SUMMARY OF PRODUCT CHARACTERISTICS

Fluorouracil Teva
Solution for Injection

1. NAME OF THE MEDICINAL PRODUCT

Fluorouracil Teva

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial containing 5 mL of solution for injection contains 250 mg of fluorouracil.
Each vial containing 10 mL of solution for injection contains 500 mg of fluorouracil.
Each vial containing 20 mL of solution for injection contains 1,000 mg of fluorouracil.
Each vial containing 100 mL of solution for injection contains 5,000 mg of fluorouracil.

Excipient with known effect:
8.21 mg/mL (0.36 mmol/mL) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless or almost colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Palliative management of carcinoma of the colon, rectum, breast, stomach and pancreas, in selected patients considered incurable by surgery or other means.
As leucovorin-fluorouracil chemotherapy combination for cancer treatment.

4.2 Posology and method of administration

Note: when using leucovorin (calcium folinate)-fluorouracil chemotherapy combination, strict caution should be exercised not to mix the 2 drugs in the same administration set because of incompatibility (see section 6.2).

Selection of an appropriate dose and treatment regime will depend upon the condition of the patient, the type of carcinoma being treated and whether fluorouracil 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, 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. Reduction of the dose is advisable in patients with any of the following:
1) Cachexia
2) Major surgery within preceding 30 days
3) Reduced bone marrow function
4) Impaired hepatic or renal function

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

Fluorouracil injection should not be mixed directly, in the same container, with other chemotherapeutic agents or intravenous additives.

Fluorouracil is applied alone and in combination with other cytostatic drugs. The fluorouracil dosage depends on the schedule opted for, the use of other cytostatic drugs, the application of radiotherapy and the method of administration. The total daily dosage will usually not exceed 1 gram.

Colorectal tumours:
The initial therapy may be given as intravenous injections or intravenous infusion. The toxicity of fluorouracil is usually higher after injection than after infusion.

As intravenous infusion, 600 mg/m² daily (with a maximum of 1 g each time) in 300–500 ml 5% glucose solution may be given during 4 hours. This dosage is repeated daily until the first side effects occur. Therapy should then be interrupted. After disappearance of the haematological and gastrointestinal side effects, a maintenance therapy is given.
Fluorouracil is also given as a continuous infusion. The dosage and duration of the infusion depends on the schedule chosen, the use of other cytostatic drugs and the application of radiotherapy. In a dosage up to 300 mg/m^2 daily for 30-60 consecutive days, toxicity will rarely occur. In higher dosages, stomatitis will be the dose-limiting side effect. A common dosage is 350 mg/m^2 daily.

As injection, 480 mg/m^2 daily is given intravenously on 3 consecutive days. If toxic side effects do not appear, 240 mg/m^2 is given intravenously on days 5, 7 and 9, followed by a maintenance therapy. The maintenance therapy consists of injections: once a week 200-400 mg/m^2 in intravenous injection.

Breast cancer:
For the treatment of breast cancer fluorouracil is given, for example, in combination with methotrexate and cyclophosphamide or in combination with doxorubicin and cyclophosphamide. The usual fluorouracil dosage in these schedules is 400-600 mg/m^2, intravenously administered on days 1 and 8, in a 28-day cycle.
In some schedules fluorouracil is administered as a continuous infusion. A common dosage is 350 mg/m^2/day.

Other types of administration:
Fluorouracil is applied as an intra-arterial 24-hour slow infusion in a dosage of 200–300 mg/m^2 daily.
Fluorouracil is also used as a continuous infusion. The dosage and duration of the infusion depends on the regimen chosen, the use of other cytostatic drugs and the application of radiotherapy. A common dosage is 350 mg/m^2/day.
When fluorouracil solution for injection is used for continuous infusion, the fact that the solution for injection has not been preserved should be taken into account.

Dosage adjustment:
The fluorouracil dose should be adjusted in accordance with the schedule below if leukocytes or thrombocytes are reduced on the first day of therapy; the lowest value determines the height of the dose.

