תאריך: נובמבר 2019

רופא/ה, רוקח/ת נכבד/ה

חברת טבע מודיעה על העדכונים הבאים בעלון לרופא של התכשיר

אוקסליפלטין טבע, תרכיז להכנת תמיסה לאינפוזיה

Oxaliplatin Teva, concentrate for solution for infusion

Contains: Oxaliplatin 5 mg/ml

עדכונים בעלון לרופא

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

Oxaliplatin in combination with 5- fluorouracil (5-FU) and folinic acid (FA) is indicated for:

Adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of the primary tumor.

Treatment of metastatic colorectal cancer.

Oxaliplatin in combination with leucovorin, irinotecan and 5-fluorouracil is indicated for the first-line treatment of patients with metastatic pancreatic adenocarcinoma (based on NCCNguidelines, version 2.2014).

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

<u>Posology</u>

The recommended dose for oxaliplatin in treatment of metastatic colorectal cancer is 85 mg/m^2 intravenously, repeated every 2 weeks until disease progression or unacceptable toxicity.

The recommended dose of oxaliplatin for the treatment of metastatic pancreatic adenocarcinoma is 85 mg/m^2 given as a 2-hour intravenous infusion, immediately followed

by leucovorin (400 mg/m^2, 2-hour intravenous infusion) with the addition after 30 minutes of irinotecan (180 mg/m^2, 90-minute intravenous infusion through a Y-connector) and immediately followed by 5-fluorouracil (400 mg/m^2 intravenous bolus followed by 2,400 mg/m^2 continuous intravenous infusion for 46 hours), in 2-week cycles up to 6 months.
Dosage given should be adjusted according to tolerability (see section 4.4).

Special Population

- *Renal impairment*

Oxaliplatin must not be administered in patients with severe renal impairment (see sections 4.3 and 5.2). In patients with mild to moderate renal impairment, the recommended dose of oxaliplatin is 85 mg/m^2 (see sections 4.3 and 5.2).~~Oxaliplatin has not been studied in patients with severe renal impairment (see section 4.3).~~

4.4 Special warnings and special precautions for use

Renal impairment
Patients with mild to moderate renal impairment should be closely monitored for adverse reactions and the dose adjusted according to toxicity (see section 5.2).
Haemolytic-uraemic syndrome (HUS) is a life-threatening side effect (see section 4.8). Oxaliplatin should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may be not reversible with discontinuation of therapy and dialysis may be required.
~~Due to limited information on safety in patient with moderately impaired renal function, administration should only be considered after suitable appraisal of the benefit/risk for the patient. In this situation, renal function should be closely monitored and dose adjusted according to toxicity.~~

….

Nausea~~.~~, Vomiting, diarrhoea, ~~and~~ dehydration and haematological changes
Gastrointestinal toxicity, which manifests as nausea and vomiting, warrants prophylactic and/or therapeutic anti-emetic therapy (see section 4.8).
Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrh~~o~~ea/emesis particularly when combining oxaliplatin with 5-fluorouracil ~~(5-FU)~~.
Cases of intestinal ischaemia, including fatal outcomes, have been reported with oxaliplatin treatment. In case of intestinal ischaemia, oxaliplatin treatment should be discontinued and appropriate measures initiated (see section 4.8).
Oxaliplatin treatment can cause duodenal ulcer (DU) and potential complications, such as duodenal ulcer haemorrhage and perforation, which can be fatal. In case of duodenal ulcer, oxaliplatin treatment should be discontinued and appropriate measures taken (see section 4.8).

Do not use oxaliplatin intraperitoneally. Peritoneal hemorrhage may occur when oxaliplatin is administered by intraperitoneal route (off-label route of administration).
If haematological toxicity occurs (neutrophils $< 1.5 \times 10^9$/l or platelets $< 50 \times 10^9$/l), administration of the next course of therapy should be postponed until haematological values return to acceptable levels. A full blood count with white cell differential should be performed prior to start of therapy and before each subsequent course.
Sepsis, neutropenic sepsis and septic shock have been reported in patients treated with oxaliplatin, including fatal outcomes (see section 4.8). If any of these events occurs, Oxaliplatin Teva should be discontinued.
Disseminated intravascular coagulation (DIC), including fatal outcomes, has been reported in association with oxaliplatin treatment. If DIC is present, oxaliplatin treatment should be discontinued and appropriate treatment should be administered (see section 4.8).
Patients must be adequately informed of the risk of diarrhoea/emesis, mucositis/stomatitis and neutropenia after oxaliplatin and 5-fluorouracil ~~(5-FU)~~ administration so ~~that~~ they can urgently contact their treating physician for appropriate management.
If mucositis/stomatitis occurs with or without neutropenia, the next treatment should be delayed until recovery from mucositis/stomatitis to grade 1 or less and/or until the neutrophil count is $\geq 1.5 \times 10^9$/l.
For ~~If~~ oxaliplatin ~~is~~ combined with 5-fluorouracil (with or without folinic acid ~~(FA)~~), the usual dose adjustments for 5-fluorouracil ~~(5-FU)~~ associated toxicities should apply.
If ~~WHO~~ grade 4 diarrhoea, grade 3-4 neutropenia (neutrophils $< 1.0 \times 10^9$/l), febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count $< 1.0 \times 10^9$/l, a single temperature of > 38.3°C or a sustained temperature of > 38°C for more than one hour), or grade 3-4 thrombocytopenia (platelets $< 50 \times 10^9$/l) occur, Oxaliplatin Teva must be discontinued until improvement or resolution, and the dose of Oxaliplatin Teva should be reduced by 25% at subsequent cycles~~from 85 mg/m^2 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting)~~, in addition to any ~~5-fluorouracil (~~5-FU~~)~~ dose reductions required.

