SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FLURO-5 DEVA 1000 mg/20 ml Solution for IV/IA Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
5-fluorouracil 1000.00 mg
Each 1 ml solution contains 50 mg 5-fluorouracil as drug substance.

Excipient(s):
Sodium hydroxide 280.00 mg (q.s.)
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Vial containing solution for injection.
Colorless, odor-free, clear particle free solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FLURO-5 DEVA may be used for treatment of several types of malignancy particularly breast cancer and the colorectal carcinoma either as a single agent or in combination.

Additionally, efficacy of FLURO-5 DEVA has been reported in patients with the gastric cancer, head and neck cancers and pancreatic carcinoma.

4.2 Posology and method of administration

Posology/frequency and duration 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 FLURO-5 DEVA is to be administered alone or in combination with other therapy. Initial treatment should be given in hospital and the total daily dose should not exceed 1 gram. It is customary to calculate the dose in accordance with patient's actual weight unless there is obesity, edema 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.
Reduction of the dose is advisable in the following events:

- Cachexia
- Major surgery within preceding 30 days
- Reduced bone marrow function
- Impaired hepatic and renal function

The following doses are intended to be guidance.

Colorectal carcinoma
Initial treatment may be in the form of an infusion or an injection, administration as the form of

infusion usually being preferred due to lesser toxicity.

Intravenous infusion:
Daily dose of 15 mg/kg body weight (600 mg/m²), but not more than 1 g per infusion, diluted in 300-500 ml of 5% glucose solution or 0.9% NaCl solution and given by intravenous infusion at a rate of 40 drops per minute over 4 hours. This dose is given on consecutive days until toxicity occurs or a total dose of 12-15 g has been reached. Some patients have received up to 30 g at the maximum rate of 1 g daily. Treatment should be interrupted until hematological and gastrointestinal toxicities resolve.
Alternatively FLURO-5 DEVA may be given as a continuous infusion over 24 hours.

Intravenous injection:
12 mg/kg body weight (480 mg/m²) may be given daily for 3 days by intravenous injection. If there are no signs of toxicity, patient may use 6 mg/kg body weight on days 5, 7 and 9.
Maintenance therapy consists of 5-10 mg/kg (200-400 mg/m²) by injection once weekly.

Breast Cancer
For treatment of breast cancer, FLURO-5 DEVA may be used in combination with methotrexate and Cyclophosphamide or with doxorubicin and Cyclophosphamide.
In this schedule, 10-15 mg/kg (400-600 mg/m²) is administered intravenously on days 1 and 8 of a 28-day therapy course.
FLURO-5 DEVA may also be given by 24-hour continuous infusion; the usual dose is 8.25 mg/kg (300 mg/m²).

Intra-arterial infusion:
5-7.5 mg/kg (200-300 mg/m²) may be given by 24 hour continuous intra-arterial infusion.

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.

Method of administration
FLURO-5 DEVA may be administered by intravenous injection, intravenous or intra-arterial infusion.

Additional information on special populations:

Renal/hepatic impairment:
Dose should be reduced in patients with renal and hepatic dysfunction.

Pediatric population:
FLURO-5 DEVA is not recommended due to safety and efficacy of its use in children is not known.

Geriatric population:
The administered dose of FLURO-5 DEVA in the elderly is similar to adult doses.

4.3 Contraindications
FLURO-5 DEVA is contraindicated in the following conditions:
- In the case of known hypersensitive to 5-fluorouracil and any other ingredients of FLURO-5

DEVA.

- In patients who are suffering from bone marrow depression after radiotherapy or treatment with other antineoplastic agents.
- In pregnant and breast feeding women.
- In the treatment of non-malignant disease.
- It should not be taken/administered with brivudine, sorivudine and its analogues. These medicines are dihydropyrimidine dehydrogenase enzyme inhibitors degrading 5- fluorouracil (see section 4.4)