% of dose	Leukocytes	Thrombocytes
100	> 3,500	> 125,000
50	2,500-3,500	75,000-125,000
0	< 2,500	< 75,000

If the number of leukocytes is 2,500-3,500/mm^3 and/or the number of thrombocytes 75,000-125,000/mm^3, it is better not to administer cytostatic drugs for one week. When the blood count has been restored the course may be continued; if not, dose reduction may be carried out.
The administration of fluorouracil should be discontinued if a bilirubin plasma concentration over 85 micromol/L is reached. If the patient has undergone major surgery within 30 days prior to administration, the recommended dosage should be reduced by a third to a half from the very beginning.

Children
No recommendations are made regarding the use of fluorouracil in children.

Elderly
Fluorouracil should be used in the elderly with similar considerations as in younger adult dosages, notwithstanding that incidence of concomitant medical illness is higher in the former group.

4.3 Contraindications

Fluorouracil should not be used in:
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Bone marrow suppression (myelosuppression)
- Marked changes in blood counts
- Severely impaired liver function
- Acute infections
- Patients in poor general health
- Patients with a known complete dihydropyrimidine dehydrogenase (DPD) deficiency (see section 4.4)
- During breast-feeding (see section 4.6)
- Recent or concomitant treatment with brivudine (see sections 4.4 and 4.5 on drug interactions)

Active vaccinations should not be performed in temporal association with fluorouracil therapy. Contact with individuals who received a polio vaccine should be avoided.

4.4 Special warnings and precautions for use

Precautions to be taken when handling and using fluorouracil
Because of the potentially mutagenic and carcinogenic effects, increased safety regulations apply to nursing staff and physicians. When handling fluorouracil, any contact with the skin and mucous membranes should be avoided. The preparation must be carried out by means of an absolutely aseptic procedure. The use of a vertical laminar airflow workbench (LAF) is recommended. Protective clothing should be worn when handling fluorouracil. Pregnant personnel should not handle fluorouracil.

Cardiotoxicity
Therapy with fluoropyrimidines has been associated with cardiotoxicity, including myocardial infarction, angina pectoris, arrhythmia, myocarditis, cardiogenic shock, sudden death, stress cardiomyopathy (Takotsubo syndrome) and changes in the ECG (including, very rarely, prolongation of the QT interval). These adverse events are more common in patients who receive a continuous infusion of fluorouracil than in the recipients of a bolus injection. A history of coronary artery disease may be a risk factor for some cardiac side effects. Caution should therefore be exercised in the treatment of patients who experienced chest pain during treatment cycles, and in patients with known heart disease. During the treatment with fluorouracil, heart function should be monitored regularly. In the case of severe cardiotoxicity, therapy should be discontinued.

Encephalopathy
Cases of encephalopathy (including hyperammonemic encephalopathy, leukoencephalopathy, posterior reversible encephalopathy syndrome [PRES] and Wernicke encephalopathy) associated with fluorouracil therapy were reported during post-marketing surveillance. Signs and symptoms of encephalopathy include mental state changes, confusion, disorientation, coma and ataxia. If any of these symptoms occur, treatment should be discontinued immediately, and serum ammonia and vitamin B1 levels should be determined. In case of elevated serum ammonia levels or vitamin B1 deficiency, appropriate treatment should be initiated.

Hyperammonemic encephalopathy often occurs concurrently with lactic acidosis.
Caution should be exercised when administering fluorouracil to patients with impaired renal and/or hepatic function. Patients with impaired renal and/or hepatic function may be at increased risk for hyperammonemia and hyperammonemic encephalopathy.

Tumor lysis syndrome
During post-marketing surveillance, there have been reports of cases of tumor lysis syndrome associated with fluorouracil therapy. Patients at increased risk of tumor lysis syndrome (e.g., patients with renal impairment, hyperuricemia, high tumor burden, rapid disease progression) should be closely monitored. Preventive measures (e.g., hydration, correction of high uric acid levels) should be considered.

Dihydropyrimidine dehydrogenase (DPD) deficiency
DPD activity is rate-limiting in the catabolism of fluorouracil (see section 5.2). Patients with DPD deficiency are therefore at increased risk of fluoropyrimidine-related toxicity, including, for example, stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity.
DPD-deficiency-related toxicity usually occurs during the first cycle of treatment or after dose increase.

