1. NAME OF THE MEDICINAL PRODUCT
5-FU

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1ml contains 50mg fluorouracil as active ingredients.

3. PHARMACEUTICAL FORM
Concentrate for solution for infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
5-Fluorouracil may be used alone or in combination for the treatment of breast cancer and colorectal calcinomars. Additionally efficacy was reported in patients with gastric cancer, head and neck cancer and pancreatic carcinoma.

4.2 Posology and method of administration

1) Infusion
A usual adult dose 5 to 15mg per kg body-weight daily (to a maximum of 0.8 to 1g daily) is dissolved in 300~500ml of 5% Dextrose solution and administered everyday for 5 days and thereafter 5~7.5mg per kg body-weight is given every other day and discontinued when side effect is observed. If there is no evidence of toxicity, this may be followed after a day be 6mg per kg body-weight in alternative day for 3 or 4 further doses.

An alternative schedule is to give 15mg per kg body-weight intravenously once a week throughout the course. The course may be repeated after a month or maintenance doses of 5 to 15mg per kg body-weight (up to a maximum of 1g) may be given weekly.

2) Intravenous Infusion
Fluorouracil may also be given by intravenous infusion, usual dose of 15mg per kg daily (to a maximum of 1g daily) being infused in 500ml of 0.9% sodium chloride or % glucose injection over 4 hours and repeated on successive days until toxicity occurs or a total of 12 to 15g has been given. Continuous infusion may also be used. The course may be repeated after 4 to 6 weeks.

3) Intra-arterial infusion
Fluorouracil has also been given by intra-arterial infusion for adults in doses to 7.5mg per kg body-weight is dissolved in 20~100ml of 5% Dextrose solution and administered 10~20 days by using an infusion pump.

4) Combination With Other Anticancer Drug
Fluorouracil is used alone or in combination in the adjuvant treatment of breast and gastro-intestinal cancer, and pancreas. It is also used with cyclophosphamide and methotrexate in the combination chemotherapy of breast cancer.

A usual adult dose of 5 to 10mg per kg body-weight daily is given in combination with other anticancer drugs everyday or intermittently once to twice a week by systemic administration method or intra-arterial infusion method.

Impaired renal function/Impaired liver function
For use in patients with disturbances of liver or kidney, special care should be taken.

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

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

4.3 Contraindications
Fluorouracil therapy is contraindicated for patients in a poor nutritional state those with depressed bone marrow function or those with potentially serious infection.

4.4 Special warnings and precautions for use
Fluorouracil should be given with care to weak or malnourished patients, to those with a history of heart disease, or to those with hepatic or renal insufficiency. Patients with a history of high-dose pelvic irradiation or treatment with alkylating agents, and those with wide-spread metastases to the bone marrow should also be treated with extreme caution. Blood cell counts should be determined frequently during therapy.
Topical fluorouracil should not be used on mucous membranes. There is a possibility of increased absorption if used excessively or on ulcerated or inflamed skin. Occlusive dressings may increase inflammatory actions. Exposure to sunlight during treatment should be avoided. Creams are preferably applied using a non-metal applicator or gloved hand; if bare fingertips are used the hands must be washed immediately afterwards.

4.5 Interaction with other medicinal products and other forms of interaction

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<thead>
<tr>
<th>AGENT</th>
<th>EFFECT</th>
<th>MECHANISM</th>
<th>MANAGEMENT</th>
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<tr>
<td>Allopurinol</td>
<td>decreased toxicity of fluorouracil</td>
<td>Possibly inhibition of thymidine phosphorylase</td>
<td>caution</td>
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<tr>
<td>Mitomycin</td>
<td>increased incidence of hemolytic-uremic syndrome</td>
<td>Unknown</td>
<td></td>
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<tr>
<td>Cimetidine</td>
<td>increased serum concentration of fluorouracil</td>
<td>Appears to interfere with fluorouracil metabolism</td>
<td>observe for increased toxicity of fluorouracil</td>
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<tr>
<td>Leucovorin</td>
<td>increased cytotoxic and toxic effects of fluorouracil</td>
<td>Leucovorin stabilizes the bond to thymidylate synthetase</td>
<td>some protocols are designed to take advantage of this effect; monitor toxicity closely</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>enhanced toxicity of fluorouracil</td>
<td>Decreased clearance of fluorouracil</td>
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<tr>
<td>Thiazide diuretics</td>
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<tr>
<td>Warfarin</td>
<td>increased effect of warfarin</td>
<td>reduced warfarin clearance</td>
<td>monitor closely</td>
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4.6 Pregnancy and lactation
4.7 Effects on ability to drive and use machines
Depending on individual susceptibility, the patient’s ability to drive a vehicle or operate machinery may be impaired.

4.8 Undesirable effects
The main adverse effects of fluorouracil are on the bone marrow and the gastrointestinal tract, and may be dose-limiting. Toxicity is schedule dependent: reducing the rate of injection to a slow infusion is associated with less haematological toxicity but does not decrease gastrointestinal toxicity. With prolonged continuous infusion in particular, the palmar-plantar erythrodysesthesia syndrome (erythema and painful desquamation of the hand and feet) may occur. Gastrointestinal toxicity may be exacerbated if fluorouracil is given with folinic acid.

