***תאריך: פברואר 2022***

**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**

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**<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:

- ~~Patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity (see section 4.4)~~
- Patients with a known complete absence of dihydropyrimidine dehydrogenase (DPD) deficiency activity (see section 4.4)

[…]

## 4.4 Special warnings and precautions for use

***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 fluoropyrimidines-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.

*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 is 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.

*Fluorouracil Therapeutic drug monitoring (TDM)*

TDM of fluorouracil may improve clinical outcomes in patients receiving continuous 5-fluorouracil infusions by reducing toxicities and improving efficacy. AUC is supposed to be between 20 and 30mg x h/L.

[...]