Complete DPD deficiency
Complete DPD deficiency is rare (0.01-0.5% of Caucasians). Patients with complete DPD deficiency are at high risk of life-threatening or fatal toxicity and must not be treated with Fluorouracil Teva (see section 4.3).

Partial DPD deficiency
Partial DPD deficiency is estimated to affect 3-9% of the Caucasian population. Patients with partial DPD deficiency are at increased risk of severe and potentially life-threatening toxicity. A reduced starting dose should be considered to limit this toxicity. DPD deficiency should be considered as a parameter to be taken into account in conjunction with other routine measures for dose reduction. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring.

Testing for DPD deficiency
Phenotype and/or genotype testing prior to the initiation of treatment with Fluorouracil Teva is recommended despite uncertainties regarding optimal pre-treatment testing methodologies. Consideration should be given to applicable clinical guidelines.
Impaired renal function may lead to increased blood uracil levels; hence, patients with moderate or severe renal impairment are at increased risk of being misdiagnosed with a DPD deficiency.

Genotypic characterisation of DPD deficiency
Pre-treatment testing for rare mutations of the DPYD gene can identify patients with DPD deficiency. The four DPYD variants, c.1905+1G>A [also known as DPYD*2A], c.1679T>G [DPYD*13], c.2846A>T and c.1236G>A/HapB3, can cause complete absence or reduction of DPD enzymatic activity. Other rare variants may also be associated with an increased risk of severe or life-threatening toxicity.
Certain homozygous and compound heterozygous mutations in the DPYD gene locus (e.g., combinations of the four variants with at least one allele of c.1905+1G>A or c.1679T>G) are known to cause complete or near complete absence of DPD enzymatic activity.
Patients with certain heterozygous DPYD variants (including c.1905+1G>A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variants) have increased risk of severe toxicity when treated with fluoropyrimidines.
The frequency of the heterozygous c.1905+1G>A genotype in the DPYD gene in Caucasian patients is around 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.

Data on the frequency of the four DPYD variants in other populations than Caucasian are limited. At the present, the four DPYD variants (c.1905+1G>A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3) are considered virtually absent in populations of African (-American) or Asian origin.

Phenotypic characterisation of DPD deficiency
For phenotypic characterisation of DPD deficiency, the measurement of pre-therapeutic blood levels of the endogenous DPD substrate uracil (U) in plasma is recommended.
Elevated pre-treatment uracil concentrations are associated with an increased risk of toxicity. Despite uncertainties on uracil thresholds defining complete and partial DPD deficiency, a blood uracil level ≥ 16 ng/ml and < 150 ng/ml should be considered indicative of partial DPD deficiency and associated with an increased risk for fluoropyrimidine toxicity. A blood uracil level ≥ 150 ng/ml should be considered indicative of complete DPD deficiency and associated with a risk for life-threatening or fatal fluoropyrimidine toxicity. Caution is required when interpreting blood uracil levels in patients with impaired renal function (see "Testing for DPD deficiency" above).

Fluorouracil therapeutic drug monitoring (TDM)
TDM of fluorouracil may improve clinical outcomes in patients receiving continuous fluorouracil infusions by reducing toxicities and improving efficacy. AUC is supposed to be between 20 and 30mg x h/L.

Other notes
Brivudine should not be used together with fluorouracil. Deaths due to this drug interaction have been reported. After the end of treatment with brivudine and before the start of therapy with fluorouracil, an interval of at least 4 weeks is required. Brivudine treatment may be initiated 24 hours after the last dose of fluorouracil (see sections 4.3 and 4.5).

In the case of an accidental administration of brivudine to patients treated with fluorouracil, effective measures must be taken to reduce the toxicity of fluorouracil. Immediate hospitalization is recommended. All measures should be taken to prevent systemic infections and dehydration.

Patients taking phenytoin concomitantly with fluorouracil should be regularly evaluated for a possible increase in phenytoin plasma levels.