4.4 Special warnings and precautions for use

- It is recommended that FLURO-5 DEVA be given only by, or under the strict supervision of a qualified physician who is conversant with the use of antimetabolites.
- All patients should be admitted to hospital for initial treatment.
- Adequate treatment with FLURO-5 DEVA is usually followed by leucopenia, the lowest white blood cell 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 leucosis count usually returns to normal by the 30^{th} day. Daily monitoring of platelet and white blood cell count is recommended. If platelets fall below 100.000 mm^3 or white blood cell count falls below 3000 mm^3, the treatment is stopped. If the total count is less than 2000 mm^3, 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 be interrupted at the first sign of stomatitis or oral ulceration, severe diarrhea, gastrointestinal ulceration, gastrointestinal bleeding and hemorrhage at any site. The margin of safety of FLURO-5 DEVA 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 dosage adjustment.
- FLURO-5 DEVA 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 FLURO-5 DEVA. Care should be therefore be exercised in treating patients who experienced chest pain during (or pre-treatment) course of treatment, or patients with a history of heart disease. Treatment should be stopped in case of severe cardiac toxicity.
- It is reported that increased toxicity in patient with reduced activity/deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD). Dihydropyrimidine dehydrogenase enzyme plays significant role in degradation of 5-fluorouracil. The nucleoside analogues such as brivudin and sorivudine can cause a sharp rise in the plasma concentration of 5-fluorouracil with accompanying toxic reactions. For this reason, a period of at least 4 weeks before starting treatment with medicines containing brivudine, sorivudine and analogues should be kept.
- Before starting treatment with 5-fluorpyrimidines, DPD enzyme activities should be checked, if required. In case of accidental administration of brivudine and sorivudine to patients treated with FLURO-5 DEVA, effective measures should be taken to reduce FLURO-5 DEVA toxicity. In such a case, immediate hospitalization is recommended, and any measure to prevent systemic infections and dehydration should be commenced.
- When FLURO-5 DEVA is taken concomitantly with medicines containing phenytoin, regular controls should be made due to possible increase of plasma phenytoin concentration.
- Special care is to be taken in high-risk patients after high-dose pelvic irradiation, after therapy with alkylating agents and in patients after adrenalectomy or hypophysectomy.
- Appropriate contraceptive measures are to be taken in men and women treated with FLURO-5 DEVA up to 3 months after stopping treatment.

This medical product contains 161 mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interactions with other medicinal products and other forms of interaction

- Both the efficacy and toxicity of FLURO-5 DEVA may be increased in combination with other cytotoxic drugs (Cyclophosphamide, Vincristine, methotrexate, cisplatin, doxorubicin) interferon-α or folinic acid.
- It has been reported to biochemically increase the antitumor efficacy or toxicity of FLURO-5 DEVA, medicines include methotrexate, metronidazole, leucovorin as well as allopurinol and cimetidine which can affect the availability of the active medicine.
- Marked elevations of prothrombin time and INR have been reported in some patients treated with initiation of warfarin therapy after FLURO-5 DEVA regimes.
- The enzyme dihydropyrimidine dehydrogenase (DPD) plays an important role in the degradation of fluorouracil. The nucleoside analogues such as brivudine and sorivudine can cause a sharp rise in the plasma concentration of 5-fluorouracil with accompanying toxic reactions. For this reason, a period of at least 4 weeks before starting treatment with medicines containing brivudine, sorivudine and analogues should be kept. Before starting treatment with 5-fluorpyrimidines, DPD enzyme activities should be checked, if required (see section 4.4)
- When FLURO-5 DEVA is taken concomitantly with medicines containing phenytoin, increases in the plasma levels of phenytoin may caused to symptoms of phenytoin intoxication occur (see section 4.4).
- FLURO-5 DEVA should not be used in combination with clozapine due to the increased risk of agranulocytosis.

4.6 Fertility, pregnancy and lactation

General Recommendation
Pregnancy category is D.

Women of child-bearing potential/Contraception
5-fluorouracil has harmful pharmacological effects on pregnancy and/or the fetus/new-born.
FLURO-5 DEVA should not be used during pregnancy unless necessary.

Pregnancy
FLURO-5 DEVA is contraindicated during pregnancy and should not be used due to its harmful effects on fetus.

Breast-feeding
Since it is not known whether FLURO-5 DEVA passes into breast milk, breast-feeding must be discontinued if the mother is treated with FLURO-5 DEVA.
FLURO-5 DEVA must not be used in breast feeding women.

Fertility
Harmful effects of 5-fluorouracil have been shown on fertility in the conducted studies.

