SUMMARY OF PRODUCT CHARACTERISTICS

SUMMARY OF MEDICINAL PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

5-Fluorouracil Ebewe 50 mg/ml – concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml concentrate for solution for infusion contains 50 mg of fluorouracil.

Other excipients with known effect:
Each ml concentrate for solution for infusion contains 14.7 mg sodium hydroxide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Colourless, clear solution.
pH value: 8.5 – 9.5

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adjuvant or palliative treatment of

- advanced colorectal cancer
- advanced stomach cancer
- advanced pancreatic cancer
- advanced and/or metastatic breast cancer
- advanced tumours in the head and neck area
- advanced cervical cancer

5-Fluorouracil Ebewe 50 mg/ml – concentrate for solution for infusion is used in adults.

4.2 Dosage and method of administration

Treatment with 5-fluorouracil must only be implemented by physicians who are experienced in tumour therapy. During the initial phase, hospitalisation of the patient must be considered.

5-fluorouracil is used in monochemotherapy and as a part of polychemotherapy. Since the method of administration and dosage recommendations for 5-fluorouracil vary widely, only the common reference values can be stated.

The exact dosage should be taken from treatment protocols which have proven effective in the treatment of the respective disease.

Dosage

Initial therapy for daily use:

- as an i.v. infusion
  15 mg/kg or 600 mg/m² for 4 hours daily - until the occurrence of adverse reactions.

- as an i.v. injection
  12 mg/kg or 480 mg/m² slowly i.v. (2 to 3 min.) on the 1st, 2nd and 3rd day;
  if no signs of toxicity are detectable - administration of 6 mg/kg or 240 mg/m² on the 5th, 7th and 9th day.

Initial therapy for weekly use:
15 mg/kg or 600 mg/m² once weekly, slowly, i.v.

Maintenance therapy:
As soon as remission has been achieved and after abatement of the adverse reactions and re-increases in leukocytes to 3000–4000/µl, platelets to 80,000–100,000/µl: 5-10 mg/kg or 200-400 mg/m² i.v. once weekly.

The maximum daily dosage of 1 g must not be exceeded.

All dosage information refers to the normal weight, meaning that in case of obesity, ascites, or oedema, appropriate standardisation must be carried out.

The treatment duration is determined by the experienced specialist or as per the treatment protocol in accordance with the type and course of the disease.

If 5-fluorouracil is combined with other cytostatics which have a similar adverse reaction profile, or with radiotherapy, the dose must be reduced accordingly. Administration can take place in the form of a 24-hour continuous drip infusion.

Method of administration

For intravenous use.
5-fluorouracil must only be applied intravenously. It can be injected or infused after being diluted with a NaCl 0.9% solution or 5% glucose.

Extravasal administration must be avoided.

Special dosage recommendations:
The recommended doses are reduced by one third to half in case of poor nutritional condition of the patient, after major surgery, in myelosuppression (leukocytes <4,000/µl, platelets <100,000/µl) and severely impaired liver and kidney function.

Renal or hepatic impairment:
Caution is advised and, if necessary, the dose must be reduced in patients with renal or hepatic impairment.

Elderly persons (aged 65 years and up):
It is not necessary to adjust the initial dosage. However, close monitoring of elderly patients is recommended.

4.3 Contraindications

5-fluorouracil must not be given in the event of:

- hypersensitivity to the active substance or to any of the excipients listed in Section 6.1
- severe blood count changes
- bone marrow suppression
- haemorrhage

- severe renal and/or hepatic impairment
- acute, severe infections (e.g. herpes zoster, varicella)
- stomatitis
- ulcers of the oral cavity and gastrointestinal tract
- pseudomembranous enteritis
- patient in a poor general state of health
- during pregnancy and breast-feeding (see Section 4.6)
- in patients with known completely absent dihydropyrimidine dehydrogenase (DPD) activity (see Section 4.4)
- recent or concomitant treatment with brivudine (see also Sections 4.4 and 4.5 for drug interactions).

Brivudine is a potent inhibitor of the 5-fluorouracil-degrading enzyme dihydropyrimidine dehydrogenase (DPD).