Damage to the intestinal wall requires symptomatic treatment commensurate with the severity, e.g., fluid replacement. Mild diarrhea may respond to antidiarrheal agents. In moderate to severe diarrhea, however, such agents do not suffice.

Before and during therapy with fluorouracil, the following follow-up examinations are recommended:
- Daily inspection of the oral cavity and pharynx for mucosal changes
- Blood count including the differential count and platelet count, before each fluorouracil administration
- Kidney parameters
- Liver function tests (LFTs)

When co-administering fluorouracil and oral anticoagulants, the prothrombin time (Quick test) should be monitored closely.

Patients should be specifically alerted to the possibility of experiencing stomatitis/mucositis, diarrhea and bleeding (especially from the gastrointestinal tract). Patients should be instructed to consult their attending physician as soon as they have the first symptoms.

Patients should also be alerted to the possibility of experiencing hair loss, which is usually reversible, and skin changes (see also section 4.8).

Pediatric population
There is insufficient experience on the efficacy and safety of fluorouracil in children.

Sodium
This drug contains 8.21 mg (0.36 mmol) sodium per mL, equivalent to 0.41% of the WHO recommended maximum daily dietary intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Brivudine: A clinically significant interaction between brivudine and fluoropyrimidines (e.g., capecitabine, fluorouracil, tegafur) was reported, which is based on an inhibition of dihydropyrimidine dehydrogenase by brivudine. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. For this reason, brivudine should not be co-administered with fluorouracil (see sections 4.3 and 4.4). After the end of therapy with brivudine, at least 4 weeks must pass before therapy with fluorouracil may be initiated. Therapy with brivudine may be initiated 24 hours after the last dose of fluorouracil.

Any treatment measure that worsens the patient's general condition or interferes with bone marrow function (e.g., other cytotoxic agents) may increase the toxicity of fluorouracil. Fluorouracil may increase the cutaneous toxicity of radiation therapy.

Calcium folinate enhances the action of fluorouracil. Serious, including sometimes lethal, diarrhea may occur as a clinical consequence of this interaction.
An accumulation of such deaths has been reported particularly in the case of the administration regimen of a single weekly I.V. bolus injection of 600 mg/m² body surface area of fluorouracil in combination with calcium folinate.

Concomitant administration of phenytoin and fluorouracil has been reported to increase the plasma levels of phenytoin, which resulted in symptoms of phenytoin intoxication (see section 4.4).

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

In female patients who received a thiazide diuretic in addition to cyclophosphamide, methotrexate and fluorouracil, the granulocyte count decreased more than after the same cytostatic cycles not containing thiazide.

In isolated cases, a drop in Quick-type PT was observed in patients treated with warfarin who also received fluorouracil alone or in combination with levamisole.

When treated with fluorouracil and levamisole, hepatotoxic effects (elevated serum levels of alkaline phosphatase, transaminases or bilirubin) are frequently observed.

Female patients with breast cancer who received combination treatment with cyclophosphamide, methotrexate, fluorouracil and tamoxifen displayed an increased risk of developing thromboembolic events.

Co-administration of vinorelbine with fluorouracil/folinic acid may cause severe mucositis leading to death.

The detection methods for bilirubin and 5-hydroxyindoleacetic acid in the urine may reveal elevated or false-positive values.

General comments:
Cytostatic agents may reduce antibody production after influenza vaccination.
Cytostatic agents may increase the risk of infection after the administration of live vaccines.

4.6 Fertility, pregnancy and breast-feeding

Contraception in men and women
Due to the genotoxic potential of fluorouracil (see section 5.3), women of childbearing potential should use effective contraception during therapy with fluorouracil and for up to 6 months after the end of treatment.
Men are advised to use effective contraception and not to father a child during therapy with fluorouracil and up to 3 months after the end of treatment.

Pregnancy
There are no adequate and well-controlled studies in pregnant women; however, fetal defects and miscarriages have been reported.

Women of childbearing potential should be advised to avoid pregnancy and to use effective contraception during and up to 6 months after the conclusion of treatment with fluorouracil.