4.7 Effects on ability to drive and use machines
Fluorouracil may induce side effects such as nausea and vomiting. It can also produce adverse events of the nervous system and visual changes which could interfere with driving or the usage of heavy machinery.

4.8 Undesirable Effects

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 (cannot be estimated from the available data).

Infections and infestations

Very common : Infection
Uncommon : Sepsis

Blood and lymphatic system disorders

Very common : Leucopenia, myelosuppression, neutropenia, granulocytopenia, pancytopenia, thrombocytopenia, anemia,
Rare : Agranulocytosis

Immune system disorders

Very common : Immunosuppression
Very rare : Anaphylactic reaction, anaphylactic shock

Endocrine disorders

Rare : Increase of T4 (total thyroxin), increase of T3 (total triiodothyronine)

Metabolism and nutrition disorders

Uncommon : Hyperuricemia

Psychiatric disorders

Rare : Confusion

Nervous system disorders

Rare : Ataxia, extrapyramidal motor reactions, cerebellar disturbances, cortical disturbances, nystagmus, headache, vertigo, Parkinson-like symptoms, pyramidal signs, euphoria, leuko-encephalopathy (leukodystrophy), speech disorders, aphasia, convulsion, coma, optic neuritis, peripheral neuropathy

Eye Disorders

Common : Conjunctivitis
Uncommon : Excessive lacrimation, ectropion, strabismus, dacryostenosis, visual changes, blepharitis, reduced vision

Cardiac disorders

Common : Back pain, tachycardia, ECG changes, angina pectoris
Rare : Arrhythmia, myocard infarctions, myocarditis, heart failure, dilated cardiomyopathy, cardiogenic shock, heart arrest, sudden cardiac death

Vascular disorders

Rare : Vasculitis, Raynaud's phenomenon, cerebral ischemia, intestinal ischemia, peripheral ischemia, thromboembolism

Respiratory, thoracic and mediastinal disorders

Uncommon : Epistaxis, dyspnea, bronchospasm

Gastrointestinal disorders
Very common : Diarrhea, nausea, vomiting, mucositis, stomatitis
Uncommon : Gastrointestinal ulceration, gastrointestinal hemorrhage

Hepatobiliary disorders
Uncommon : Liver cellular damage
Rare : Liver necrosis

Skin and subcutaneous tissue disorders
Very common : Alopecia, palmar-plantar erythrodysesthesia
Uncommon : Dermatitis, hyperpigmentation, hypopigmentation, changes of nail (including nail loss), onycholysis, exanthema, dry skin, urticaria, photosensitivity, recall phenomenon

General disorders and administration site conditions
Very common : Fever, fatigue
Uncommon : Thrombophlebitis

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to Turkey Pharmacovigilance Center (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone number: +90 800 314 00 08; fax: +90 312 218 35 99)

4.9 Overdose
Manifestations of overdose of FLURO-5 DEVA are nausea, vomiting, diarrhea, stomatitis, esophago-pharyngitis, gastrointestinal ulceration and bleeding, hemorrhage and bone marrow depression in any site (including thrombocytopenia, leucopoenia and agranulocytosis).
No known specific antidote of FLURO-5 DEVA.
Patients who have been exposed to an overdose of FLURO-5 DEVA should be monitored hematologically for at least 4 weeks and when abnormalities appear, appropriate therapy should be utilized.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antimetabolites (Pyrimidine analogues)
ATC code: L01BC02

5-fluorouracil, an analogue of pyrimidine, is an antineoplastic agent that acts as a uracil antimetabolite. The mechanism of action of 5-fluorouracil has not been fully determined. It inhibits DNA synthesis by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase. It inhibits thymidylate synthetase at least in three different ways. These ways are deoxyribonucleotide, 5-flouro-2-deoxyuridine and 5 phosphate of the drug. In addition, 5-fluorouracil inhibits RNA synthesis by producing a fraudulent RNA and interfering with RNA synthesis.
It also inhibits utilization of uracil in RNA synthesis by blocking uracil phosphatase.

5.2 Pharmacokinetic properties

General properties
Absorption: Following an intravenous administration of 5-fluorouracil, no intact drug can be detected in the plasma after 3 hours.

