1. **Name of the medicinal product**
   5 - Fluorouracil “Ebewe”

2. **Composition**
   1 vial/ampoule of 5ml contains 250mg 5-fluorouracil as active ingredient.
   1 vial/ampoule of 10ml contains 500mg 5-fluorouracil as active ingredient.
   1 vial of 20ml contains 1000mg 5-fluorouracil as active ingredient.
   1 vial of 100ml contains 500mg 5-fluorouracil as active ingredient.

3. **Drug form**
   Concentrate for solution for injection and infusion.

4. **Clinical particulars**

4.1. **Indications**
   Palliative treatment of several cancer forms as monotherapy or as combination therapy in colorectal cancer and breast cancer. Also in malignant tumours of the stomach, pancreatic gland and liver. Fluorouracil is indicated in ovarian cancer, cervical cancer, urinary bladder and prostate cancer as well as in head and neck tumours. Adjuvant therapy after surgical operations (e.g., postoperative chemoprophylaxis in mammary carcinoma) and before radiotherapy.

4.2. **Dosage and route of administration**
   **Dosage**
   Starting therapy in daily use:
   - as IV infusion
     15mg/kg or 600mg/m² over 2-4 hours daily till side effects arise.
   - as IV injection
     12mg/Kg or 480mg/m² IV slowly (2-3min) on day 1, 2, and 3; if no toxic signs appear - administration of 6mg/Kg or 240mg/m² on day 5, 7 and 9 is recommended.
   Starting therapy in weekly use:
   - 15mg/Kg or 600mg/m² once weekly IV slowly
   - 24-hours-continuous infusion:
   - 5-7mg/kg/day or 200mg/m²/day.

   **Maintenance therapy:**
   With remission indicated by a decrease in side effects and/or a rebound in leucocytes to 3,000-4,000/μl and in thrombocytes to 80,000-100,000/μl:
   5-10mg/kg or 200-400mg/m² IV are given once weekly. Do not exceed 1g of maximum daily dose. Therapy is determined by the experienced physician according to the type and course of the disease. The maintenance therapy is 5-10mg/kg IV once weekly. The dosages mentioned refer to ideal body weight, e.g., in case of adiposity or oedema corresponding dose adjustment must be carried out.

   **Particular recommendations:**
   The recommended dose should be reduced by one third to one half in patients with poor nutritional status, in patients after surgical intervention and in cases of myelosuppression (leucocytes <4,000/μl, thrombocytes <100,000/μl).
   Therapy must be interrupted immediately if the following symptoms appear:
   Gastrointestinal reactions (stomatitis, mucositis, severe diarrhoea, severe vomiting ulcers, haemorrhage), Leucocytes <3,000/μl, thrombocytes <80,000/μl, CNS side
effects (including ataxia and tremor) and cardiac side effects. Treatment should only be continued after side effects have subsided and the patient’s general condition allows. The start of a new therapy is not recommended in severe gastrointestinal, cardiac or neurological toxic manifestations. The dosage of 5-fluorouracil in combination with other cytostatic agents which cause similar side effects or in combination with radiation therapy must be reduced accordingly. Administration may be carried out as a 24-hour continuous intravenous drip infusion.

**Route of administration**
Fluorouracil is mainly administered IV. It may be given as bolus injection or infused diluted in a 0.9% NaCl solution or a glucose 5% solution. Prepared infusion solutions have a shelf-life of 24 hours. Infusion rate is at liberty.

Intravenously:
- as bolus (slow injection)
- as short infusion
- as infusion over 4 to 24 hours (monotherapy and combination therapy)
- through-injection pump (in-patient or out-patient).

Intraarterially, Intracavitary for irrigation of:
- pleura
- peritoneum.

If extravasation occurs, no special measures are to be taken.
For single use only. Only clear, colourless to slightly yellow solutions (dark yellow coloured solutions refer to a higher decomposition rate) should be used. Sedimentation caused by storage at low temperature may be dissolved by shaking and moderate heat up to 60°C - please let cool before use. In literature efficacy loss through adsorption of fluorouracil by the glass container of the infusion is described.

4.3. Contraindications
Hypersensitivity to one of the drug components; severe changes in the blood count, bone marrow depression, haemorrhaga; malabsorption, severe impairment of liver and renal function; severe infections, herpes zoster, varicella, stomatitis, ulcerations of oral cavity and the gastrointestinal tract, pseudomembranous enteritis. Care is to be taken in cases of extensive liver metastasis (decreased metabolism).