In patients with dihydropyrimidine dehydrogenase deficiency, normal 5-fluorouracil doses trigger increased adverse reactions. If serious adverse reactions occur, monitoring of the DPD activity can be appropriate. Patients with dihydropyrimidine dehydrogenase deficiency must not be treated with 5-fluorouracil.

Vaccinations with live vaccines must not be implemented in a temporal connection with 5-fluorouracil treatment. Any contact with poliomyelitis vaccines should be avoided.

4.4 Special warnings and precautions for use

Precautions for handling and using 5-fluorouracil

Due to possible mutagenic and carcinogenic effects, increased safety measures apply to hospital staff and physicians. During the handling of 5-fluorouracil, any contact with the skin and mucous membranes must be avoided, otherwise immediate cleaning with water and soap is necessary. If the eyes are contaminated, they must be immediately rinsed with water and medical attention must be sought. All precautions must be taken to enable absolutely aseptic work. The use of a working area with laminar flow is recommended. Protective clothing must be worn while handling 5-fluorouracil.

Pregnant personnel must not work with 5-fluorouracil.

Cardiotoxicity

Treatment with fluoropyrimidines was associated with cardiotoxicity, including myocardial infarction, angina pectoris, arrhythmia, myocarditis, cardiogenic shock, sudden death and changes in the ECG (including very rare cases of prolongation of the QT interval). These adverse reactions occur more frequently in patients who receive a continuous infusion with 5-fluorouracil than those receiving bolus injections. A known history of coronary heart disease can be a risk factor for cardiac adverse reactions. Caution is therefore indicated when treating patients who have experienced chest pain during the treatment cycles and in patients with known heart disease. During treatment with fluorouracil, heart function should be monitored regularly. In the case of severe cardiotoxicity, treatment should be discontinued.

Encephalopathy

After the market launch, cases of encephalopathy (including hyperammonaemic encephalopathy and leucoencephalopathy) that were associated with treatment with 5-fluorouracil were reported. Signs and symptoms of encephalopathy include changes in mental state, disorientation, coma or ataxia. If one of these symptoms occurs, the treatment should be stopped immediately and the serum ammonia values should be tested. In the case of elevated serum ammonia values, ammonia-lowering treatment must be initiated.

Caution is advised when administering fluorouracil to patients with impaired renal and/or hepatic function. In patients with impaired renal and/or hepatic function, there may be an increased risk of hyperammonaemia and hyperammonaemic encephalopathy.

Dihydropyrimidine dehydrogenase (DPD) deficiency
The enzyme dihydropyrimidine dehydrogenase (DPD) plays an important role in the reduction of 5-fluorouracil. Nucleoside analogues, such as brivudine and sorivudine, can lead to a strong increase in plasma concentrations of 5-fluorouracil and other fluoropyrimidines and a resulting increase in toxicity. For this reason, an interval of at least 4 weeks should be observed between using fluorouracil and brivudine, sorivudine and analogues.

Brivudine may not be used together with 5-fluorouracil. Deaths due to this medicinal product interaction have been reported. Therefore, after the end of therapy with brivudine and prior to initiation of therapy with 5-fluorouracil, an interval of at least 4 weeks must be observed. Therapy with brivudine can be initiated 24 hours after the last dose of 5-fluorouracil (see Sections 4.3 and 4.5). If necessary, the determination of the DPD enzyme activity is indicated before starting treatment with 5-fluorouracil.

In the event of accidental administration of brivudine to patients treated with 5-fluorouracil, effective measures should be taken to reduce 5-fluorouracil toxicity. Immediate admission to a hospital is recommended. All measures for preventing systemic infections and dehydration should be initiated.

Rare, unexpected and severe toxicity when using 5-FU, such as stomatitis, diarrhoea, mucositis, neutropoenia and neurotoxicity, were explained with impaired DPD activity. Patients with low or absent DPD activity – an enzyme that is involved in the degradation of fluorouracil – have an increased risk of severe, life-threatening or fatal adverse reactions caused by fluorouracil. Although a DPD deficiency cannot be defined precisely, it is known that patients with specific homozygous or specific complex heterozygous mutations in the DPYD gene locus (e.g. DPYD*2A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variants) potentially resulting in complete or nearly complete absence of enzymatic DPD activity (as determined in laboratory tests) have the highest risk of a life-threatening or fatal adverse reaction and must not be treated with 5-fluorouracil (see section 4.3). There is no proven dosage that is safe for patients with completely absent DPD activity.
Patients with specific heterozygous DPYD variants (including DPYD*2A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variants) showed an increased risk of severe toxicity when treated with fluoropyrimidines.

