

## Summary of Product Characteristics

### 1 NAME OF THE MEDICINAL PRODUCT

5-Fluorouracil “Ebewe” 50 mg/ml, concentrate for solution for infusion.

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 50 mg 5-Fluorouracil.

For a full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless to slightly yellow, aqueous solution.

### 4 CLINICAL PARTICULARS

#### 4.1 Therapeutic Indications

Palliative treatment, in single as well as in combination therapy, of common carcinomas.

#### 4.2 Posology and method of administration

##### Adults only:

##### Intravenous Infusion:

15 mg/kg or 600mg/m<sup>2</sup> diluted in 300 - 500 ml of glucose injection BP in 0.9% sodium chloride, given over 2-4 hours daily, until side effects occur. Total daily dose should not exceed 1 gram.

##### Initial treatment with weekly application:

15 mg/kg or 600 mg/m<sup>2</sup> once a week slowly i.v.

##### 24 hours long term infusion:

5-7 mg/kg/day or 200 mg/m<sup>2</sup>/day

An interval of 4-6 weeks should be allowed between courses.

##### Maintenance therapy:

An initial intensive course may be followed by maintenance therapy providing there are no significant toxic effects. In all instances, toxic side effects must disappear before maintenance therapy is started.

Therapy consists of 5-15 mg/kg i.v. once weekly

Special Dosage Recommendations:

With:	Dose reduction
<ul style="list-style-type: none"><li>poor nutrition status</li><li>after major surgery</li><li>with myelosuppression: leukocytes &lt; 4000/<math>\mu</math>l, thrombocytes &lt; 100.000/<math>\mu</math>l</li></ul>	30-50%
<ul style="list-style-type: none"><li>gastrointestinal reactions (stomatitis, mucositis, severe diarrhoea, severe vomiting, ulceration, bleeding)</li><li>leukocytes &lt; 3,000/<math>\mu</math>l, platelets &lt; 80,000/<math>\mu</math>l</li><li>neurological side effects (including ataxia and tremor)</li></ul>	Immediate interruption of therapy with 5-Fluorouracil
<ul style="list-style-type: none"><li>severe gastrointestinal</li><li>severe cardiac or</li><li>severe neurological toxicity-reactions</li></ul>	Further therapy is not recommended.
<ul style="list-style-type: none"><li>reduced liver function (biotransformation can be reduced)</li><li>reduced kidney function (elimination can be reduced)</li></ul>	Dependent on organ function an individual dose reduction can be necessary.
In combination with <ul style="list-style-type: none"><li>other cytotoxics, which show a similar profile of side effects</li><li>radiation treatment</li></ul>	Dose reduction according to the expected side-effects.
In elderly patients with age-dependent reduction of kidney function	Individual dose reduction

Children:

5-Fluorouracil is not recommended for use in children.

**Maximum daily dose:** of 1g may not be exceeded.

**Duration of treatment:** will be determined by an experienced oncologist according to nature and clinical course of treatment.

4.3 Contraindications

Hypersensitivity to one of the components of the drug. Use in seriously debilitated patients or in those with severe changes in blood count, bone marrow suppression (especially after radiotherapy), haemorrhage; malabsorption, severe decreased liver and kidney function.

Use in the presence of severe infections, herpes zoster, varicella; stomatitis, ulcerations in the mouth and the gastrointestinal tract, pseudomembraneous enteritis, severe diarrhoea.

Serious debility.  
Plasma bilirubin greater than 85  $\mu$ mol/l.  
Active vaccination should be avoided during 5-FU therapy.

Use in pregnant or breast-feeding women.

Use in the treatment of non-malignant disease.  
(Caution is recommended if extended liver metastases exist due to decreased degradation).

#### 4.4 Special warnings and precautions for use

It is recommended that Fluorouracil be given only by, or under the strict supervision of, a qualified oncologist who is experienced in the use of potent antimetabolites and has the facilities for regular monitoring of clinical, biochemical and haematological effects during and after administration.

All patients should be admitted to hospital for initial treatment.

Adequate treatment with Fluorouracil is usually followed by leucopenia, the lowest white blood cell (W.B.C.) count commonly being observed between the 7th and 14th day of the first course, but occasionally being delayed for as long as 20 days.

The count usually returns to normal by the 30th day. Daily monitoring of platelet and W.B.C. count is recommended and treatment should be stopped if platelets fall below 100,000 per mm<sup>3</sup> or the W.B.C. count falls below 3,500 per mm<sup>3</sup>. If the total count is less than 2000 per mm<sup>3</sup>, and especially if there is granulocytopenia, it is recommended that the patient be treated with appropriate measures to prevent systemic infection.

Treatment should also be stopped at the first sign of oral ulceration or if there is evidence of gastrointestinal side effects such as stomatitis, diarrhoea, bleeding from the G.I. tract or haemorrhage at any site. The ratio between effective and toxic dose is small and therapeutic response is unlikely without some degree of toxicity. Care must be taken therefore, in the selection of patients and adjustment of dosage.

