תאריך: פברואר 2020

רופא/ה, רוקח/ת נכבד/ה

חברת טבע מודיעה על העדכונים הבאים בעלון לרופא של התכשיר:

Fluorouracil Teva

50 mg/ml, solution for injection

פלואורואורציל טבע, 50 מ"ג/מ"ל, תמיסה להזרקה

Contains: fluorouracil 50 mg/ml

עדכונים בעלון לרופא

<u>התוויה כפי שאושרה בתעודת הרישום:</u>

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.

<u>ברצוננו להודיע שהעלון לרופא עודכן, בפירוט שלהלן כלולים העדכונים העיקריים בלבד (תוספות מסומנות באדום והסרות מידע כטקסט מחוק):</u>

4.3 Contraindications

Fluorouracil should not be used in the case of:
- 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 known complete absence of dihydropyrimidine dehydrogenase (DPD) activity (see Section 4.4)
- During Pregnancy and breast-feeding (see Section 4.6)
- Recent or concomitant treatment with brivudine (see Sections 4.4 and 4.5 on drug interactions)

In patients with dihydropyrimidine dehydrogenase (DPD) deficiency, the commonly used fluorouracil doses cause increased side effects. If severe adverse effects occur, control of DPD activity may be indicated. Patients with a DPD deficiency should not be treated with fluorouracil.

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

[...]
Cardiotoxicity
Treatment with fluoropyrimidines was associated with cardiotoxicity, including myocardial infarction, angina, arrhythmias, myocarditis, cardiogenic shock, sudden death, and ECG changes (including, in very rare cases, 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 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
During post-marketing surveillance, cases of fluorouracil treatment-related encephalopathy (including hyperammonemic encephalopathy and leukoencephalopathy) were reported. 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 levels should be determined. If serum ammonia levels are elevated, ammonia-lowering treatment should be initiated.
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.

Dihydropyrimidine dehydrogenase (DPD) deficiency
A rare, unexpected and severe toxicity associated with the use of 5-FU, manifesting as stomatitis, diarrhea, mucositis, neutropenia and neurotoxicity, was explained with impaired DPD activity. Patients with a low or no DPD activity (an enzyme involved in the degradation of fluorouracil) are at increased risk for serious, life-threatening or fatal side effects caused by fluorouracil. Although a DPD deficiency cannot be clearly defined, it is known that patients with certain homozygous or certain complex heterozygous mutations in the DPYD locus (e.g. DPYD*2A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3 variants), which may result in a complete or nearly complete absence of enzymatic DPD activity (as determined in laboratory experiments), are at greatest risk for life-threatening or fatal adverse events and should not be treated with fluorouracil (see Section 4.3). There is no proven dosage that is safe for patients with a complete absence of DPD activity.

Patients with certain heterozygous DPYD variants (including DPYD*2A, c.1679T> G, c.2846A> T and c.1236G>A/HapB3 variants) were at increased risk for severe toxicities when treated with fluorouracil.
The frequency of heterozygous DPYD*2A genotypes in the DPYD gene in Caucasian patients is about 1%, 1.1% for c.2846A>T, 2.6% to 6.3% for c.1236G>A/HapB3 variants, and 0.07% to 0.1% for c.1679T>G. Genotyping for these alleles is recommended to identify patients at increased risk for

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 may also be associated with an increased risk of severe toxicities.
Special care must be exercised in patients with partial DPD deficiency (such as those with heterozygous mutations in the DPYD locus), where the benefit of fluorouracil outweighs the risk, taking into account the suitability of an alternative non-fluoropyrimidine chemotherapy regimen. Regular follow-up with dose adjustment according to toxicity must be performed. In these patients, a reduced initial dose should be considered to avoid severe toxicity. There is not enough 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 resulted in a greater reduction in enzymatic activity than the other variants, which was associated with a higher risk of side effects. The effects of a reduced dose on efficacy are currently uncertain. Therefore, if there are no severe toxicities, the dose could be increased while the patient is being monitored carefully. Patients who tested negative for the allele mentioned above may still be at high risk for serious adverse events.
Patients with an undiagnosed DPD deficiency, who are treated with fluorouracil, as well as patients who tested negative for specific DPYD variants, may experience life-threatening toxicities that clinically manifest as an acute overdose (see Section 4.9). In case of acute toxicity grade 2 – 4, therapy should be discontinued immediately. A permanent discontinuation should be considered based on the clinical assessment of the onset, duration and severity of the observed toxicity.

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 cytostatic 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.

[...]

4.7 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

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 I.V. bolus injections in adequate doses (nadir: 9th to 14th [to 20th] day of treatment; normal values usually achieved after the 30th day).
[...]

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.

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.

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.

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.

General disorders and administration site conditions

Common: Delayed wound healing, fatigue, general weakness, fatigue and listlessness.

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.