Fluorouracil-TEVA 50 mg/ml
Fluorouracil 50 mg/ml injection

Summary of the product characteristics

1. NAME OF THE MEDICATION
Fluorouracil-TEVA, injection fluid 50 mg/ml.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
The injection fluid contains 50 mg/ml 5-fluorouracil as active ingredient.

3. PHARMACEUTICAL FORM
Injection fluid.

4. CLINICAL DATA

4.1 Therapeutic indications
For the palliative treatment of malignant tumours, primarily of rectum, colon and mamma tumours, and also in gastric carcinoma, cervical carcinoma and other carcinomas of the uterus, ovarian cancer, bladder cancer. 5-Fluorouracil does not replace surgical or other therapeutic measures.

4.2 Dosage and administration

General
5-Fluorouracil is administered intravenously. The dosage is generally determined on the basis of the body weight: in obese patients or in patients who, due to ascites oedemas or other types of fluid retention, have an increased body weight, the ideal body weight is the basis for the dosage determination.

The recommended doses for the initial therapy, mentioned below, should be reduced by 1/3 to half in the following cases:
- in a poor nutritional condition of the patient;
- after major surgery (up to 30 days before the start of the therapy);
- in an impaired bone marrow function (leukocytes < 5 000 x 10^6/l, thrombocytes < 100 000 x 10^6/l);
- in an impaired hepatic or renal function.

The total daily dose of 5-fluorouracil will usually not exceed 1 g.

Initial therapy (monotherapy in colon cancer)
The initial therapy may be given as i.v. injection or i.v. infusion. In general, the toxicity of the preparation is larger after injection than after infusion.

Infusion
600 mg/m² a day (a maximum of 1 g each time), diluted with 300 to 500 ml 5% glucose solution is given as an i.v. infusion over 4 hours. This dose is repeated daily until the first side effects occur (stomatitis, diarrhoea, leukopaenia and/or thrombopaenia): the therapy is then discontinued. After the gastrointestinal side effects have disappeared and the leukocytes have increased again to 3 000 to 4 000 x 10^6/l and the thrombocytes have increased again to 80 000 to 100 000 x 10^6/l, a maintenance treatment is initiated.

Injection
480 mg/m² i.v. each day on three consecutive days. If no toxic side effects (stomatitis, diarrhoea, leukopaenia and/or thrombopaenia) have occurred, 240 mg/m² per day is given i.v. on days 5, 7 and 9. If these side effects do not occur, a maintenance treatment is initiated; if the side effects do occur, the maintenance treatment is delayed until the side effects have disappeared (as stated above under 'Infusion').

Maintenance therapy
This consists of i.v. injections, 200-400 mg/m² once a week. Toxic side effects rarely occur in this case, but they remain the limiting factor in the therapy.

Other administrations
5-Fluorouracil may also be given in combination with other anti-cancer drugs or radiotherapy. In these cases, the recommended dose should be reduced. The preparation has also been used in the form of a 24-hour intra-arterial slow infusion (200-300 mg/m² daily).

For the treatment of mamma carcinoma, 5-fluorouracil is among others given in combination with methotrexate and cyclophosphamide, or in combination with doxorubicin and cyclophosphamide. The usual 5-fluorouracil dosage in these schedules is 400-600 mg/m², administered intravenously on days 1 and 8, within a 28-day cycle.

4.3 Contra-indications
- leukocytes < 5 000 x 10^6/l;
- thrombocytes < 100 000 x 10^6/l;
- extensive previous radiotherapy of the pelvis and the myeloid bones;
- very extensive metastases into the bone marrow or the myeloid bones;
- highly negative nitrogen balance;
- infections;
- pregnancy.

