1. NAME OF THE MEDICINAL PRODUCT

5-Fluorouracil "Ebewe"

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 50mg fluorouracil as active ingredient.
For excipients, see 6.1.

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 carcinomas.

Additionally efficacy was reported in patients with gastric cancer, head and neck cancer and pancreatic carcinoma.

4.2 Posology and method of administration

Selection of an appropriate dose and treatment regime will depend upon the condition of the patient, the type of carcinoma being treated and whether 5-Fluorouracil is to be administered alone or in combination with another therapy.
Initial treatment should be given in hospital and the total daily dose should not exceed 1 gram.
Daily monitoring of platelet and W.B.C. counts is recommended and treatment should be interrupted if platelets fall below 100,000/mm^3 or the W.B.C. count falls below 3000/mm^3.
It is customary to calculate the dose in accordance with the 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.

5-Fluorouracil injection can be given by intravenous injection, intravenous or intra-arterial infusion.

The following dosages are intended as a guide only.

Colorectal carcinomas

The initial treatment may be in the form of an infusion or injection, the former usually being preferred because of lesser toxicity.

Intravenous infusion:
A daily dose of 15mg/kg body weight (600mg/m^2), but not more than 1g per infusion, is diluted in 300–500ml of 5% glucose solution or in 300–500ml of 0.9% sodium chloride solution and given over 4 hours.
This dose is given on consecutive days until toxicity occurs or a total dose of 12–15g has been reached. Some patients have received up to 30 g at a maximum rate of 1g daily.
Treatment should be interrupted until haematological and gastrointestinal toxicity resolves.
Alternatively 5-Fluorouracil may be given as a continuous infusion over 24 hours.

Intravenous injection:
12mg/kg body weight (480mg/m^2) may be given daily for 3 days by intravenous injection. If there are no signs of toxicity, the patient [may/will receive] 6mg/kg body weight (240mg/m^2) on days 5, 7 and 9.

Maintenance therapy consists of 5–10mg/kg (200–400mg/m^2) by intravenous injection once weekly.
In all instances, toxic side effects must disappear before maintenance therapy is started!

Breast cancer

For treatment of breast cancer, 5-Fluorouracil may be used in combination, e.g. with methotrexate and cyclophosphamide or with doxorubicin and cyclophosphamide.
In this schedule, 10–15mg/kg (400–600mg/m^2) is administered intravenously on days 1 and 8 of a 28-day therapy course.
5-Fluorouracil may also be given by 24 hour continuous infusion, the usual dose is 8.25mg/kg (350mg/m^2).

Other methods of administration

Intra-arterial infusion
A daily dose of 5–7.5mg/kg (200–300mg/m^2) may be given by 24 hour continuous intra-arterial infusion. In specific situations, a regional infusion may be given for the treatment of the primary tumor or metastases.

Reduction of the dose is advisable in patients with any of the following:
- cachexia,
- major surgery within the preceding 30 days,
- reduced bone marrow function,
- impaired hepatic or renal function.

There are no dosage recommendations for 5-Fluorouracil use in children.
In the elderly, 5-Fluorouracil dosage is similar to that used in younger adults.

4.3 Contraindications

5-Fluorouracil is contraindicated in patients with:

- hypersensitivity to [5-]Fluorouracil;
- bone marrow depression, especially after radiotherapy or treatment with other antineoplastic agents;
- severe changes in blood counts;
- hemorrhages;
- stomatitis, ulcerations in the mouth and the gastrointestinal tract;
- severe diarrhoea;
- severe hepatic and/or renal dysfunction;
- severe infectious diseases;
- serious debility;
- plasma bilirubin greater than 85µmol/l.

4.4 Special warnings and special precautions for use

It is recommended that 5-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.

Adequate treatment with 5-Fluorouracil is usually followed by leukopenia, the lowest white blood cell (W.B.C.) count commonly being observed between days 7 and 14 of the first course, but occasionally being delayed for as long as 20 days.
The WBC count usually returns to normal by day 30. Daily monitoring of platelet and W.B.C. counts is recommended and treatment should be interrupted if platelets fall below 100,000/mm^3 or the W.B.C. count falls below 3000/mm^3.
If the total [WBC] count is less than 2000/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 also be interrupted at the first sign of stomatitis or oral ulceration, severe diarrhoea, gastrointestinal ulceration, gastrointestinal bleeding and haemorrhage at any site.

The margin of safety of 5-FU is a narrow one and therapeutic response is unlikely without some degree of toxicity. Therefore care must be taken in the selection of patients and adjustment of dosage.