Pregnancy and lactation period:
Animal experiments showed adverse fetal reactions. Although there are no indications for adverse effects in humans, 5-fluorouracil is strictly contraindicated during pregnancy. Since it is unknown if 5-fluorouracil is excreted in breast milk, women treated with 5-fluorouracil must abstain from nursing.

4.4-Warnings and precautionary measures
Treatment with 5-fluorouracil must only be carried out by physicians specialised in the chemotherapy end only in a hospital setting; adjustments to therapy are only to be made in the hospital. When therapy is started, blood count controls are often necessary (every 2-3 days). During maintenance therapy blood count, liver and renal function must be monitored regularly before each dose administration. Before every administration the oral cavity must be examined and faecal matter are to be tested for occult blood. Particular care is to be taken in risk patients after high-dose pelvic irradiation, after therapy with alkylating substances and in cases of severe
bone metastasis. If fluorouracil is given in combination with methotrexate, methotrexate must be administered 24 hours in advance to achieve optimal effect (not vice versa). Vaccinations with live vaccines must not be given during 5-fluorouracil therapy. This is also indicated for persons who are in close contact with the patient. Since anaphylactic reactions may occur, shock treatment must be available before therapy with 5-fluorouracil is initiated.

4.5. Drug interactions
For therapeutical use in combination with calciumfolinate (folinic acid) please consult the international literature. In combination with other cytostatic agents (interferon-α, cyclophosphamide, vincristine, methotrexate, cisplatine, doxorubicine) and with folic acid both the efficacy and toxicity of 5-fluorouracil may be increased. In combination with other myelosuppressive substances a dose adjustment is required; simultaneous or previous radiotherapy may also require a dose reduction. The cardiotoxicity of anthracyclines can increase. Combination with folic acid can cause severe diarrhoea. Aminoputazone, phenylbutazone and sulphonamide must not be administered before and during treatment with 5-fluorouracil. Allopurinol reduces toxicity and efficacy of 5-fluorouracil. Chlorodiazepoxide, disulfiram, griseofulvin and isoniazide can increase the activity of 5-fluorouracil. The appearance of a haemolytic uraemic syndrome was observed after long-term therapy with 5-fluorouracil in combination with mitomycin.

4.6. Pregnancy and lactation
Strict contraception must be guaranteed before, during and after 5-fluorouracil therapy, for male and female patients alike. If a pregnancy is desired after therapy has been discontinued genetic consultation is recommended.

4.7. Effects on ability to drive and use machines
The ability of the patients to drive or operate machinery may be impaired.

4.8. Side effects
- Haematological:
  Myelosuppression with leucopenia and neutropenia, anemia, immunosuppression.
- Gastro-intestinal tract:
  Anorexia, mucositis, stomatitis. neck pain, pharyngitis, oesophagitis, enteritis, ulcers (inclusive oral cavity), haemorrhages, malabsorption; nausea, vomiting and diarrhoea can be treated with anti-emetics or antidiarrheal agents.
- Skin:
  Dermatitis, dry skin, transient exanthema, urticaria, pruritus, photosensitivity, alopecia, hyperpigmentation, acne, furunculosis, fissuring, telangiectasia, dermatorrhagiae; rarely loss of nails and nail changes; palmar and plantar erythema subside usually 5-7 days after 5-fluorouracil therapy has been discontinued; it may also be treated with pyridoxine (100-150mg/day).
- Cardiovascular:
  precordialgia, ischaemis, transient ECG-changes, cardiac infarction.
- Nervous system:
  seldom confusion, somnolence, ataxia, euphoria, photophobia, nystagmus, retrobulbar neuritis. dysarthria, reversible disturbances of CNS function.
• **Miscellaneous:**
  Haemolytic anaemia, liver damage (rarely necrosis), renal impairment, hyperuricemia, disturbances in spermatogenesis and ovulation, bronchospasms up to anaphylactic shock, cough, nose bleeds, very seldom increased lacrimal flow and stenosis of the lacrimal duct.
• **Laboratory tests:**
  Thyroxin (T4) and triiodothyronine (T3) may increase slightly (patients remain clinically euthyroid). Testing methods for bilirubin and 5-hydroxyindolacetic acid in urine may show increased or wrong positive values; plasmaalbumin decreases.

4.9. **Overdosage**

**Acute:**
psychotic, reactions, somnolence, increased effect of sedative drugs, increased alcohol toxicity. If sedation is required, diazepam IV may be administered in low doses (eg starting with 5mg) with careful monitoring of the cardiocirculatory and respiratory system.