The frequency of heterozygous DPYD*2A genotypes in the DPYD gene in Caucasian patients is approximately 1%, 1.1% for c.2846A>T, 2.6%–6.3% for c.1236G>A/HapB3 variants and 0.07% to 0.1% for c.1679T>G. Genotyping on this allele is recommended to identify patients at increased risk of severe toxicities. Information on the frequency of these DPYD variants in populations other than Caucasians is limited. It cannot be ruled out that other rare variants can also be associated with an increased risk of severe toxicity.

In patients with partial DPD deficiency (such as those with heterozygous mutations in the DPYD gene locus) where the benefit of 5-fluorouracil outweighs the risk - taking into consideration the suitability of an alternative non-fluoropyrimidine chemotherapy regimen - it is necessary to proceed with extreme caution. Regular checks with dosage adjustments must be performed depending on toxicity. In these patients, a reduction in the starting dose can be considered to avoid severe toxicity. There is insufficient data to recommend a specific dose in patients with partial DPD activity measured with a specific test. It was reported that the DPYD*2A, c.1679T>G variants led to a greater reduction in enzymatic activity than the other variants, associated with a higher risk of adverse reactions. The effect of a reduced dose on efficacy is currently uncertain. Therefore, if there is no severe toxicity, the dose may be

increased while the patient is monitored carefully. Patients who have tested negative for the above-mentioned allele may still have a high risk of serious adverse reactions.

Life-threatening toxicity can occur in patients with unknown DPD deficiency who were treated with 5-fluorouracil as well as patients who tested negative for specific DPYD variants, manifesting in the form of acute overdose (see Section 4.9). In the case of acute toxicity of grade 2–4, treatment must be stopped immediately. A permanent interruption should be considered based on the clinical evaluation of the start, duration and severity of the observed toxicity.

Due to the possibility of occurrence of an anaphylactic reaction, the usual anti-shock control means should be provided prior to use of 5-fluorouracil.

Patients receiving phenytoin concomitantly with 5-fluorouracil should be examined regularly due to potentially elevated phenytoin plasma levels.

Damage to the intestinal wall requires symptomatic treatment depending on severity, for example fluid substitution. Mild diarrhoea can be treated with antidiarrhoeal drugs. However, these are not sufficient with moderate to severe diarrhoea.

Prior to and during treatment with 5-fluorouracil, the following tests are recommended:
- daily inspection of the oral cavity and throat with regard to changes in the mucous membranes
- Blood count including differential blood count and platelets before each administration of 5-fluorouracil and every 2-3 days at the start of treatment
- Retention values at regular intervals
- Liver values at regular intervals
- Determination of uric acid levels
- Examination of stool for occult blood

Patients must be informed about the possible occurrence of stomatitis/mucositis, diarrhoea and bleeding (especially from the gastrointestinal tract). They must be informed that they should inform the responsible physician at the first signs. Immediate discontinuation of treatment is required in case of the following symptoms: gastrointestinal reactions (stomatitis, mucositis, severe diarrhoea, severe vomiting, ulcers, bleeding), leukocytes <3,000/µl, platelets <80,000/µl, central (including ataxia and tremor) and cardiac adverse reactions.

Treatment may only be continued after the adverse reactions have subsided and if the patient's general condition permits it. In the case of severe gastrointestinal, cardiac or neurological toxicity symptoms, it is generally advisable not to resume treatment.

If 5-fluorouracil and oral anticoagulants are administered simultaneously, the Quick value must be monitored closely.

Special caution is indicated for high-risk patients after high-dose pelvic radiation, after therapy with alkylating agents, with extensive bone metastases and extensive liver metastases (reduced degradation!) and cachectic patients.

In combination with methotrexate, methotrexate is to be applied to achieve an optimal effect up to 24 hours before 5-fluorouracil (not reversed!).