4.4 Special warnings and special precautions for use
If stomatitis and diarrhoea occur, the treatment should be interrupted until these symptoms have disappeared, and may be continued again with a lower dose, such as 2/3 or 1/2. If, during the initial therapy, ulcerations and haemorrhages of the gastrointestinal mucosa or haemorrhages elsewhere occur, the administration of the preparation should be stopped immediately. During the initial phase of the therapy, the blood count should be checked every 2 to 3 days; during the maintenance therapy once every 1 or 2 weeks. In the treatment of both man and woman, contraceptive measures should be taken up to 3 months after withdrawal of the therapy. If 5-fluorouracil is spilled, rinse with plenty of water.

4.5 Interaction with other medication and other types of interaction
Pharmacodynamic interaction may occur with other anti-cancer drugs: the therapeutic and toxic effects are enhanced. Methotrexate and 5-fluorouracil show a complicated interaction pattern. Concurrent administration of thymidine and 5-fluorouracil increases the plasma half life of 5-fluorouracil. The combination, however, does not result in an increased therapeutic index of 5-fluorouracil. Concurrent administration of folinic acid in high doses and 5-fluorouracil may result in an increased chemotherapeutic effect of 5-fluorouracil. Concurrent administration of allopurinol and 5-fluorouracil results in 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 increase in the chemotherapeutic effect of 5-fluorouracil has not been established unambiguously. After administration of 5-fluorouracil, parts of the body that are exposed to the sun may show hyperpigmentation.

4.6 Use in pregnancy and lactation
Pregnancy is an absolute contra-indication.

4.7 Influence on the ability to drive and to handle machines
No information is available about the effect of Fluorouracil-TEVA on these functions. If extreme fatigue occurs as a side effect, the driving of motor vehicles or the handling of machines is advised against.

4.8 Side effects
- anorexia and/or nausea, occasionally vomiting;
- diarrhoea; do not give a laxative during the course;
- stomatitis: this mostly occurs on the lower lip in the form of small epithelial defects (‘blisters’);
- haemorrhagings of various localizations, particularly in the tractus digestivus;
- isolated cases of precordial pain and temporary ECG changes;
- leukopaenia: mostly occurring at a later stage (9th-15th day), usually after the aforementioned, but sometimes it is the first toxic symptom. Assessment on the
plasma levels of about 10\% of the dose administered. If the decrease is < 3,000 x 10\(^6\) /l, daily monitoring. If < 1,500 x 10\(^3\) pt/l admission into hospital.
- thrombocytopenia: occurring in a minority of cases, but very persistent if it occurs. May be a reason for discontinuation of the therapy.
- Other:
  Dermatitis mainly occurs in i.a. administration.
Late symptoms may be: alopecia (20\%) and sometimes mucosa disorders of the upper airways. Particularly at the start of the course there may be symptoms of a dry throat. Nail changes (band formation) may occur. The skin pigmentation appears to increase under the influence of the sunlight, and prolonged exposure to the sun is therefore advised against. A number of patients complain about severe fatigue, particularly the day following the weekly injections. In these cases it may be necessary to use a lower dose or to increase the time interval between 2 injections, for example by giving the injections every 2 weeks.

Neurological side effects are rare, but their frequency increases if high doses of 5-Fluorouracil are used or in case of an intensive daily treatment. Cerebellum malfunctioning, manifesting itself in ataxia, for example, has been observed. Occular toxicity, particularly acute and chronic conjunctivitis, may occur.
Suffusion of the eyes has been observed. Mucositis, particularly after a continuous infusion, may occur. Allergic reactions of a dermatological nature have been described. Other, less frequent side effects include: fever, fatigue, hyponatremia, epistaxis, necrosis of nasal cartilage and photosensitivity. Animal tests have shown 5-Fluorouracil to be teratogenic. In man, the possibility of 5-fluorouracil having an effect on fertility should be taken into account. In some test systems the agent was mutagenic. A possible carcinogenic effect should be taken into account.