5-Fluorouracil should be used with caution in patients with reduced renal or liver function or jaundice. Care should be exercised in treating patients who experienced chest pain during [prior] courses of treatment, or patients with a history of heart disease. Treatment should be stopped in case of severe cardiac toxicity.
Special care is to be taken in high-risk patients after high-dose pelvic irradiation and after therapy with alkylating agents and in patients after adrenalectomy or hypophysectomy.

Appropriate contraceptive measures are to be taken for men and women treated with 5-Fluorouracil up to 3 months after stopping treatment.

4.5 Interactions with other medicaments and other forms of interaction

[Therapeutic] treatment in combination with calcium folinate (folinic acid) is described in the literature. When combined with calcium folinate, 5-FU may have more pronounced side effects and cause severe diarrheas.

Both the efficacy and toxicity of 5-Fluorouracil may be increased when 5-FU is used in combination with other cytotoxic drugs (cyclophosphamide, vincristine, methotrexate, cisplatin, doxorubicin), interferon-α or folinic acid.

In combination with other myelosuppressive substances, dosage adjustment is necessary; concomitant or previous radiation therapy may require dosage reduction. The cardiotoxicity of anthracyclines may be increased.

Aminophenazone, phenylbutazone and sulfonamides should not be administered before and during treatment.

Concurrent use of allopurinol may reduce the toxicity and efficacy of 5-FU.

Chlordiazepoxide, disulfiram, griseofulvin and isoniazid can increase the efficacy of 5-Fluorouracil.

Vaccines: The common defence mechanism is decreased by Fluorouracil, thereby the immunologic response is decreased. Live vaccines can lead to an increased replication of the virus.

After long-term treatment with 5-Fluorouracil in combination with mitomycin the appearance of a haemolytic-uraemic syndrome was reported.

4.6 Pregnancy and lactation

There is insufficient knowledge about the effects of treatment with 5-Fluorouracil on pregnancy in the absence of concomitant treatment (cytotoxic drugs, radiation therapy). After administration of 5-Fluorouracil during pregnancy – always in combination with other potentially damaging forms of treatment – there have been reports of children born with anomalies as well as reports of children born healthy even after administration of 5-Fluorouracil in the first trimester of pregnancy.
In animal studies (see Section 5.3.)
5-Fluorouracil has been shown to be teratogenic and fetotoxic in various animal species. Furthermore, animal studies have produced evidence of fertility damaging effects.
The use of 5-FU is discouraged during pregnancy, especially during the first trimester. Expected benefits of treatment should be weighed against potential risks to the fetus in each individual case.
It is not known if 5-Fluorouracil is excreted in human milk. Nursing mothers should stop breastfeeding during treatment with 5-Fluorouracil.

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

Infections and infestations

Uncommon:
Fever

Blood and the lymphatic system disorders:

Very common:
Leukopenia and thrombocytopenia are common and the precautions described above should be followed.

Common:
Agranulocytosis, anaemia and bone marrow depression.

Immune system disorders:

Uncommon:
Allergic reactions

Metabolism and nutrition disorders

Very rare:
Patients with low levels of DPD activity of any case (incl. DPD-inhibitors like eniluracil or antiviral drug soruvidine) are at highest risk to develop severe and prolonged adverse reactions shortly after initiation of a 5-FU-treatment. An initial screening of DPD activity is recommended.

Nervous system disorders:

Common:
A transient reversible cerebellar syndrome, including ataxia, a reversible confusional state and extrapyramidal motor and cortical disturbances, which usually respond to withdrawal of 5-Fluorouracil, may occur.

Uncommon:
Somnolence

Very rare:
Brain infarction has been reported during combined chemotherapy (for example: 5-FU + mitomycin C or cisplatin).

Eye disorders :

Rare:
There have been reports of conjunctivitis, excessive lacrimation, dacryostenosis, visual changes, photophobia and optic neuritis.

Cardiac disorders:

Uncommon
Cases of chest pain, ischemia, ECG abnormalities, left ventricular dysfunction.

Rare:
Myocardial infarction

Vascular disorders:

Uncommon:
Epistaxis
Hypotension
Thrombophlebitis

Gastrointestinal disorders:
Very common:
There may also be, mucositis - e.g. stomatitis, oesophagitis, pharyngitis, or proctitis -.

Common:
Diarrhoea, nausea and vomiting are common and can be treated symptomatically.
Anorexia

Uncommon:
Gastrointestinal ulceration and bleeding.