5-fluorouracil can act mutagenically. Men who are treated with 5-fluorouracil are therefore advised not to father children during treatment and for up to 6 months after the start of treatment, and to seek advice on sperm conservation due to the possibility of severe disorders of spermatogenesis as a result of treatment. Women must not become pregnant during therapy with 5-fluorouracil and must take effective contraceptive measures.
Genetic counselling is recommended for patients who wish to have children after treatment.

Paediatric population:
Not enough research has been done on the efficacy and safety of 5-fluorouracil in children and adolescents.

5-Fluorouracil Ebewe contains sodium
This medicinal product contains up to 9.31 mg sodium per ml or 186.20 mg per maximum daily dose, equivalent to 9.31% of the maximum daily sodium uptake with food of 2 g as recommended by the WHO.

4.5 Interactions with other medicinal products and other forms of interaction

Please note that the following information can also refer to recently administered drugs.

Brivudine:
A clinically significant interaction was described between brivudine and fluoropyrimidines (e.g. capecitabine, 5-fluorouracil, tegafur), which is based on inhibition of the dihydropyrimidine dehydrogenation by brivudine. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Therefore, brivudine must not be used together with 5-fluorouracil (see Sections 4.3 and 4.4). After the end of therapy with brivudine, it is necessary to wait at least 4 weeks before therapy with 5-fluorouracil can be started. Therapy with brivudine may start 24 hours after the last dose of 5-fluorouracil. If necessary, the determination of the DPD enzyme activity is indicated before starting treatment with 5-fluorouracil.

All therapeutic measures that worsen the physical state of the patient or have myeloid effects (e.g. other cytostatics) may increase the toxicity of 5-fluorouracil.

Fluorouracil can intensify the toxic effect on the skin caused by radiation therapy.

Calcium folinate may potentiate the effects of 5-fluorouracil. As a clinical consequence of this interaction, severe, sometimes fatal diarrhoea can occur. An accumulation of such deaths was particularly associated with an administration regimen of IV bolus injection of 600 mg 5-fluorouracil per m^2 body surface area once weekly in combination with calcium folinate.

In concomitant administration of phenytoin and 5-fluorouracil, there were reports of an increase in plasma concentrations of phenytoin, which led to symptoms of phenytoin intoxication.

Cimetidine, metronidazole, allopurinol and interferons can increase the plasma levels of 5-fluorouracil. This can increase the toxic effects of 5-fluorouracil.

In female patients who received diuretics of the thiazide type in addition to cyclophosphamide, methotrexate and 5-fluorouracil, the number of granulocytes was more significantly reduced than after the same number of cytostatic cycles without thiazide.

Concomitant administration of 5-fluorouracil and warfarin may lead to prolongation of the prothrombin time, therefore this should be closely monitored. In individual cases, a drop in the Quick value was observed in patients who were treated with warfarin and additionally 5-fluorouracil alone or in combination with levamisole.

During concomitant treatment with 5-fluorouracil and levamisole, hepatotoxic effects (increase in alkaline phosphatase, transaminases, or bilirubin) are often observed.

In patients with breast cancer who received combination treatment with cyclophosphamides, methotrexate, 5-fluorouracil and tamoxifen, there was an increased risk of occurrence of thromboembolic events.

In the case of concomitant administration of vinorelbine and 5-fluorouracil/folinic acid, severe and potentially fatal mucositis may occur.

The assay techniques for bilirubin and 5-hydroxyindole-acetic acid in urine can result in elevated or false positive values.

Aminophenazone, phenylbutazone and sulphonamides should not be given before and during treatment.

Chlordiazepoxide, disulfiram, griseofulvin and isoniazide can intensify the effects of 5-fluorouracil.

After long-term use of 5-fluorouracil in combination with mitomycin, haemolytic-uraemic syndrome was reported.

Very rarely, the occurrence of cerebral infarction has been reported in a temporal association with a 5-fluorouracil therapy in combination with other chemotherapeutic agents (mitomycin C or cisplatin).

General information
Cytostatics can reduce the formation of antibodies after an influenza vaccination.
Cytostatics can increase the risk of serious infections after administration of live vaccines.

Incompatibilities
5-fluorouracil may only be diluted with a physiological saline solution or a 5% glucose solution.
5-fluorouracil must not be mixed with other substances in an infusion.

