Physician's Package Insert

FLUOROURACIL 50mg/ml
SOLUTION FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT
Fluorouracil 50mg/ml, Solution for Injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
A sterile, isotonic solution of 50 mg fluorouracil per ml solution for injection. Fluorouracil solution for injection has not been preserved and is therefore meant for single use.

3. PHARMACEUTICAL FORM
Solution for injection. Clear, colourless or almost colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
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.

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.

Fluorouracil is applied alone and in combination with other cytostatic drugs. The fluorouracil dosage depends on the schedule opted for, the use of other cytostatic drugs, the application of radiotherapy and the method of administration. The total daily dosage will usually not exceed 1 gram.

**Colorectal tumours:**
The initial therapy may be given as intravenous injections or intravenous infusion. The toxicity of fluorouracil is usually higher after injection than after infusion.

As intravenous infusion, 600 mg/m² daily (with a maximum of 1 g each time) in 300–500 ml 5% glucose solution may be given during 4 hours. This dosage is repeated daily until the first side effects occur. Therapy should then be interrupted. After disappearance of the haematological and gastrointestinal side effects, a maintenance therapy is given.
Fluorouracil is also given as a continuous infusion. The dosage and duration of the infusion depends on the schedule chosen, the use of other cytostatic drugs and the application of radiotherapy. In a dosage up to 300 mg/m² daily for 30-60 consecutive days, toxicity will rarely occur. In higher dosages stomatitis will be the dose-limiting side effect. A common dosage is 350 mg/m² daily.

As injection, 480 mg/m² daily is given intravenously on 3 consecutive days. If toxic side effects do not appear, 240 mg/m² is given intravenously on days 5, 7 and 9, followed by a maintenance therapy. The maintenance therapy consists of injections: once a week 200-400 mg/m² in intravenous injection.

**Breast cancer:**
For the treatment of breast cancer fluorouracil is given, for example, in combination with methotrexate and cyclophosphamide or in combination with doxorubicin and cyclophosphamide. The usual fluorouracil dosage in these schedules is 400-600 mg/m², intravenously administered on days 1 and 8, in a 28-day cycle.
In some schedules fluorouracil is administered as a continuous infusion. A common dosage is 350 mg/m²/day.

**Other types of administration:**
5-fluorouracil is applied as an intra-arterial 24-hour slow infusion in a dosage of 200–300 mg/m² daily.
Fluorouracil is also used as a continuous infusion. The dosage and duration of the infusion depends on the regimen chosen, the use of other cytostatic drugs and the application of radiotherapy. A common dosage is 350 mg/m²/day.
When fluorouracil solution for injection is used for continuous infusion, the fact that the solution for injection has not been preserved should be taken into account.
**Dosage adjustment:**
The fluorouracil dose should be adjusted in accordance with the schedule below if leukocytes or thrombocytes are reduced on the first day of therapy; the lowest value determines the height of the dose.

<table>
<thead>
<tr>
<th>% of dose</th>
<th>Leukocytes</th>
<th>Thrombocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>&gt; 3,500</td>
<td>&gt; 125,000</td>
</tr>
<tr>
<td>50</td>
<td>2,500-3,500</td>
<td>75,000-125,000</td>
</tr>
<tr>
<td>0</td>
<td>&lt; 2,500</td>
<td>&lt; 75,000</td>
</tr>
</tbody>
</table>

If the number of leukocytes is 2500-3500 /mm³ and/or the number of thrombocytes 75000-125000 /mm³, it is better not to administer cytostatic drugs for one week. When the blood count has been restored the course may be continued; if not, dose reduction may be carried out.

The administration of fluorouracil should be discontinued if a bilirubin plasma concentration over 85 micromol/L is reached. If the patient has undergone major surgery within 30 days prior to administration, the recommended dosage should be reduced by a third to a half from the very beginning.

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.

4.3 Contraindications
Fluorouracil must not be administered during pregnancy and lactation and to patients with a bone marrow dysfunction, caused by tumour infiltration, cytotoxic drugs or radiotherapy. Fluorouracil is not intended for the treatment of patients in a poor nutritional condition. It must also not be administered to patients with infections. Also see ‘Posology and method of administration’.

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 mm$^3$ or the W.B.C. count falls below 3,500 per mm$^3$. If the total count is less than 2,000 mm$^3$, 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 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 men and women must take contraceptive measures during therapy and up to 6 months after discontinuation of therapy.
When fluorouracil is spilled, a lot of water should be used for rinsing (see ‘Instructions for use and handling and disposal’).

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 sorivudine, 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, sorivudine 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, phosphonacetyl-L-aspartate (PALA), allopurinol, hydroxyurea, dipyridamol and leucovorin (folic 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

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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 have 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.
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.

4.7 Effects on ability to drive and use machines

There is no information available about the effect of this agent on the ability to drive. Fluorouracil may cause nausea and vomiting as well as adverse events of the nervous system and visual changes. The patient should therefore take care in activities requiring concentration, such as participating in traffic and handling machines.