Very rare:
Liver cell damage
Lethal liver necrosis

Skin and subcutaneous tissue disorders:

Common:
Alopecia may be seen in a substantial number of cases, but it is reversible.

Uncommon:
Other side effects include dermatitis, skin alterations - e.g. dry skin, fissure, erosion, erythema, rash, pruritus - photosensitivity, allergic skin reactions, pigmentation, streaky hyperpigmentation or depigmentation near the veins, changes in the nails or loss of nails. Palmar-Plantar Erythrodysesthesia Syndrome has been reported as an unusual complication of high dose bolus or protracted [continuous] therapy with 5-Fluorouracil.

Musculoskeletal, connective tissue and bone disorders:

Uncommon:
nasal bone necrosis

Renal and urinary disorders:

Uncommon:
Renal failure

Reproductive system and breast disorders:

Uncommon:
disturbances of spermatogenesis and ovulation

General disorders and administration site conditions:

Uncommon:
Tiredness

Investigations:

Very rare:
Scattered reports have been related prolonged prothrombon time to coadministration of 5-fluorouracil and warfarin. Gemcitabine may increase the systemic 5-FU exposure.

4.9 Overdosage

Symptoms:
Acute:
psychotic reactions, somnolence, increased effectiveness of sedative drugs, increased alcohol toxicity.

If sedation is necessary, diazepam can be administered i.v. in small doses (e.g. starting with 5mg) with cardiovascular and pulmonary monitoring.

Chronic:
Bone marrow depression to the point of agranulocytosis and critical thrombocytopenia, hemorrhagic tendency, ulcerations in the gastrointestinal tract, diarrhea, alopecia.

Therapy:
There is no known specific antidote. Infusions of leukocyte or platelet concentrates may/ should be administered prophylactically. Attention is to be paid to adequate hydration and diuresis; electrolyte imbalances should be corrected. Hemodialysis is not usually necessary. The patient should be observed carefully to detect haematologic and gastrointestinal late complications as early as possible. Further treatment should be symptomatic.

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:
There are large inter- and intraindividual differences in the absorption of 5-Fluorouracil from the gastrointestinal tract after oral administration. 5-FU is also subject to hepatic first-pass extraction in the liver.
The bioavailability is between 0% and 80%.
5-Fluorouracil "Ebewe" is administered only intravenously and intraarterially.

Distribution:
After intravenous administration 5-Fluorouracil is distributed throughout the body and is found especially in fast proliferating tissues such as the bone marrow, intestinal mucosa and neoplasia; 5-Fluorouracil crosses the blood-brain barrier and the placenta.
The substance shows a volume of distribution of 0.12L/kg body weight, the plasma protein binding is about 10%.

Biotransformation:
5-FU metabolism occurs in the liver and is similar to uracil metabolism . 5-Fluorouracil is rapidly converted enzymatically to its active metabolite, dihydro-5-Fluorouracil, whose half-life is significantly longer than that of 5-FU. Additional[,] nontoxic decomposition products are carbon dioxide and urea.

Elimination:
The mean plasma elimination half-life is about 10 to 20 minutes and dose dependent. No intact drug can be detected in the plasma three hours after intravenous administration.
5-Fluorouracil is primarily (60–80%) expired as carbon dioxide via the lungs. Secondarily, 5-Fluorouracil is eliminated renally as unchanged parent drug (7–20%), approximately 90% of it within the first hour. Renal clearance is about 170–180ml/min. If kidney function is decreased the substance is eliminated slowly.

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

Do not store above 25°C – do not refrigerate or freeze. Keep container in the outer carton, in order to protect from light. Remove solution from vial immediately before use.

If a precipitate has formed as a result of exposure to low temperatures, redissolve by heating to 60°C accompanied by vigorous shaking. Allow to cool to body temperature prior to use.

6.5 Nature and contents of container

The vial is made of hydrolytic glass (class I) and packed in a carton.
Ampoules of hydrolytic glass (class I), packed in a carton.
5 ampoules containing 250mg/5ml of fluorouracil, each.
5 ampoules containing 500mg/10ml of fluorouracil, each.
1 vial containing 250mg/5ml of fluorouracil.
1 vial containing 500mg/10ml of fluorouracil.
1 vial containing 1000mg/20ml of fluorouracil.
1 vial containing 5000mg/100ml of fluorouracil.

6.6 Instructions for use/handling

As with other cytotoxic drugs, special 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 seek 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. MANUFACTURER

EBEWE Pharma Ges.m.b.H. Nfg.KG
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8. DATE OF (PARTIAL) REVISION OF THE TEXT

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