Incompatibilities were reported with the following active substances:
Cisplatin, cytarabine, diazepam, doxorubicin, droperidol, filgrastim, gallium nitrate, leucovorin, methotrexate, metoclopramide, morphine, ondansetron, parenteral nutrient solutions, vinorelbine.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy
5-fluorouracil may be mutagenic and must not be administered during pregnancy (see section 4.3). Women of childbearing age must ensure effective contraception during treatment and up to 6 months thereafter. If there is a pregnancy during treatment, the possibility of genetic counselling must be considered.

Animal experiments showed teratogenic reactions on the foetus.

5-fluorouracil presumably causes serious harm to the unborn child when used during pregnancy.

Breastfeeding
As it is not known whether 5-fluorouracil passes into breast milk, women who receive the product must not breastfeed. If its use is absolutely necessary during breastfeeding, weaning must take place beforehand (see Section 4.3).

Fertility
5-fluorouracil can cause genetic harm. Men who are treated with 5-fluorouracil are therefore advised not to father children during as well as up to 6 months after treatment. Due to the possibility of severe spermatogenesis disorders as a result of therapy with 5-fluorouracil, a consultation regarding sperm conservation is recommended prior to treatment.

4.7 Effects on ability to drive and operate machinery

5-fluorouracil may cause nausea, vomiting, adverse reactions of the nervous system and changes in vision and thus indirectly affect the ability to drive or use machines. Therefore, you should not drive or use machines during treatment with 5-fluorouracil.

4.8 Undesirable effects

The most common and most serious adverse reactions of 5-fluorouracil are bone marrow toxicity and gastrointestinal symptoms.

The evaluation of adverse reactions is based on the following frequencies:

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)
Unknown (frequency cannot be estimated from the available data)

Blood and lymphatic system disorders
Very common: Myelosuppression (leucopoenia, neutropoenia, thrombocytopenia), anaemia
Common: febrile neutropoenia
Very rare: Agranulocytosis, pancytopoenia

Infections and parasitic disorders:
Very common: Infections
Common: Immunosuppression with increased risk of infection
Rare: sepsis

Immune system disorders
Rare: General allergic reactions, anaphylaxis, anaphylactic shock

Endocrine disorders
Not known: Total thyroxine (T_4) and total triiodothyronine (T_3) in the serum can increase without elevation of the free T_4 and TSH and without clinical signs of hyperthyroidism (patients remain clinically euthyroid)

Metabolism and nutrition disorders
Very common: Hyperuricaemia

Psychiatric disorders
Rare: Confusion

Nervous system disorders
Uncommon: Nystagmus, headache, dizziness, symptoms of Parkinson's disease, pyramidal signs, euphoria, somnolence
Rare: Peripheral neuropathy (in combination with radiotherapy)
Very rare: Dysgeusia, (leuco-) encephalopathy with ataxia, acute cerebral syndrome, dysarthria, confusion, disorientation, myasthenia, aphasia, convulsion or coma
Unknown: Hyperammonaemic encephalopathy

Eye disorders
Uncommon: Increased lacrimation and stenosis of the tear canal, blurred vision, disorders of eye motility, inflammation of the optic nerves, double vision, reduced visual acuity, photophobia, conjunctivitis, inflammation of the eye lids, ectropion due to scar formation and fibrosis of the lacrimal glands

Cardiac disorders
Very common: Ischaemic ECG abnormalities

Common: Angina pectoris-like chest pain
Uncommon: Arrhythmia, myocardial infarction, myocardial ischaemia, myocarditis, heart failure, dilative cardiomyopathy, cardiogenic shock
Very rare: Cardiac arrest, sudden cardiac death
Not known: Pericarditis

Vascular disorders
Uncommon: Hypotension
Rare: Thrombophlebitis
Unknown: Cerebral, intestinal and peripheral ischaemia, Raynaud's syndrome, thromboembolism

Respiratory, thoracic and mediastinal disorders
Very common: Bronchospasm, epistaxis