**Chronic:**
Bone marrow depression with agranulocytosis and critical thrombopenia, tendency to haemorrhage, ulcerations of the gastrointestinal tract, diarrhoea, alopecia.

**Measures:**
Specific antidotes are not available. Infusions of leucocyte or thrombocyte concentrate infusions, infection prophylaxis. Forced diuresis can be suitable to achieve volume and mineral balance equilibrium. Haemodialysis is generally not necessary. To recognise latent haematologic and gastrointestinal complications in time, strict monitoring is indicated. in case of diarrhoea: tinctura opii if therapy with 5-fluorouracil is continued in spite of cardiac side effects, the administration of vasodilatatory drugs is indicated to avoid spasms of coronary arteries.

5. **Pharmacological properties**

5.1. **Properties and efficacy**
The antimetabolite fluorouracil is a fluorinated pyrimidine. After metabolic transformation into 5-fluoro-deoxyuridin-monophosphate (F-dUMP) the methylation reaction of the deoxyuridilic acid to thymidylic acid is blocked. In this way fluorouracil inhibits the DNA synthesis and causes the incorporation of 5-F-dUMP as an “inappropriate” precursor in the RNA, the synthesis of which is also inhibited. 5-fluorouracil acts cell cycle phase specific, particularly on the S-phase. A maximum of efficacy of the substance is observed in rapid proliferative tissues (bone marrow, skin and mucosa).

5.2. **Pharmacokinetics**
Oral absorption of 5-fluorouracil occurs inconsistantly (0-80%).
The substance has a distribution of 0.12 l/kg BW (after 15mg/kg BW Iv) and is found particularly in rapid proliferative tissues such as bone marrow, intestinalmucosa and neoplasise; 5-fluorouracil crosses the blood-brain-barrier. 5-fluorouracil is metabolized in the liver and metabolisation is similar to uracil. 5-fluorouracil is enzymatically transformed into the active metabolite dihydro-5-fluorouracil, which
shows a significantly longer half-life than 5-fluorouracil. Non-toxic metabolites are CO₂ and urea. The plasma half-life (alpha-phase) is between 8 and 22 minutes. The elimination half-life (beta-phase) is approximately 20 hours because of the presence of active metabolites in the tissue; this beta-phase is dose-dependent. 5-fluorouracil is primarily excreted from the lungs in expired CO₂ (60-80%). 7-20% of 5-fluorouracil is renally eliminated unchanged, thereby approximately 90% of the medication is eliminated within the first hour. Renal clearance is approximately 170-180ml/min. In cases of renal impairment the accumulation is eliminated slowly. In liquor maximum concentration is reached after 1.5-2 hours and is approximately 50% of the plasma concentration. Pharmacokinetics in special clinical pictures: in azotemia (due to renal impairment) a corresponding dose adjustment in spite of the small renal elimination (approximately 15%) is recommended, because bone marrow function may be impaired. In case of impaired liver function a dose adjustment is also recommended.

6. pharmaceutical particulars
6.1. Incompatibilities
5-Fluorouracil may only be diluted in physiological sodium chloride solution or in 5% glucose solution. 5-Fluorouracil may not be mixed with other substances in one infusion.

6.2. Storage
Store at room temperature up to 25°C, away from light. If the product is stored at low temperatures (around 5°C) precipitations can be observed. These precipitations can be dissolved by a light warming at 60°C and shaking. Cool before use. Keep in a safe place out of the reach of children.

6.3. Presentation and packs
5-Fluorouracil “Ebewe” 250mg: 1 vial of 5ml,
5-Fluorouracil “Ebewe” 500mg: 1 vial of 10ml,
5-Fluorouracil “Ebewe” 1000mg: 1 vial of 20ml,
5-Fluorouracil “Ebewe” 5000mg: 1 vial of 100ml,
5-Fluorouracil “Ebewe” 250mg: 5 ampoules of 5ml.
5-Fluorouracil “Ebewe” 500mg: 5 ampoules of 10ml.

6.4. Instructions for handling staff
As with all cytostatic drugs care is to be taken when handling 5-fluorouracil. If contamination occurs, immediately wash with soap and wafer the contaminated parts. Pregnant woman must avoid contact with 5-fluorouracil. 5-fluorouracil is inactivated:
- 700°C
- liquor natrii hypochlorosi diluted with 10 parts of water
- NaOH concentrated for several hours
For single use only. Use only freshly prepared solutions. Use only clear and colourless solutions. Take care in handling, avoid skin contact.

7. Manufacturer
EBEWE Arznetmittel Ges.m.b.H., A- 4886 Unterach, Austria. Europe