

יולי 2016

רופא/ה, רוקח/ת נכבד/ה
חברת טבע מודיעה שמשרד הבריאות אישר את העדכונים הבאים בעלון של התכשיר:

FLUOROURACIL 50mg/ml

פלואורואורציל 50 מ"ג/מ"ל

Contains: Fluorouracil 50mg/ml

עדכונים בעלון לצרכן במתכונת עלון לרופא

התוויה כפי שאושרה בתעודת הרישום:

Palliative management of carcinoma of the colon, rectum, breast, stomach and pancreas, in selected patients considered incurable by surgery or other means. As leucovorin-fluorouracil chemotherapy combination for cancer treatment.

העלון עודכן.
בפירוט שלהלן כלולים העדכונים העיקריים בלבד (תוספות מסומנות באדום והסרות מידע כטקסט מחוק):

4.2 Posology and method of administration

Note: when using leucovorin (calcium folinate) –fluorouracil chemotherapy combination, strict caution should be exercised not to mix the 2 drugs in the same administration set because of incompatibility (see section 6.2).

Selection of an appropriate dose and treatment regime will 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 should be used as the basis for the 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.

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

Children

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

Elderly

Fluorouracil should be used in the elderly with similar considerations as in younger adult dosages, notwithstanding that incidence of concomitant medical illness is higher in the former group.

4.4 Special warnings and precautions for use

It is recommended that fluorouracil be given only 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.

Fluorouracil is contraindicated in patients who have a poor nutritional state.

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 2000mm³, 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 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 gastrointestinal tract of haemorrhage at any site, oesophagopharyngitis or intractable vomiting. Fluorouracil should be resumed only when the patient has recovered from the above signs. 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. Treatment should be stopped in case of severe toxicity.

Fluorouracil should be used with extreme caution in poor risk patients who have recently undergone surgery, have a history of high-dose irradiation of bone marrow-bearing areas (pelvis, spine, ribs, etc.) or prior use of another chemotherapeutic agent causing myelosuppression, have a widespread involvement of bone marrow by metastatic tumours, or those with reduced renal or liver function, jaundice or who have a poor nutritional state.

Fluorouracil should also be used with caution in patients with heart disease. Isolated cases of angina, ECG abnormalities and rarely, myocardial infarction have been reported following administration of fluorouracil. Care should be therefore be exercised in treating patients who experience chest pain during courses of treatment, or patients with a history of heart disease.

Careful consideration should be given to re-administration of fluorouracil after a documented cardiovascular reaction (arrhythmia, angina, ST segment changes) as there is a risk of sudden death. Severe toxicity and fatalities are more likely in poor risk patients, but have occasionally occurred in patients who are in relatively good condition. Any form of therapy which adds to the stress of the patient, interferes with nutritional uptake or depresses the bone marrow function, will increase the toxicity of fluorouracil. If therapy is continued careful monitoring of the patient is required.

The cytotoxic drug fluorouracil must only be used under strict monitoring of a specialist with experience in cancer chemotherapy. The treatment should take place in a hospital where physicians are familiar with cancer chemotherapy. Both man and woman must take contraceptive measures during therapy and **up to 6** ~~for 3~~ months after discontinuation of therapy.

When fluorouracil is spilled, a lot of water should be used for rinsing (see 'Instructions for use and handling').

Fluorouracil should only be applied with utmost care in patients who recently underwent high dose-radiation therapy of the pelvis, in patients recently treated with alkylating cytotoxic drugs, in patients who underwent adrenalectomy or hypophysectomy and in patients with reduced hepatic or renal function.

Rarely, unexpected, severe toxicity (e.g., stomatitis, diarrhea, neutropenia and neurotoxicity) associated with fluorouracil has been attributed to deficiency of dipyrimidine dehydrogenase activity. A few patients have been rechallenged with 5-fluorouracil and despite fluorouracil dose lowering, toxicity recurred and progressed with worse morbidity. Absence of this catabolic enzyme appears to result in prolonged clearance of fluorouracil.