Distribution: It distributes into tumors, intestinal mucosa, bone marrow, liver and other tissues. It crosses the placenta and cerebrospinal fluid. Distribution studies have shown a higher concentration of 5-fluorouracil and its metabolites in the tumor cell than in surrounding tissue or in corresponding normal tissue. The volume of distribution ranges from 0.1 to 0.4 L/kg.
Plasma protein binding of 5-fluorouracil is 10%. There is a longer persistence of 5-fluorouracil in some tumor cells than in normal tissues due to impaired uracil catabolism.

Biotransformation:
A small portion of fluorouracil is anabolized in the tissues to 5-fluoro-2-deoxyuridine and then to 5-fluoro-2-deoxyuridine-5-monophosphate, the active metabolite of the drug. The major portion of the drug is metabolized in the liver. A portion of metabolites are excreted as respiratory carbon dioxide and other a portion of it is excreted as urea, alpha-fluoro-beta-guanidopropionic acid, and alpha-fluoro-beta-ureidopropionic acid in urine. Following IV administration, approximately 5% of the dose is excreted in urine as unchanged within 6 hours however major portion of it excreted as respiratory carbon dioxide.

Excretion: Following IV administration, the plasma half-life averages 16 minutes. However, half-life is 8 to 20 minutes and is dose dependent.

Linearity/Non-linearity: The average plasma half-life of 5-fluorouracil is dose proportional. Kinetic of FLURO-5 DEVA is linear as IV administrated.

Characteristics in patients
Renal Impairment: Excretion of medicine is reduced in case of renal dysfunction.

5.3 Preclinical safety data
Preclinical information has not been included because the toxicity profile of fluorouracil has been established after many years of clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium hydroxide
Water for injection

6.2 Incompatibilities
5-fluorouracil is incompatible with calcium folinate, carboplatin, cisplatin, cytarabine, diazepam, doxorubicin, droperidol, filgrastim, gallium nitrate, methotrexate, metoclopramide, morphine, ondansetrone, parenteral nutrition, vinorelbine, and other anthracyclines.
As FLURO-5 DEVA is alkaline, it is recommended that admixture with acidic medicines and preparations or unstable substances in the presence of alkali should be avoided.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store at room temperature below 25°C, protected from light. Use immediately after opening.
Do not refrigerate or freeze.
If stored at low temperature (round 5°C) precipitate may form. This precipitate can be re-dissolved by heating to 60°C and shaking. In this case, cool to body temperature prior to use.

FLURO-5 DEVA is for single use after first opening or dilution.

6.5 Nature and contents of container
Type I glass, amber-colored vial with gray bromobutyl rubber stopper, aluminum cap with flip- off top.
Each cardboard box contains a vial containing 20 ml of concentrated solution and patient leaflet.

6.6 Special precautions for disposal and other handling
FLURO-5 DEVA vial should be used only by or under the direct supervision of a qualified physician who is experienced in the use of cancer chemotherapy.

Contamination:
5-fluorouracil is an irritant agent, thus contact with skin and mucous membranes should be avoided. In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline. A bland cream may be used to treat the transient stinging of the skin. Consult a physician to medical advice if the eyes are affected or if the solution is inhaled or ingested.

Preparation guidelines:
FLURO-5 DEVA can be prepared for administration only by professionals who have been trained in the safe use of chemotherapeutic agents. Preparation should only be carried out in a special space. Operations such as preparation of medicine and transfer to syringes should be carried out only under aseptic conditions, in separate dedicated spaces for cytotoxics and the personnel carrying out these procedures should be adequately protected with clothing, gloves, eye shield and mask.
Pregnant personnel are advised not to handle chemotherapeutic agents.

Disposal
Remnants of the medicinal product as well as all materials that have been used for dilution or for infusion and administration must be destroyed according to hospital standard procedures applicable to cytotoxic agents in accordance with local requirements related to the disposal of hazardous waste.

7. MARKETING AUTHORIZATION HOLDER
DEVA Holding A.Ş.
Halkalı Merkez Mah.Basın Ekspres Cad. No: 1
34303 Küçükçekmece-Istanbul/TURKEY

8. MARKETING AUTHORIZATION NUMBER
230/6

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorization: 14.03.2011
Date of last renewal:

10. DATE OF REVISION OF THE TEXT
06.11.2018