If this drug is used during pregnancy, or if the woman becomes pregnant whilst on therapy with this drug, she should be fully informed of the potential hazard to the fetus, and advised to undergo genetic counseling.
Fluorouracil should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

Breast-feeding
Women should not breast-feed during treatment.

Fertility
Fluorouracil may have mutagenic effects. Therefore, men treated with fluorouracil are advised not to father a child during treatment and up to 3 months thereafter.

4.7 Effects on ability to drive and use machines

Fluorouracil may indirectly affect the ability to drive or use machines by causing nausea and vomiting. Therefore, during treatment with fluorouracil, driving a car and using machines should be avoided.

4.8 Undesirable effects

The most common and significant side effects of fluorouracil are bone marrow toxicity and gastrointestinal symptoms.

The frequency of adverse reactions is defined using the following convention:

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*
not known	*Frequency cannot be estimated from available data*

Infections and infestations

Very common:	Infections.
Common:	Immunosuppression with an increased infection rate.
Rare:	Sepsis.

Blood and lymphatic system disorders

Common:	Myelosuppression, neutropenia, thrombocytopenia and anemia, febrile neutropenia.
Rare:	Agranulocytosis, pancytopenia.

Myelosuppression is common and is one of the dose-limiting adverse events (see sections 4.2 and 4.4). Mild to extremely severe cases of neutropenia and thrombocytopenia, as well as agranulocytosis, anemia and pancytopenia have all been reported.
The degree of myelosuppression (NCI grades 1 to 4) depends on the method of administration (I.V. bolus injection or continuous intravenous infusion) and the dosage regimen.
Neutropenia occurs after each course of treatment as an I.V. bolus injections in adequate doses (nadir: 9^{th} to 14^{th} [to 20^{th}] day of treatment; normal values usually achieved after the 30^{th} day).

Immune system disorders

Rare:	Generalized allergic reactions including anaphylactic shock.

Endocrine disorders

Not known:	Increases in serum levels of total thyroxine (T4) and total triiodothyronine (T3), with no increase in free T4 and TSH, and no clinical signs of hyperthyroidism.

Metabolism and nutrition disorders

Common:	Hyperuricemia.
Not known:	Lactic acidosis, tumor lysis syndrome, hypertriglyceridemia, vitamin B1 deficiency.

Nervous system disorders

Rare:	Nystagmus, headache, dizziness, Parkinson's symptoms, pyramidal signs and euphoria. Peripheral neuropathy (in combination regimens with radiation therapy).
Very rare:	Dysgeusia. (Leuko-)encephalopathy with symptoms such as ataxia, speech disorders, confusion, disorientation, muscle weakness, aphasia, seizures or coma.
Not known:	Hyperammonemic encephalopathy, posterior reversible encephalopathy syndrome (PRES), Wernicke encephalopathy.

Eye disorders

Rare:	Excessive flow of tears, blurred vision, disorders of ocular motility, optic neuritis, diplopia, loss of vision, photophobia, conjunctivitis, blepharitis, scar-related ectropion, and tear-duct fibrosis.

Cardiac disorders

Common:	Ischemic changes in ECG.
Uncommon:	Chest pain resembling angina pectoris.
Rare:	Arrhythmias, myocardial infarction, myocarditis, heart failure, dilated cardiomyopathy and cardiogenic shock.
Very rare:	Cardiac arrest and sudden cardiac death.
Not known:	Pericarditis, stress cardiomyopathy (Takotsubo syndrome).

Cardiotoxic side effects usually occur during or a few hours after the first administration cycle.

Patients with pre-existing coronary artery disease or cardiomyopathy are at an increased risk of developing cardiotoxic side effects.

Vascular disorders

Rare:	The occurrence of thrombophlebitis has been reported.
Not known:	Cerebral, intestinal and peripheral ischemia, Raynaud's syndrome and thromboembolism.

Respiratory, thoracic and mediastinal disorders

Common:	Bronchospasm, epistaxis.