Gastrointestinal disorders
Very common: Gastrointestinal disorders (sometimes life-threatening) such as mucositis (stomatitis, pharyngitis, oesophagitis, proctitis), anorexia, (watery) diarrhoea, nausea, vomiting (see also section 4.4)
Uncommon: Dehydration, ulcers and bleeding in the gastrointestinal tract, necrotic rejection

Hepatobiliary disorders
Uncommon: Liver cell damage, stoneless cholecystitis
Very rare: liver necrosis (cases with fatal outcome)

Skin and subcutaneous tissue disorders
Very common: alopecia, palmar-plantar erythrodysaesthesia syndrome (so-called "hand-foot syndrome") with dysaesthesia, redness, swelling, pain and scaling of the skin on the palms and soles of the feet
Uncommon: dermatitis, changes in the skin (dry skin, erosion/fissures, erythema, pruritic maculopapular skin rash), exanthema, urticaria, photosensitivity, hyperpigmentation of the skin, stripe-like hyperpigmentation or depigmentation near veins, nail changes (e.g. diffuse superficial blue pigmentation, hyperpigmentation, nail dystrophy, pain and thickening of the nail bed, paronychia), onycholysis

Reproductive system and breast disorders
Uncommon: disorders of spermatogenesis and ovulation

General disorders and administration site conditions
Very common: delayed wound healing, exhaustion, general asthenia, fatigue, lack of drive, fever

Description of selected adverse reactions
Blood and lymphatic system disorders
Myelosuppression is one of the dose-limiting adverse reactions (see also Section 4.2). The degree of severity (NCI Grade I–IV) of myelosuppression depends on the type of administration (IV bolus injection or IV continuous infusion) and the dosage. Neutropoenia occurs after each therapy cycle with an IV bolus injection with adequate doses (nadir: 9th–14th–(20th) day of therapy; normal values: usually after day 30).

Cardiac disorders
Cardiotoxic effects usually occur during or within a few hours after the first treatment cycle. In patients with pre-existing coronary heart disease or cardiomyopathy, there is an increased risk of cardiotoxicity.

Gastrointestinal disorders

The severity level (NCI Grade I–IV) of gastrointestinal adverse reactions depends on the dosage and method of administration. In the case of a continuous IV infusion, stomatitis is more likely to be the dose-limiting factor than myelosuppression.

Skin and subcutaneous tissue disorders
So-called hand-foot syndrome begins with dysaesthesia of the palms and soles of the feet, with reddening, swelling, pain and scaling of the skin in the further course. It is **very common** after continuous IV administration and **common** after i.v. bolus injection.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

Bundesamt für Sicherheit im Gesundheitswesen
Traisengasse 5
1200 VIENNA
AUSTRIA
Fax: +43 (0) 50 555 36207
Website: http://www.basg.gv.at/

4.9 Overdose

Symptoms of an overdose
In the event of an overdose, the symptoms listed under adverse reactions such as nausea, vomiting, diarrhoea, severe mucositis, ulcers and bleeding in the gastrointestinal tract, bone marrow depression (thrombocytopoenia, leucopoenia, agranulocytosis) occur at a higher rate/with greater severity.

acute:
Psychotic reactions, somnolence, potentiation of the effects of sedating medicinal products, increased alcohol toxicity.

If sedation is necessary, diazepam IV. may be administered in small doses (e.g. starting with 5 mg) while monitoring circulation and respiration.

chronic:
Bone marrow depression up to agranulocytosis and critical thrombopoenia, bleeding tendency, gastrointestinal tract ulcers, diarrhoea, hair loss.

Therapeutic measures
If symptoms of intoxication occur, administration of 5-fluorouracil should be stopped immediately. Measures for symptomatic treatment must be taken.
Infusions of leukocyte or platelet concentrate, infection prophylaxis. Forced diuresis to compensate the volume and mineral balance can be favourable. Haemodialysis is generally not necessary. Careful monitoring to detect haematological and gastrointestinal delayed complications in a timely manner.
Permanent myelosuppression must be treated under inpatient conditions. This includes, if necessary, substitution of the missing blood components and antibiotic therapy. The patient may need to be moved into an aseptic room.

Haematological monitoring is recommended up to 4 weeks after an overdose.