The most pronounced and dose-limiting toxic effects of fluorouracil are on the normal, rapidly proliferating cells of the bone marrow and the lining of the gastrointestinal tract. The immunosuppressive effect of fluorouracil may cause a higher incidence of microbial infections, delayed wound healing and bleeding of the gums.

Nucleoside analogues, e.g. Brivudin and sorivudin, which affect DPD activity may cause increased plasma concentrations and increased toxicity of fluoropyrimidines. 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.

4.5 Interaction with other medicinal products and other forms of interaction

Various purines, pyrimidines, and antimetabolites have shown biochemical modulation of fluorouracil in in vitro test systems. Purines include inosine, guanosine, guanosine-5'-phosphate and deoxyinosine. Pyrimidines include thymidine, uridine and cytidine. Antimetabolites include methotrexate, tamoxifen, interferon, phosphonoacteyl-L-aspartate (PALA), allopurinol, hydroxyurea, dipyridamol and leucovorin (folinic acid). Synergistic cytotoxic interactions, such as those involving fluorouracil with leucovorin, have shown

beneficial therapeutic effects, particularly in colon cancer. However, the drug combination may result in increased clinical toxicity (gastrointestinal side effects) of the fluorouracil component. Other drugs include metronidazole and cimetidine. Pretreatment with cimetidine prior to intravenous fluorouracil increased the fluorouracil area under the concentration versus time curve (AUC) by 27%. The total body clearance was reduced by 28%. This may lead to increased plasma concentrations of fluorouracil.

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

A clinically significant interaction between the antiviral sorivudine and fluorouracil prodrugs, resulting from inhibition of dihydropyrimidine dehydrogenase by sorivudine or chemically related analogues. Caution should be taken when using fluorouracil in conjunction with medications which may affect dihydropyrimidine dehydrogenase activity.

Combination therapy with fluorouracil and levamisole has been associated with multifocal inflammatory leukoencephalopathy (MILE). Symptoms may include memory loss, confusion, paraesthesia, lethargy, muscle weakness, speech disturbances, coma and seizures. The cerebrospinal fluid may show mild pleiocytosis, and computed tomography and magnetic resonance scans may show lesions in the white matter suggestive of demyelination. If this syndrome occurs, treatment should be discontinued immediately. The condition is at least partially reversible if fluorouracil and levamisole are discontinued, and corticosteroids given. The use of levamisole and fluorouracil is no longer recommended by NH&MRC 'Clinical Practice guidelines: The prevention, early detection and management of colorectal cancer'. This combination regimen has been superseded by fluorouracil and leucovorin.

Increased phenytoin plasma concentrations have been reported during concomitant use of phenytoin with capecitabine or its metabolite fluorouracil. Formal interaction studies between phenytoin and capecitabine have not been conducted, but the mechanism of interaction is presumed to be inhibition of CYP2C9 isoenzyme system by capecitabine. Serum levels of phenytoin sustained above the optimal range may produce encephalopathy, or confusional states (delirium psychosis), or rarely irreversible cerebellar dysfunction. Therefore, patients taking phenytoin concomitantly with capecitabine or fluorouracil should be regularly monitored for increased phenytoin plasma levels.

Vaccination with a live vaccine should be avoided in patients receiving 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.

Patients with leukaemia who are in remission should not receive vaccines containing weakened viruses until three months has elapsed since their last chemotherapy session. Furthermore, immunisation with orally administered vaccines containing the poliomyelitis virus must be postponed for those persons coming into direct contact with the patient, particularly family members.