Gastrointestinal disorders

Common:	Mucositis (stomatitis, esophagitis, proctitis), watery diarrhea, nausea and vomiting.
Rare:	Dehydration as well as ulcers and bleeding in the gastrointestinal tract.
Not known:	Pneumatosis intestinalis, enterocolitis, colitis (including necrotizing colitis).

Gastrointestinal side effects are common and may be life-threatening.
Mucositis (stomatitis, esophagitis, proctitis), watery diarrhea, nausea and vomiting (ranging from mild to severe), and a calculous cholecystitis have been reported (see also section 4.4). The severity (NCI grades 1 through 4) of gastrointestinal adverse effects depends on the dosage regimen and method of administration. In administration by continuous intravenous infusion, stomatitis rather than myelosuppression is the dose-limiting factor.

As long as inflammations, ulcers or diarrhea persist, the use of fluorouracil should be avoided.

Hepatobiliary disorders

Rarely, liver cell damage and, in isolated cases, liver necrosis were observed, some of which were lethal.

Skin and subcutaneous tissue disorders

The so-called "hand-foot syndrome" with dysesthesia as well as redness, swelling, pain and peeling of the skin on the palms and soles occurs more frequently after administration as a continuous I.V. infusion than after I.V. bolus injections.

Common:	Alopecia (usually reversible).
Rare:	Exanthema, dry skin with fissures, dermatitis, urticaria, photosensitivity, hyperpigmentation of the skin and streaky hyperpigmentation or pigment loss along the vein course. Nail changes (e.g., diffuse superficial bluish pigmentation, hyperpigmentation, nail dystrophy, pain and thickening of the nail bed, paronychia) and onycholysis.
Not known:	Cutaneous lupus erythematosus (CLE).

General disorders and administration site conditions

Common:	Delayed wound healing, exhaustion, general weakness, fatigue and listlessness.
Not known:	Local reaction due to extravasation (pain, swelling, erythema).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il.

4.9 Overdose

Symptoms of intoxication
As a result of an overdose, the following side effects usually occur more frequently:
Nausea, vomiting, diarrhea, severe mucosal inflammation, ulcers and bleeding in the gastrointestinal tract, bone marrow suppression (thrombocytopenia, leukocytopenia, agranulocytosis).

Handling intoxication
In the case of intoxication, the administration of fluorouracil should be discontinued immediately. Symptomatic treatment should be initiated. Treatment of a marked myelosuppression should be administered on an inpatient basis. It may consist of the substitution of missing blood components, and antibiotic treatment. The transfer of the patient into a germ-free room may become necessary.
Follow-ups of blood counts should be performed up to 4 weeks after the overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, antimetabolites, ATC code: L01BC02.

Fluorouracil fluorinated pyrimidine derivative, itself without antineoplastic effects. The inhibition of cell division occurs after metabolism by the active metabolites 5-fluorouridine triphosphate (FUTP) and 5-fluorodeoxyuridine monophosphate (FdUMP).

Known mechanisms of action:
- Blockage of DNA synthesis (inhibition of thymidilate synthetase by FdUMP).
- Inhibition of RNA synthesis (formation of a defective RNA by incorporation of FUTP).
- DNA strand breaks after incorporation of fluorodeoxyuridine triphosphate (phosphorylated FdUMP) into the DNA.

The inhibitory effects are particularly evident in cells that grow rapidly and thus absorb fluorouracil to a greater extent.

5.2 Pharmacokinetic properties

Half-life
After intravenous administration of fluorouracil (5-FU), the (monophasic) elimination half-life is 10–20 minutes and is dose-dependent; a biphasic half-life of 8 and 40 minutes has been reported. Three hours after administration, 5-FU plasma levels are no longer measurable.

Distribution
The distribution corresponds to the total body fluid.
Fluorouracil crosses the blood-cerebrospinal fluid barrier.

Biotransformation
Approximately 85% of the administered dose is metabolized. Active metabolites are the intracellularly formed 5-fluorouridine triphosphate (FUTP) and 5-fluorodeoxyuridine monophosphate (FdUMP). In addition to the active metabolites, 5-FU is mainly metabolized in the liver to inactive metabolites (major metabolites: 5-fluorouridine, 5-fluorodeoxyuridine) and catabolized to uracil. Carbon dioxide, urea and other metabolites are also produced.