If treatment with 5-fluorouracil is to be continued despite cardiac adverse reactions, the administration of vasodilators is indicated to avoid spasms of the coronary arteries.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, antimetabolites, pyrimidine analogues, ATC code: L01BC02

The antimetabolite 5-fluorouracil represents a fluorinated pyrimidine. 5-fluorouracil is activated enzymatically with deoxyfluorouracil monophosphate. This inhibits the activity of thymidylate synthetase and thus the synthesis of deoxythymidine monophosphate by means of complex formation. This results in a phase-specific inhibition of DNA synthesis. Furthermore, dioxyfluoronucleotides inhibit the new synthesis of pyrimidine nucleotides.

Calcium folinate forms a relatively stable ternary complex with 5-fluorouracil and thymidilate synthetase, thereby prolonging the inhibitory effects of 5-fluorouracil on thymidilate synthetase. This results in potentiation of the cytotoxic effects of 5-fluorouracil.

5-fluorouracil acts in the cell cycle in a phase-specific manner, especially on the S-phase. The effect of the substance is particularly pronounced in rapidly proliferating tissues (bone marrow, skin and mucous membranes).

5.2 Pharmacokinetic properties

5-fluorouracil is also catabolised by the enzyme dihydropyrimidine dehydrogenase (DPD) into the significantly less toxic form of dihydro-5-fluorouracil (FUH2). The enzyme dihydropyrimidinase splits the pyrimidine ring into 5-fluoroureidopropionic acid (FUPA). Finally, the ß-ureidopropionase splits FUPA into α-fluoro-ß-alanine (FBAL) that is excreted with the urine. The activity of dihydropyrimidinase dehydrogenase (DPD) determines the rate. A deficiency of DPD can lead to increased toxicity of 5-fluorouracil (see sections 4.3 and 4.4).

5-fluorouracil is only incompletely absorbed by the oral route (0-80%).

The substance has a distribution of 0.12 l/kg BW (after 15 mg/kg BW IV.) and is particularly recovered in rapidly proliferating tissues such as bone marrow, intestinal mucous membranes and neoplasias; 5-fluorouracil passes the blood-brain barrier.

Metabolism takes place in the liver and is similar to that of uracil. 5-fluorouracil undergoes rapid enzymatic conversion into the active metabolite dihydro-5-fluorouracil, which has a significantly longer half-life than 5-fluorouracil. Other non-toxic degradation products include carbon dioxide and urea.

The plasma half-life (alpha phase) is between 8 and 22 minutes. The elimination half-life (beta phase) reaches approximately 20 hours due to the active metabolites in the tissues and is dose-dependent.

5-fluorouracil (60-80%) is primarily exhaled as carbon dioxide via the lungs. Secondarily, 5-fluorouracil is excreted unchanged by the renal route (approx. 7-20%); approx. 90% within the first hour. Renal clearance is about 170-180 ml/min. The substance is excreted slowly if renal function is impaired.

In the cerebrospinal fluid, the maximum concentration is reached after approximately 1.5 – 2 hours and equals approximately 50% of the plasma concentration.

Kinetics in special clinical situations: despite the low renally eliminated portion (approx. 15%), due to impairment of bone marrow function with azotaemia (as a consequence of renal insufficiency) and any interference with platelets, a dosage adjustment that corresponds to the degree of renal insufficiency and the reaction of the individual patient is indicated. If liver function impairment is impaired, a dosage adjustment should also be considered.

5.3 Preclinical safety data

Toxicity
The cell division inhibitory effect of 5-fluorouracil primarily affects rapidly proliferating tissues - both tumour-producing and healthy tissues. Accordingly, toxicities are displayed particularly in the bone marrow, with leucopoenia, thrombocytopoenia, gastrointestinal tract bleeding, and secondarily in the form of infections.

Reproductive toxicity / mutagenicity / carcinogenicity
In various in-vitro cultures, fluorouracil shows mutagenic potential (various Salmonella typhimurium strains, micronucleus test in mice; in high concentrations, it causes chromosomal strand breaks in hamster fibroblasts). In-vivo, male rats showed chromosomal aberrations and changes in spermatogenesis ranging to infertility. In female rats, fluorouracil reduced fertility and induced chromosomal aberrations in the embryos. Lesser effects were observed in rabbits.