4.8 Undesirable effects

Frequencies are defined using the following convention:
Very common (≥1/10),
Common (≥ 1/100 to < 1/10),
Uncommon (≥ 1/1,000 to < 1/100),
Rare (≥ 1/10,000 to < 1/1,000),
Very rare (< 1/10,000),
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, dacyrostenosis, 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.

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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.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

Symptoms of overdosage include one or more of the side effects, in severe form. In prolonged therapy the toxic effects will be more prominent. Haemodialysis may be used to remove fluorouracil. If necessary, general adjunctive measures must be taken and a blood transfusion must be given.

Patients in which an overdose of fluorouracil is detected should be closely monitored for at least 4 weeks.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

5-fluorouracil belongs to the antimetabolites. It is a pyrimidine antagonist which the body converts into two active metabolites: 5-fluorodeoxyuridine-5’-phosphate (5-FdUMP) which binds to thymidylate synthetase and inhibits the DNA synthesis, and 5-fluorouridine-5’-triphosphate (5-FUTP), which is incorporated into r-RNA, resulting in RNA synthesis inhibition. Resistance may occur, probably due to an accelerated catabolism of fluorouracil, a reduction in the enzymes which convert fluorouracil into nucleotides and a reduced affinity of the enzyme thymidylate synthetase for 5-FdUMP.

5.2 Pharmacokinetic properties

Absorption:

For fluorouracil an extensive first pass effect and a saturable hepatic metabolism were observed. After oral administration large inter-individual and intra-individual differences in plasma levels are seen. In doses of 400-600 mg/m² the bioavailability is approximately 28% (0-75%). The maximum plasma concentration of 0-44 µg/ml is reached after 5–300 minutes.

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**Distribution:**
Fluorouracil is distributed over the entire body, including the brain.

**Protein binding:**
About 10% of the fluorouracil in the plasma is weakly bound to plasma proteins.

**Penetration into bone marrow:**
Fluorouracil penetrates into bone marrow.

**Penetration into the liquor:**
Fluorouracil penetrates into the central nervous system to a small degree; the extent of the penetration proves to be dependent on the rate of administration and the dose given, in which extension of the infusion time leads to a sharp decrease in the penetration into the liquor.

**Placental passage:**
Fluorouracil crosses the placenta.

**Biotransformation:**
Fluorouracil is metabolised in the tissues into 5-fluorouridine and 5-fluorodeoxyuridine. Fluorouracil is primarily catabolised in the liver, resulting in formation of dihydro-fluorouracil, urea, CO₂, ammonia and α-fluoro-β-alanine as inactive metabolites. There are strong indications that the catabolic biotransformation route is saturable. This may – particularly after high oral dosages – lead to unexpectedly high plasma levels.

**Elimination:**
The plasma half-life of fluorouracil is approximately 10 minutes with possibly a terminal half-life of about 2 hours.

After a single intravenous administration less than 10-15% is excreted into urine as unchanged fluorouracil within 6 hours; more than 90% is eliminated in the first hour. After intravenous infusion of fluorouracil during a period of 96 hours, no more than 3% is excreted into urine as unchanged fluorouracil. After intra-arterial hepatic infusion a minimum of 50% 5-fluorouracil is metabolised during the first pass in the liver. Fluorouracil is also excreted in the tears and saliva, but to a small extent. Impaired renal and/or hepatic functions may lead to a prolonged elimination half-life of fluorouracil.

5.3 **Preclinical safety data**

No particulars.

6. PHARMACEUTICAL PARTICULARS

6.1 **List of excipients**

Sodium hydroxide, hydrochloric acid, 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.

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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-spoke, 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.

6.4 Storage

Fluorouracil solution for injection should be stored in the original package, protected from light and at a 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.

6.5 Nature and contents of container

Vials of 5 ml, 10 ml, 20 ml and 100 ml containing 50 mg/ml fluorouracil;
Packs of 1 vial. Not all package sizes may be marketed.

6.6 Instructions for use and handling and disposal

Any contact with the fluid should be avoided. During preparation a strictly aseptic working technique should be applied; the use of gloves, mouth cap, safety glasses and protective clothing are necessary as protective measures. The use of a vertical laminar airflow (LAF) hood is recommended. During administration, gloves must be used. In waste disposal the nature of this product must be taken into account.
Should the solution come into contact with the skin, mucous membranes or eyes, rinse immediately with plenty of water. The skin may be thoroughly washed with soap.

7. PRODUCT REGISTRATION NUMBER: 035.69.25702
8. MANUFACTURER
Pharmachemie B.V., Haarlem, The Netherlands
For
Abic Ltd. (Teva Group)

9. LICENCE HOLDER
Salomon, Levin & Elstein Ltd., P.O.Box 3696, Petach Tikva, 49133