תאריך: דצמבר 2019

רופא/ה, רוקח/ת נכבד/ה

חברת טבע מודיעה על העדכונים הבאים בעלון לרופא של התכשיר:

ETOPOSIDE, concentrate for solution for infusion

אטופוסיד, תמיסה מרוכזת להכנת תמיסה לעירוי

Contains: Etoposide 20 mg/ml

עדכונים בעלון לרופא

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

- Hodgkin's disease.
- Malignant (non-Hodgkin's) Lymphomas, especially of the Histiocytic variety.
- Acute Non-Lymphocytic leukemia.
- Management of refractory testicular tumors and of small cell lung cancer.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Concomitant use of yellow fever vaccine or other live vaccines is contraindicated in immunosuppressed patients (see section 4.5).
Lactation (see section 4.6)
~~Severe myelosuppression, unless when this is caused by the underlying disease.~~
~~Severe hepatic impairment.~~

4.4 Special warnings and precautions for use

[...]
Impaired renal function
In patients with moderate (CrCl =15 to 50 mL/min), or severe (CrCl <15ml/min) renal impairment undergoing haemodialysis, etoposide should be administered at a reduced dose (see section 4.2).

Haematological parameters should be measured and dose adjustments in subsequent cycles considered based on haematological toxicity and clinical effect in moderate and severe renal impaired patients.

Tumour lysis syndrome
Tumour lysis syndrome (sometimes fatal) has been reported following the use of etoposide in association with other chemotherapeutic drugs. Close monitoring of patients is needed to detect early signs of tumour lysis syndrome, especially in patients with risk factors such as bulky treatment-sensitive tumours, and renal insufficiency. Appropriate preventive measures should also be considered in patients at risk of this complication of therapy.
[...]

~~***The occurrence of leukopenia with a leucocyte count below 2,000/mm^3 is an indication to withhold further therapy until the blood counts have sufficiently recovered (usually after 10 days).***~~
~~***The administration of etoposide should be terminated at the occurrence of thrombocytopenia.***~~

~~***Great care should be taken on giving etoposide to patients who have, or have been exposed to infection with herpes zoster.***~~
~~***Peripheral blood counts and liver function should be monitored.***~~

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other drugs on the pharmacokinetics of etoposide
Concomitant phenytoin therapy is associated with increased etoposide clearance and reduced efficacy, and other enzyme-inducing antiepileptic therapy may be associated with increased etoposide clearance and reduced efficacy.
[...]

Effect of etoposide on the pharmacokinetics of other drugs
Co-administration of antiepileptic drugs and etoposide can lead to decreased seizure control due to pharmacokinetic interactions between the drugs.
[...]

4.6 Fertility, pregnancy and lactation

[...]
Pregnancy
There are no or limited amount of data from the use of etoposide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). In general etoposide can cause fetal harm when administered to pregnant women. Etoposide should not be used during pregnancy unless the clinical condition of the woman requires treatment with etoposide. Women of childbearing potential should be advised to avoid becoming pregnant. Women of childbearing potential have to use effective contraception during and up to 6 months after treatment. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be informed of the potential hazard to the fetus.

Breastfeeding
Etoposide is ~~It is not known whether these drugs are~~ excreted in human milk. There is~~Because many drugs are excreted in human milk and because of the~~ a potential for serious adverse reactions in nursing infants from etoposide. A decision must ~~should~~ be made whether to discontinue breast-feeding or to discontinue etoposide, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman (see section 4.3).
[...]

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Etoposide may cause adverse reactions that affect the ability to drive or use machines such as fatigue, somnolence, nausea, vomiting, cortical blindness, hypersensitivity reactions with hypotension. Patients who experience such adverse reactions should be advised to avoid driving or using machines.

4.8 Undesirable effects

[...]

Tabulated summary of adverse reactions

The following frequencies have been used:The following adverse reactions were reported from etoposide clinical studies and post-marketing experience. These adverse reactions are presented by system organ class and frequency, which is defined by the following Verycategories: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse Reaction (MedDRA Terms)
Nervous system disorders	~~Very common~~ common	~~neurotoxicities (e.g., somnolence, fatigue)~~ dizziness
	uncommon	neuropathy peripheral
	rare	Transient cortical blindness transient, neurotoxicities (*e.g.*, somnolence and fatigue), optic neuritis, seizure
Vascular disorders	common	~~Hemorrhage,~~hypertension, transient systolic hypotension following rapid intravenous administration
	uncommon	haemorrhage
Respiratory, thoracic and mediastinal disorders	~~uncommon~~ rare	~~Bronchospasm, coughing, laryngospasm~~ interstitial pneumonitis, pulmonary fibrosis~~, apnoea~~
	not known	bronchospasm
Hepatobiliary disorders	very common	alanine aminotransferase increased, alkaline phosphatase increased, aspartate amino transferase increased, bilirubin increased, hepatotoxicity
General disorders and administration site conditions	very common	asthenia, malaise
	common	extravasation, phlebitis~~, fatigue~~
	rare	pyrexia

[...]

Description of selected adverse reactions

Haematological Toxicity

Leucopenia and severe leucopenia (less than 1,000 cells/mm^3) were observed in ~~60~~ 91% and ~~7~~ 17%, respectively, for etoposide. Thrombocytopenia and severe thrombocytopenia (less than 50,000 platelets/mm^3) were seen in ~~28 41~~ 23% and ~~4 20~~ 9%, respectively, for etoposide. Reports of fever and infection were also very common in patients with neutropenia treated with etoposide. Bleeding has been reported.

[...]

Hypersensitivity
Anaphylactic reactions (see section 4.4), manifested by chills, tachycardia, bronchospasm, dyspnoea, diaphoresis, pyrexia, pruritus, hypertension or hypotension, syncope, nausea, and vomiting have been reported to occur in 3 % (7 of 245 patients treated with etoposide in 7 clinical studies) of patients treated with etoposide.

Acute fatal reactions associated with bronchospasm have also been reported with etoposide. Apnoea with spontaneous resumption of breathing following cessation of infusion have also been reported.
[...]

Paediatric population
The safety profile between paediatric patients and adults is expected to be similar.

4.9 Overdose

Total doses of 2.4 g/m^2 to 3.5 g/m^2 administered intravenously over three days have resulted in severe mucositis and myelotoxicity.
[...]

A specific antidote is not available. Treatment should therefore be symptomatic and supportive, and patients should be closely monitored. Etoposide and its metabolites are not dialyzable.
[...]

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר האינטרנט של משרד הבריאות
http://www.health.gov.il, וניתן לקבלו מודפס ע"י פניה לחברת טבע.