Fluorouracil should be used with caution in patients with reduced renal or liver function or jaundice. Isolated cases of angina, ECG abnormalities and rarely, myocardial infarction have been reported following administration of Fluorouracil. Care should therefore be exercised in treating patients who experience chest pain during courses of treatment, or patients with a history of heart disease.

Fluorouracil has been shown to be carcinogenic in animals. The possibility of a similar effect should be borne in mind when designing the long-term management of the patient.

#### 4.5 Interaction with other medicinal products and other forms of interaction

Therapeutic treatment in combination with Calcium folinate (folinic acid) is described in the literature. In combination with Calcium folinate the side-effects of Fluorouracil may be increased and may cause severe diarrhoea.

In combination with other cytotoxics (Interferons, Cyclophosphamide, Vincristine, Methotrexate, Cisplatin, Doxorubicin) efficacy as well as toxicity of 5-Fluorouracil may be increased.

In combination with other myelosuppressive substances, dosage adjustment is necessary; concomitant or previous radiation therapy may require dosage reduction. The cardiotoxicity of anthracycles may be increased. Aminophenazone, phenylbutazone and sulfonamides should not be administered before and during treatment.

Various agents have been reported to biochemically modulate the antitumour efficacy or toxicity of Fluorouracil. Common drugs include Methotrexate, Metronidazole, folinic acid and Cimetidine which can affect the availability of the active drug.

Chlordiazepoxide, Disulfiram, Griseofulvin and Isoniazid can increase the efficacy of 5-Fluorouracil.

Sulphonamide should not be administered before or during treatment.

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.

Cimetidine may increase the plasma level of 5-fluorouracil.

Metronidazol may increase the plasma level and the toxicity of 5-fluorouracil.

Levamisol may increase the hepatotoxicity of 5-fluorouracil.

Thiazides may increase the bone marrow toxicity of anticancer drugs.

Vinorelbin in combination with 5-fluorouracil /folinic acid may induce serious mucositis.

Allopurinol may reduce the toxicity and efficacy of 5-fluorouracil.

When 5-Fluorouracil and Warfarin are used together there is the possibility of abnormally elevated international normalised ration (INR) readings which would require modification of Warfarin dosage and frequency of INR testing.

## 4.6 Fertility, pregnancy and lactation

In animal studies adverse reactions on the foetus were observed and 5-Fluorouracil is strictly contraindicated during pregnancy and breast feeding. It is recommended to use a non-hormonal contraception, during treatment.

## 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 Undesirable effects

During treatment with 5-Fluorouracil the following side-effects were observed:

### *Infections and infestations:*

*Uncommon* > 0.1% - <1%

Fever

### *Blood and lymphatic system disorders:*

*Very common* > 10%

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

*Common* >1% - < 10%

Agranulocytosis, anaemia and bone marrow depression.

### *Immune system disorders:*

*Uncommon* > 0.1% - < 1%

Allergic reactions

### *Metabolism and nutrition disorders:*

*Very rare* < 0.01%

Patients with low levels of dihydropyrimidine dehydrogenase deficiency (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-Fluorouracil treatment. An initial screening of DPD activity is recommended.

### *Nervous system disorders:*

*Common* > 1% - < 10%

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* > 0.1% - < 1%

Somnolence

*Very rare < 0.01%*

Leukoencephalopathy, which was reversible upon immediate withdrawal, has been reported. Patients with dihydropyrimidine dehydrogenase deficiency may be at increased risk. DWI (Diffusion-Weighted Imaging) may be helpful for the diagnosis of leukoencephalopathy. Brain infarction has been reported during combined chemotherapy (for example: 5-Fluorouracil + mitomycin C or cisplatin).

*Eye disorders:*

*Rare > 0.01% - < 1%*

Myocardial infarction

*Very rare < 0.01%*

Cardiogenic shock

*Vascular disorders:*

*Uncommon > 0.1% - < 1%*

Epistaxis, hypotension, thrombophlebitis

*Gastrointestinal disorders:*

*Very common > 10%*

There may also be mucositis – e.g. stomatitis, oesophagitis, pharyngitis, or proctitis.

*Common > 1% - < 10%*

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

*Uncommon > 0.1% - < 1%*

Gastrointestinal ulceration and bleeding.

*Very rare < 0.01%*

Liver cell damage. Lethal liver necrosis.

*Skin and subcutaneous tissue disorders:*

*Common > 1% - 10%*

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

*Uncommon > 0.1% - < 1%*

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 infusion or protracted continuous infusion therapy with 5-Fluorouracil.

*Musculoskeletal, connective tissue and bone disorders:*

*Uncommon > 0.1% - < 1%*

Nasal bone necrosis

*Renal and urinary disorders:*

*Uncommon > 0.1% - < 1%*

Renal failure

*Reproductive system and breast disorders:*

*Uncommon > 0.1% - < 1%*

Tiredness

*Investigations:*

*Very rare:*

Scattered reports have been related prolonged prothrombin time to coadministration of 5-Fluorouracil and warfarin. Gemcitabine may increase the systemic 5-Fluorouracil exposure.

