SANDOZ A Novartis Division

מאי 2022

רופא/ה רוקח/ת נכבד/ה,

חברת נוברטיס ישראל בע"מ מבקשת להודיעכם על עדכון העלון של התכשיר:

שם תכשיר	מספר רישום
Fluorouracil "EBEWE" 50 MG/ML	130-30-30866-00

מרכיב פעיל: FLUOROURACIL

התוויות רשומות:

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.

בהודעה זו מצויינים רק הסעיפים בהם בוצעו שינויים מהותיים בלבד בעלון לרופא .

4.2 Posology and method of administration

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

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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 a known complete ~~absence of~~ dihydropyrimidine dehydrogenase (DPD) ~~activity~~ deficiency (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~~

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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 “EBEWE” 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 lifethreatening 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.

~~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.~~

6.2 Incompatibilities

Fluorouracil should only be diluted with ~~physiological~~ 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.

~~Fluorouracil must not be diluted with strongly buffered solutions with pH <8, since fluorouracil precipitates in this environment. Do not mix with other chemotherapeutic solutions.~~

Incompatibilities with following substances have been reported:

~~Folinic acid, carboplatin,~~ C~~c~~isplatin, cytarabine, ~~diazepam~~, doxorubicin, calcium folinate, methotrexate, vinorelbine, diazepam, droperidol, filgrastim, gallium nitrate, metoclopramide, morphine, ondansetron, parenteral nutrition solutions.~~droperidol, filgrastim, gallium nitrate, leucovorin, methotrexate, metoclopramide, morphine, ondansetron, parenteral nutrition solutions, vinorelbine and other anthracyclines.~~

~~Calcium folinate~~

~~Fluorouracil must not be mixed in the same infusion with calcium folinate because a precipitate may form. Fluorouracil 50 mg/ml with calcium folinate 20 mg/ml, with or without dextrose 5% in water, has been shown to be incompatible when mixed in different amounts and stored at 4° C, 23° C or 32° C in polyvinyl chloride containers.~~

~~5-Fluorouracil Ebewe solution for injection/infusion must not be mixed with other medicinal products, including oxaliplatin or irinotecan.~~

6.4 Special precautions for storage

Store below 25ºC. Do not refrigerate or freeze.

~~Store in the original packaging in order to protect the content from light.~~

מלבד השינויים המפורטים מעלה, קיימים בעלון עדכונים נוספים.

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות:

https://israeldrugs.health.gov.il/#!/byDrug

כמו כן ניתן לקבל את העלון המודפס על ידי פניה לבעל הרישום – נוברטיס ישראל בע"מ.

לעדכונכם בברכה,

מגר' דפנה סנדובסקי,

רוקחת ממונה חטיבת סנדוז,

נוברטיס ישראל בע"מ