Leucopenia, thrombocytopenia, stomatitis, gastrointestinal ulceration and bleeding, diarrhoea, or haemorrhage from any site, are signs that treatment should be stopped. The nadir of the white cell count may occur from 7 to 20 days after a dose, and counts usually return to normal after about 30 days. Thrombocytopenia is usually at a maximum 7 to 17 days after a dose. Anaemia may also occur. Nausea and vomiting, rashes, and alopecia are common. Ocular irritation, central neurotoxicity (notable cerebellar ataxia), and myocardial ischaemia have occurred.

Local inflammatory and photosensitivity reactions have occurred following topical use. Dermatitis and, rarely, erythema multiforme have been reported.

4.9 Overdose
The symptoms of overdose are qualitatively similar to the undesirable effect: diarrhoea, nausea and vomiting (an anti-emetic may be given for nausea and vomiting), chest pain, tachycardia, breathlessness, ECG changes and confusional state. Palmar-plantar Erythrodysesthesia Syndrome has been reported as an unusual complication of high dose bolus or protracted continuous therapy with Fluorouracil.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
5-Fluorouracil is an antimetabolite and, as a pyrimidine antagonist, inhibits cell division by interfering with DNA synthesis. 5-FU itself is devoid of antineoplastic activity. This activity arises in the body after enzymatic conversion of 5-FU to the phosphorylated forms of 5-Fluorouridine and 5-Fluorodeoxyuridine.

5.2 Pharmacokinetic properties
Absorption of fluorouracil from the gastrointestinal tract is unpredictable and fluorouracil if usually given intravenously and fluorouracil is usually given intravenously. Little is absorbed when fluorouracil is applied to healthy skin.

After intravenous injection fluorouracil is cleared rapidly from plasma with a mean half-life of about 16 minutes. It is distributed throughout body tissues and fluids including crossing the blood-brain barrier to appear in the CSF, and disappears from the plasma within about 3 hours. Within the target cell fluorouracil is converted to 5-fluorouridine.
minophosphate and floxuridine monophosphate (5-fluorodeoxyuridine monophosphate),
the former undergoing conversion to the triphosphate which can be incorporated into
RNA while the latter inhibits thymidylate synthetase. About 15% of an intravenous dose
is excreted unchanged in the urine within 6 hours. The remainder is inactivated
primarily in the liver and is catabolised via dihydropyrimidine dehydrogenase similarly to
endogenous uracil. A large amount is excreted as respiratory carbon dioxide; urea and
other metabolites are also produced.

5.3 Preclinical safety data

Reports from animal studies are to be seen in connection with the pharmacologic effect
of the substance. In rats 5-Fluorouracil induced chromosomal aberrations in the
spermatogonium and temporary infertility. In some species (for example rats, mice,
rabbits and monkeys) teratogenic and fetotoxic effects have been reported at dosages
comparable to human doses on a mg/kg basis (without correction for a possible lower
systemic exposure in laboratory animals than in patients.) 5-Fluorouracil proved
mutagenic in some test systems. In spite of a lack of useful data on carcinogenic effects,
a carcinogenic potential of 5-Fluorouracil is to be expected because of its mechanism of
action and known mutagenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Water for injection, Sodium hydroxide.

6.2 Incompatibilities
5-Fluorouracil must be diluted in physiological sodium chloride solution or 5%
glucose solution.
According to the stability report 5-Fluorouracil was found to be stable for 24 hours in
0.9% sodium chloride at concentrations of 0.6mg/ml and 4.0mg/ml. in 5% glucose it
was found to be stable up to 24 hours at a concentration of 0.6mg/ml and 4.0mg/ml.
There was no incompatibility with any of the tested vehicles.
According to “Note for Guidance Maximum shelf life for sterile products after first
opening or following reconstitution” published by European Agency for the Evaluation of
Medicinal Products from a microbiological point of view infusions should not be stored
longer than 24 hours unless dilution has taken place in controlled and validated aseptic
conditions.
5-Fluorouracil must not be mixed with other drugs in the same infusion.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store at controlled room temperature between 15°C ~ 25°C.
Safety guidelines for the Handling, Preparation and Administration of Parenteral
Antineoplastic drugs.

6.5 Nature and contents of container
Inj. 5-FU 250mg is colorless, sterile, non-pyrogenic aqueous solution in 5ml and pack in
a box of 10 vials PBKD/880131A
Inj. 5-FU 500mg is colorless, sterile, non-pyrogenic aqueous solution in 10ml and pack
in a box of 10 vials MAL19985879A
6.6 Special precautions for disposal and other handling
As with other cytotoxic drugs, Spesial care is to be taken in handling 5-Fluorouracil. Wear protective gloves, a face mask and protective clothing and, if at all possible, work in a room designated for this purpose. Contact with skin and mucosae must be avoided. If such contact does occur, clean carefully with water and soap. In case of eye contact, rinse with copious amounts of water and see a medical attention immediately. Pregnant women must not handle 5-Fluorouracil.

Use the solution immediately after dilution. Handle according to the guidelines for cytostatics. Handle with care, avoid skin contact.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
2009/11/13