Antimetabolites showed carcinogenic properties in animal trials. However, the risk of developing secondary tumours appears to be lower in humans than with alkylating substances.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection and sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

5-Fluorouracil Ebewe must only be diluted with saline or 5% glucose solution.
5-fluorouracil must not be mixed with other substances in an infusion.

5-fluorouracil must not be diluted with strongly buffered solutions with a pH <8, since 5-fluorouracil would precipitate in this environment. Do not mix with other chemotherapeutic solutions.

Incompatibilities were reported with the following active substances:
fluorouracil is incompatible with folinic acid, carboplatin, cisplatin, cytarabine, diazepam, doxorubicin, droperidol, filgrastim, gallium nitrate, methotrexate, metoclopramide, morphine, ondansetron, parenteral nutrition, vinorelbine and other anthracyclines.

Calcium folinate
Calcium folinate must not be mixed with 5-fluorouracil in the same infusion, as a precipitate may form. It has been shown that 5-fluorouracil 50 mg/ml is incompatible with calcium folinate 20 mg/ml with or without dextrose 5% in water when it is mixed in different quantities and stored in containers made of polyvinyl chloride at 4°C, 23°C or 32°C.

5-Fluorouracil Ebewe solution for injection/infusion must not be mixed with other medicines, including oxaliplatin or irinotecan.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

Do not refrigerate or freeze.
Store in the original package in order to protect from light.

For single use only.
Only use clear and colourless to pale yellow solutions.

If precipitations occur due to storage at low temperatures, they can be dissolved by carefully heating to 60°C and shaking. Allow to cool before administration.

Shelf life after dilution
Dilution can be performed with sodium chloride 0.9% solution or 5% glucose solution. Stability data for concentrations of 0.35 mg/ml and 15 mg/ml have shown that the maximum storage time of the ready-to-use 5-fluorouracil solution for infusion is 28 days.
This storage time refers both to storage in the refrigerator (2–8°C), including protection from light, as well as storage at room temperature (20–25°C) with or without protection from light.
The chemical and physical stability of the ready-to-use infusion preparation was proven to be over 28 days, but the ready-to-use solution must be used immediately from a microbiological perspective. If it is not used immediately, the storage conditions of the ready-to-use infusion preparation prior to administration become the responsibility of the user and normally do not exceed 24 hours at 2–8°C, unless dilution has taken place under controlled and validated aseptic conditions.

6.5 Nature and contents of container

1 / 5 injection vials containing 5 ml
1 / 5 injection vials containing 10 ml
1 / 5 injection vials containing 20 ml
1 injection vial containing 100 ml

Injection vials made from Type 1 amber glass vials with/without a transparent plastic container (Onco-Safe).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Due to possible mutagenic and carcinogenic effects, increased safety measures apply to hospital staff and physicians. During the handling of 5-fluorouracil, any contact with the skin and mucous membranes must be avoided, otherwise immediate cleaning with water and soap is necessary. If the eyes are contaminated, they must be immediately rinsed with water and medical attention must be sought. All precautions must be taken to enable absolutely aseptic work. The use of a working area with laminar flow is recommended. Protective clothing must be worn while handling 5-fluorouracil.

Pregnant personnel must not work with fluorouracil.

Inactivation:
* 700°C
* Dilute sodium hypochlorite (Liquor Natrii hypochlorosi) with 10 parts water
* Concentrated NaOH over several hours

The finished solution should be used immediately after preparation.
Precipitates resulting from storage at low temperatures can be dissolved by shaking and cautious heating to 60°C – allow to cool before application.

The literature describes a loss of efficacy by adsorption of 5-fluorouracil in the glass infusion container.

Handling and disposal specifications specified for cytostatic agents must be observed.

Unused medicines or waste materials should be disposed of according to national regulations.

7. MARKETING AUTHORISATION HOLDER

EBEWE Pharma Ges.m.b.H. Nfg. KG, 4866 Unterach, Austria

8. MARKETING AUTHORISATION NUMBER

1-22397

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16/02/1998
Date of last renewal: 20/08/2013

10. DATE OF REVISION OF THE TEXT

February 2020

PRESCRIPTION-ONLY/PHARMACY-ONLY
Prescription only. Available in pharmacies only. Repeat dispensing prohibited.