~~Pharmacodynamic interactions may occur with other cytostatic drugs; the therapeutic and toxic effects will be potentiated. Methotrexate and 5-fluorouracil show a complicated interaction pattern. Concomitant administration of thymidine and 5-fluorouracil increase the plasma half-life of 5-fluorouracil. The combination, however, does not lead to an increased~~

~~therapeutic index of 5-fluorouracil. Concomitant administration of folinic acid in high dosages and 5-fluorouracil may result in an increased cytotoxic effect of 5-fluorouracil. Concomitant administration of allopurinol and 5-fluorouracil leads to a change in the pattern of side effects. Although the combination of allopurinol and 5-fluorouracil allows for a higher dosage of 5-fluorouracil, an increased cytotoxic effect of 5-fluorouracil has not been unequivocally established. After administration of 5-fluorouracil sun-exposed parts of the body may show hyperpigmentation.~~

4.6 Fertility, pregnancy and lactation

See 'Contraindications'. During fluorouracil therapy no breast feeding should be given.

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.

4.8 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).

Blood and lymphatic system disorders:

Very common: Myelosuppression (leucopenia, pancytopenia and thrombocytopenia); agranulocytosis, anaemia

Immune system disorders:

Rare: Hypersensitivity reactions, generalised anaphylactic and allergic reactions.

Psychiatric disorders:

Uncommon: Euphoria.

Rare: , a reversible confusional state may occur.

Very rare: Disorientation.

Eye disorders:

Systemic fluorouracil treatment has been associated with various types of ocular toxicity.

Uncommon: Incidences of excessive lacrimation, dacryostenosis, visual changes and photophobia.

Vascular disorders:

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

Uncommon: Hypotension

Gastrointestinal disorders:

Very common: Diarrhoea, nausea and vomiting are observed quite commonly during therapy and may be treated symptomatically. An anti-emetic may be given for nausea and vomiting. Additionally, events of anorexia, stomatitis (symptoms include soreness, erythema or ulceration of the oral cavity or dysphagia); proctitis, oesophagitis

Uncommon: gastrointestinal ulcerations and bleeding (may result in therapy being discontinued).

Skin and subcutaneous tissue disorders:

Very common: Alopecia may be seen in a substantial number of cases, particularly females, but is reversible.

Palmar-plantar erythrodysesthesia syndrome has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-fluorouracil. 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: Other side effects include dermatitis, pigmentation, changes in nails, (e.g. diffuse superficial blue pigmentation, hyperpigmentation, nail dystrophy, pain and thickening of the nail bed, paronychia) dry skin, fissure erosion, erythema, pruritic maculopapular rash, exanthema, photosensitivity, hyperpigmentation of the skin, streaky hyperpigmentation or depigmentation near the veins.

General disorders and administration site conditions:

Very common: Malaise, weakness

Not known: Fever, vein discolouration proximal to injection sites

Cardiac disorders:

Very common: ECG changes

Common: angina pectoris-like chest pain

Uncommon: , arrhythmia, myocardial infarction, myocardial ischaemia dilative cardiomyopathy

Very rare: Cardiac arrest and sudden cardiac death

Special attention is advisable in treating patients with a history of heart disease or those who develop chest pain during treatment.

Nervous system disorders:

Uncommon: Nystagmus, headache, dizziness, symptoms of Parkinson's disease, pyramidal signs, and somnolence.

Very rare: Cases of leucoencephalopathy have also been reported. With symptoms including ataxia, acute cerebellar syndrome, dysarthria, myasthenia, aphasia, convulsion or coma in patients receiving high doses of 5-fluorouracil and in patients with dihydropyrimidine dehydrogenase deficiency, kidney failure.