Elimination
15% of the administered amount is excreted unchanged within 6 hours by the kidneys, of which about 90% within the first hour.

Fluorouracil is further catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD) to the much less toxic 5,6-dihydro-fluorouracil (FUH2). The enzyme dihydropyrimidinase cleaves the pyrimidine ring to 5-fluoro-ureido-propionic acid (FUPA). Finally, β-ureido-propionase splits FUPA to α-fluoro-β-alanine (FBAL), which is excreted in the urine. The activity of dihydropyrimidine dehydrogenase (DPD) is rate-limiting. DPD deficiency may increase the toxicity of fluorouracil (see sections 4.3 and 4.4).

5.3 Preclinical safety data

Acute toxicity
See section 4.9 Overdose.

Chronic toxicity
Fluorouracil has a preferential effect on proliferating cells, which is why bone marrow depression and damage to the mucous membrane of the gastrointestinal tract are the principal consequences.

Mutagenic and carcinogenic potential
Fluorouracil has been shown to be mutagenic in several *in vitro* and *in vivo* mutagenicity tests. There is a suspicion of a mutagenic effect in humans.
Animal experiments with fluorouracil have not provided any indications of a carcinogenic effect. However, fluorouracil belongs to a substance class that promises tumorigenic effects.

Reproductive toxicity
Fertility and teratogenicity studies in various animal species have suggested an embryotoxic and teratogenic potential, as well as impaired fertility and reproductive behavior.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide
Hydrochloric acid or Sodium hydroxide for pH adjustment
Water for injections

6.2 Incompatibilities

Fluorouracil should only be diluted with normal saline or a 5% glucose solution.

Fluorouracil should not be mixed with other substances in the same I.V. injection or infusion, as a precipitate may form.

Incompatibilities with the following substances have been reported:
Cisplatin, cytarabine, doxorubicin, calcium folinate, methotrexate, vinorelbine, diazepam, droperidol, filgrastim, gallium nitrate, metoclopramide, morphine, ondansetron, parenteral nutrition solutions.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Shelf life after first opening of the container and after preparation of the ready-to-use solution for infusion:

Once a dose is taken from the vial with a chemo-mini-spike, the shelf life will not exceed 72 hours at room temperature (no higher than 25°C) and protected from light, unless pricking or diluting took place under controlled and validated aseptic conditions.
Before use, the solution may be diluted with 0.9% sodium chloride solution or 5% glucose solution, if necessary.
After dilution of Fluorouracil Teva solution for injection in 5% glucose solution or in 0.9% sodium chloride solution, a chemical and physical shelf life was established of a minimum of 48 hours at room temperature (no higher than 25°C).
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. Dilution should take place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Keep out of the reach and sight of children!

Fluorouracil Teva solution for injection should be stored in the original package, in order to protect from light and at a temperature of 15°C–25°C. If stored as indicated, this medicinal product can be used until the date stated on the package.
Do not store in refrigerator or freezer. If a precipitate is formed as a result of exposure to low temperatures, this precipitate should be completely dissolved again before use, by heating up the injection vial to 60°C with vigorous shaking. Before use, the solution should be cooled off to body temperature.

Use only clear solutions.

For storage conditions of the diluted medicinal product after first opening of the container and after preparation of the ready-to-use solution for infusion, see section 6.3.

6.5 Nature and contents of container

1 vial containing 250 mg/5 mL solution for injection
1 vial containing 500 mg/10 mL solution for injection
1 vial containing 1,000 mg/20 mL solution for injection
1 vial containing 5,000 mg/100 mL solution for injection

Packs of 1 vial.
Not all package sizes may be marketed.

6.6 Special precautions for disposal and other instructions for handling

Disposal regulations for cytostatic agents must be observed!

7. LICENCE HOLDER AND MANUFACTURER

Teva Israel Ltd.,
124 Dvora HaNevi'a St., Tel Aviv 6944020, Israel.

8. REGISTRATION NUMBER

035.69.25702

The leaflet was revised in February 2025.