, operators should put on gloves, face masks, 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.

Disposal:

All materials that have been utilised for dilution and administration should be disposed of according to standard procedures (incineration).

Diluents:

Fluorouracil injection 25 mg/ml, solution for injection, may be diluted with 5 % glucose or 0.9 % sodium chloride intravenous infusions immediately before parenteral use. The remainder of solutions should be discarded after use; do not make up into multi-dose preparations.

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.

Administrative Data**7. MARKETING AUTHORISATION HOLDER**

medac
Gesellschaft für klinische Spezialpräparate mbH
Fehlandtstr. 3
20354 Hamburg
Germany

8. MARKETING AUTHORISATION NUMBER

PL 11587/0021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 February 2003/2 April 2009

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June 2009