Not known: Peripheral neuropathy may occur

~~Haematotoxicity is frequent. After intravenous injection the leukocytes dropped to lowest point in 9-14 days. Thrombocytes were reduced to a minimum in 7-17 days.~~

~~Thrombocytopenia is less frequent than leukopenia and appears to recover less rapidly. In general, normal values are reached again within 30 days. The severity of the haematotoxicity appears to be less after infusion than after injection of fluorouracil.~~

~~Gastrointestinal toxicity is also frequent: stomatitis, anorexia, nausea, vomiting and diarrhoea. Stomatitis is often the first sign of toxicity. Diarrhoea often occurs immediately after stomatitis. Haemorrhages at various sites were less frequent; they mainly occurred in the tractus digestivus.~~

~~Mucositis is more frequent after intra-arterial administration or after the use of high dosages, particularly following a continuous infusion. Proctitis was rarely reported.~~

~~Dermatological toxicity may occur. Dermatitis in the form of maculopapular skin rash on the extremities and alopecia were often observed. These side effects are generally reversible. Nail changes were sometimes reported. The pigmentation of particularly skin areas that had been exposed to radiotherapy, and the veins used for intravenous administration, increases under the influence of sunlight. After continuous infusion with fluorouracil some cases of palmar/plantar syndrome were described.~~

~~Pharyngitis and oesophagitis were occasionally observed.~~

~~Other side effects: Neurological side effects are rare, but their frequency increases in case of high dosages of fluorouracil or intensive daily treatment. Cerebellar dysfunction was observed, manifesting itself in ataxia, among others. Eye toxicity, particularly acute and chronic conjunctivitis, occurs. Epiphora was observed. Rare cases of precordial pain and transient ECG changes were reported. Allergic reactions of a dermatological nature were described. Other, less frequent side effects include: fever, fatigue, hypotension, epistaxis, necrosis of nasal cartilage and photophobia.~~

~~Fluorouracil proved to be teratogenic in animal tests. In humans, the possibility of fluorouracil affecting fertility should be taken into account.~~

~~In some test systems fluorouracil is mutagenic. Animal studies of a limited scope show no carcinogenicity. Insufficient information is available about carcinogenicity in humans.~~

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.

Due to the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Pharmaceutical Precautions

Once a dose is taken from the vial with a chemo-mini-spike, the shelf life will not exceed 72 hours at room temperature (no higher than 25°C) and protected from light, unless pricking or diluting took place under controlled and validated aseptic conditions.

Before use, the solution may be diluted with 0.9% sodium chloride solution or 5% glucose solution, if necessary.

After dilution of Fluorouracil solution for injection in 5% glucose solution or in 0.9% sodium chloride solution, a chemical and physical shelf life was established of a minimum of 48 hours at room temperature (no higher than 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. Dilution should take place in controlled and validated aseptic conditions.

If stored as indicated below, this medicinal product can be used until the date stated on the package.

~~After dilution of Fluorouracil solution for injection in 5% glucose solution or in 0.9% sodium chloride solution, a chemical and physical shelf life was established of a minimum of 48 hours at room temperature (no higher than 25°C).~~

~~From a microbiological point of view, the product should be used immediately. If not, the shelf lives and conditions after opening and prior to administration will be the administrator's responsibility. In general the shelf life will not exceed 8 hours at room temperature (no higher than 25°C), unless pricking or diluting took place under controlled and validated aseptic conditions.~~

~~If stored as indicated below, this medicinal product can be used until the date stated on the package.~~

6.4 Storage

Fluorouracil solution for injection may be stored in the original package, protected from light and at temperature of 15°C – 25°C. Do not store in refrigerator or freezer. If a precipitate is formed as a result of exposure to low temperatures, this precipitate should be completely dissolved again before use, by heating up the injection vial to 60°C with vigorous shaking. Before use, the solution should be cooled off to body temperature.

~~Fluorouracil solution for injection may be stored in the original package, protected from light and at temperatures between 15°C—25°C. Do not store in refrigerator or freezer. If a precipitate is formed as a result of exposure to low temperatures, redissolve it by heating to 60°C with vigorous shaking, and allow to cool to body temperature prior to use. The expiry date is stated on the package. An opened Fluorouracil solution should be used within 8 hours because of the lack of preservative.~~

העלון נשלח לפרסום במאגר התרופות שבאתר האינטרנט של משרד הבריאות <http://www.health.gov.il>,
וניתן לקבלו מודפס ע"י פניה לחברת טבע.