4.9 Treatment of overdosage

Symptoms
The possibility of a fluorouracil overdosage is unlikely in connection with the mode of administration. Nevertheless, the following symptoms may be observed in case of overdosage: nausea, vomiting, diarrhoea, gastrointestinal ulcnerations and haemorrhages and bone marrow suppression (including thrombocytopenia, leukopenia and agranulocytosis).

Treatment
No specific antidote is known. Patients who have been exposed to an overdose of fluorouracil should be closely monitored haematologically for a minimum of four weeks. If defects occur, an appropriate therapy should be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
The antimetabolite, as pyrimidine antagonist, inhibits the cell division due to its interference with the synthesis of the deoxyribonucleic acid. 5-Fluorouracil itself does not have an antineoplastic activity. This activity develops itself in the body after the enzymatic conversion of 5-fluorouracil into the phosphorylated forms of 5-fluorouridine and 5-fluorodesoxy-uridine.

5.2 Pharmacokinetic properties
After intravenous administration of 15 mg 5-fluorouracil per kg body weight, maximum plasma levels of about 10\(^7\) M may be reached within approximately ¼ hour. After a continuous infusion, the maximum plasma levels achieved are approximately 1.000 times lower.
5-Fluorouracil diffuses well into the tissues in the body, and crosses the blood-brain barrier as well. In the cell, 5-fluorouracil is converted into the active metabolites 5-fluorodesoxy-uridine-5-phosphate and 5-fluorouridine-5-triphosphate. In the liver, 5-fluorouracil is decomposed mainly into uracil.
Depending on the mode of administration, the excretion into the urine is no more than about 15\% of the dose administered. The hepatic route is the main elimination route. After a single intravenous dose, the plasma half life is 10-20 minutes.

5.3 Data from the preclinical safety research
No particular data.

6. PHARMACEUTICAL DATA

6.1 List of inactive ingredients
Sodium hydroxide, water for injection.

6.2 Incompatibilities
No data known.

6.3 Shelf life
The shelf life of the unopened vial, stored at room temperature (15-25 °C) and protected from the light is 2 years.
After one dose is taken from the vial with a Chemo-Mini-Spike, the vial of 5 g/100 ml is chemically and physically stable for 72 hours if kept at room temperature (15-25 °C) and protected from light.
The solution, however, has not been preserved, so that the microbiological shelf life will depend on the aseptic procedures.

Dilutions containing 0.5 mg fluorouracil per ml in 0.9\% NaCl or 5\% glucose have a shelf life of 48 hours at room temperature (15-25 °C) if prepared under strictly aseptic conditions.

6.4 Special precautions for storage
Fluorouracil-TEVA should be stored at room temperature (15-25°C) and protected from light. If, due to cooled storage (< 15 °C) a precipitate is formed in the solution, this precipitate should be completely dissolved again before use, by heating the injection vial up to 80°C and shaking it. Before use, the solution should be cooled off to body temperature (see USP XXIII, page 679).

6.5 Package quantities
Glass vials with injection fluid of 5 ml = 250 mg, 10 ml = 500 mg, 20 ml = 1000 mg and 100 ml = 5 g.

6.6 Instructions for use/processing instructions
In the use of the 5 g/100 ml vial, an aseptic procedure should be used (use of LAF cabinet).
N.B. The 5 g/100 ml vial is meant for the consecutive preparation of several fluorouracil administrations, but not for conventional multi-dose administrations in which the vial can be pierced several times.
This presentation is neither meant for doses higher than are stated in the section ‘Dosage and administration’.

7. NAME AND PERMANENT ADDRESS OF THE OFFICIAL PLACE OF BUSINESS OF THE HOLDER OF THE MARKETING LICENCE

TEVA Pharma B.V.
Computerweg 10
3542 DR UTRECHT
The Netherlands

8. NUMBER OF THE MARKETING LICENCE

Fluorouracil-TEVA 50 mg/ml is registered under RVG 11900.

9. DATE OF APPROVAL/REVIEW OF THE SUMMARY

October 1998.