## 4.9 Overdose

The symptoms and signs of overdosage are qualitatively similar to the adverse reactions and should be managed as indicated under section 4.4, “Special warnings and precautions for use” and section 4.8, “Undesirable effects”.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Fluorouracil is an analogue of uracil, a component of ribonucleic acid. The drug is believed to function as an antimetabolite. After intracellular conversion to the active deoxynucleotide, it interferes with the synthesis of DNA by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase. Fluorouracil may also interfere with RNA synthesis.

### 5.2 Pharmacokinetic properties

After intravenous administration, Fluorouracil is distributed through the body water and disappears from the blood within 3 hours. It is preferentially taken up by actively dividing tissues and tumours after conversion to its nucleotide. Fluorouracil readily enters the C.S.F and brain tissue.

Following IV administration, the plasma elimination half-life averages about 16 minutes and is dose- dependent. Following a single IV dose of Fluorouracil approximately 15% of the dose is excreted unchanged in the urine within 6 hours; over 90% of this is excreted in the first hour. The remainder is mostly metabolised in the liver by the usual body mechanisms for uracil.

### 5.3 Preclinical safety data

Fluorouracil has been shown to be carcinogenic in animals (see section 4.4, Special warnings and precautions for use).

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Water for injections  
Sodium hydroxide

### 6.2 Incompatibilities

5-Fluorouracil is incompatible with Carboplatin, Cisplatin, Cytarabine, Diazepam, Doxorubicin, other Anthracyclines and possibly Methotrexate.

Formulated solutions are alkaline and it is recommended that a mixture with acidic drugs or preparations should be avoided.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

As packaged for sale: 2 years.

Physical and chemical stability of Infusion solutions of 5-Fluorouracil in 5% glucose and in 0.9% sodium chloride with a concentration of 0.35mg/ml and 15.0mg/ml, stored in the refrigerator, at room temperature with light protection and under influence of light, could be demonstrated for 28 days. Microbiological stability was not tested, therefore it is recommended to use Fluorouracil "Ebewe" infusion solutions immediately.

Administered in combination with Calciumfolinat "EBEWE"

A mixture of 1000mg Calciumfolinat "Ebewe" (100ml Calciumfolinat "EBEWE" 10mg/ml) with 5000mg 5-Fluorouracil "Ebewe" (100ml at 50mg/ml) and 40ml physiologic saline solution in infusion pumps (e.g. type "Easy pump") has been stable at room temperature for 48 hours.

**6.4 Special precautions for storage**

Do not store above 25°C.

Do not refrigerate or freeze.

Store the vial in the outer carton to protect from light.

**6.5 Nature and contents of container**

Clear vial made of hydrolytic (type I) glass with a grey bromobutyl rubber stopper, packed singly in a carton: The vial may be packaged in a plastic screwcap Onkosafe container with a transparent cap, contained in the outer carton or the vial may be packaged directly into the outer carton.

5 ml Vial, containing 5 ml of solution

10 ml Vial, containing 10 ml of solution

20 ml Vial, containing 20 ml of solution

100 ml Vial, containing 100 ml of solution

Not all pack sizes may be marketed

**6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product**

Fluorouracil is an irritant, contact with skin and mucous membranes should be avoided.

Diluents

5-Fluorouracil "Ebewe" may be diluted with Glucose or Sodium Chloride Injection or Water for Injections immediately before parenteral use. The remainder of solutions should be discarded after use: do not make up into multidose preparations.

5-Fluorouracil "Ebewe" should only be prepared for administration by professionals who have been trained in the safe use of the preparation. Preparation should only be carried out in a designated area.

Preparation (Guidelines)

1. Pregnant personnel should not handle cytotoxic agents.
2. Refer to local cytotoxic guidelines before commencing.
3. The personnel carrying out these procedures should be adequately protected with appropriate personal protection equipment, including e.g. suitable protective clothing, mask, gloves and eye shields.
4. Appearance of the product after reconstitution is a colourless clear solution.

Administration

For instructions on administration, see section 4.2, Posology and method of administration.

Contamination

**Eye contact:** Irrigate immediately with water and seek medical advice.

**Skin contact:** Wash thoroughly with soap and water and remove contaminated clothing.

**Inhalation, Ingestion:** Seek medical advice.

In the Event of spillage, trained personnel wearing appropriate personal protective equipment, as outlined above, should mop the spilled material with a spill kit or sponge kept in the area for that purpose. Rinse the area with copious amounts of water. Put all solutions and sponges into a designated impervious suitable high risk waste disposal bag and then seal it.

Disposal

Syringes, containers, absorbent materials, solutions and any other contaminated material should be placed in a designated impervious container and incinerated, in accordance with local procedures.

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.

For single use only.

## **7 MARKETING AUTHORISATION HOLDER**

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

## **8 MARKETING AUTHORISATION NUMBER**

PA 789/5/1

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 13 September 2002

Date of last renewal: 12 March 2010

## **10 DATE OF REVISION OF THE TEXT**

July 2011