SANDOZ A Novartis Division

ספטמבר 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

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**<u>התוויות רשומות:</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.

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

**4.3 Contraindications**

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- During ~~Pregnancy and~~ breast-feeding (see Section 4.6)

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**4.4 Special warnings and precautions for use**

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*Cardiotoxicity*

Treatment with fluoropyrimidines ~~was~~ has been associated with cardiotoxicity, including myocardial infarction, angina pectoris, arrhythmias, myocarditis, cardiogenic shock, sudden death, stress cardiomyopathy (Takotsubo syndrome) 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 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*

During post-marketing surveillance, there have been reports of cases of ~~fluorouracil treatment-related~~ encephalopathy (including hyperammonemic encephalopathy~~and~~, leukoencephalopathy and posterior reversible encephalopathy syndrome [PRES]) associated with 5-fluorouracil treatment. ~~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.

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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.

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## 4.6 Fertility, pregnancy and breast-feeding

*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.
5-fluorouracil should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.
~~Fluorouracil may have mutagenic effects and should not be used during pregnancy. Women of childbearing potential should use effective contraception during chemotherapy and up to 6 months thereafter. If pregnancy occurs during treatment, the possibility of genetic counseling should be used.~~
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*Fertility*

Fluorouracil may have mutagenic effects. Therefore, men treated with fluorouracil are advised not to father a child during treatment and up to 3 ~~6~~ months thereafter.

## 4.8 Undesirable effects

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*Metabolism and nutrition disorders*

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| Common: | Hyperuricemia. |
| Not known: | Lactic acidosis, tumor lysis syndrome. |

*Nervous system disorders*

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| 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). |

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*Cardiac disorders*

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| Common: | Ischemic changes in ECG. Uncommon: Chest pain resembling angina pectoris. |
| Rare: | Arrhythmias, myocardial infarction, myocarditis, heart failure, dilated cardiomyopathy and cardiogenic shock. |

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| Very rare: | Cardiac arrest and sudden cardiac death. |
| Not known: | Pericarditis, stress cardiomyopathy (Takotsubo syndrome). |

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*Gastrointestinal disorders*

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| 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. |

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*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.

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| 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.<br>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). |

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