……

Cardiac
QT prolongation may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes, which can be fatal (see section 4.8). Caution should be exercised in patients with a history or a predisposition for prolongation of QT, those who are taking medicinal products known to prolong QT interval, and those with electrolyte disturbances such as hypokalemia, hypocalcaemia, or hypomagnesaemia. In case of QT prolongation, oxaliplatin treatment should be discontinued (see sections 4.5 and 4.8).

Musculoskeletal and connective tissue
Rhabdomyolysis has been reported in patients treated with oxaliplatin, including fatal outcomes. In case of muscle pain and swelling, in combination with weakness, fever or darkened urine, oxaliplatin treatment should be discontinued. If rhabdomyolysis is confirmed, appropriate measures should be taken. Caution is recommended if medicinal products

associated with rhabdomyolysis are administered concomitantly with oxaliplatin (see sections 4.5 and 4.8).

Combined therapy of oxaliplatin with leucovorin, irinotecan and 5-fluorouracil (FOLFIRINOX)

Risk of neutropenia: Patients treated with FOLFIRINOX may receive prophylactic G-CSF, as per American Society of Clinical Oncology (ASCO) guidelines and/or current institutional guidelines, to reduce the risk or manage neutropenia complications (febrile neutropenia, prolonged neutropenia or neutropenic infection). Primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features (e.g., age>65 years, poor nutritional status, or other serious comorbidities) that predispose them to increased complications from prolonged neutropenia. The use of G-CSF has been shown to limit the incidence and severity of neutropenia.

When using oxaliplatin in combination with leucovorin, irinotecan and 5-fluorouracil, beyond the information contained in the leaflet of oxaliplatin, the information in the leaflets of each of the other drugs as part of combination therapy should also be checked.

4.5 Interactions with other medicinal products and other forms of interaction

….

Caution is advised when oxaliplatin treatment is co-administered with other medicinal products known to cause QT interval prolongation. In case of combination with such medicinal products, the QT interval should be closely monitored (see section 4.4).

Caution is advised when oxaliplatin treatment is administered concomitantly with other medicinal products known to be associated with rhabdomyolysis (see section 4.4).

4.6 Pregnancy and lactation

In animal studies, reproductive toxicity was observed. Consequently, oxaliplatin is not recommended during pregnancy and in women of childbearing potential not using contraceptive measures. ~~Based on the results of animal studies and the pharmacological action of the compound, the use of oxaliplatin during pregnancy is advised against, in particular during the first trimester.~~

The use of oxaliplatin ~~therapy~~ should only be considered after suitably appraising the patient of the risk to the foetus and with the patient's consent.

…

4.8 Undesirable effects

MedDRA Organ System Classes	Very Common	Common	Uncommon	Rare	~~Very rare[1]/ Unknown[2]~~
Investigations	– Hepatic enzyme~~s~~ increase~~,~~ – Blood alkaline phosphatase increase~~,~~ – Blood bilirubin increase~~,~~ – Blood lactate dehydrogenase ~~(LDH)~~ increase~~,~~ – Weight increase (adjuvant setting)	– Increased Blood creatinine increase ~~level,~~ – Weight decrease (metastatic setting)			
Blood and lymphatic system disorders*	– Anaemia – Neutropenia~~,~~ – Thrombocytopenia~~,~~ – Leukopenia~~,~~ – Lymphopenia	– Febrile neutropenia		– Immunoallergic thrombocytopenia – Haemolytic anaemia	~~Hemolytic uremic syndrome[2]**~~
Nervous system disorders*	– Peripheral sensory neuropathy~~,~~ – Sensory disturbance~~,~~ – Dysgeusia~~,~~ – Headache	– Dizziness~~,~~ – Motor neuritis~~,~~ – Meningism		– Dysarthria~~,~~ – Reversible Posterior Leukoencephalopathy syndrome (RPLS, or – PRES)** (see section 4.4)~~***~~	~~Convulsion[2]**~~
Eye disorders		– Conjunctivitis~~,~~ – Visual disturbance		– Transiently reduced Visual acuity reduced transiently~~,~~ – Visual field disturbances~~,~~ – Optic neuritis – Transient vision loss, reversible following therapy discontinuation	

MedDRA Organ System Classes	Very Common	Common	Uncommon	Rare	~~Very rare[1] / Unknown[2]~~
Ear and labyrinth disorders			- Ototoxicity	- Deafness	
Respiratory, thoracic and mediastinal disorders	- Dyspnoea~~,~~ - Cough~~ing,~~ - Epistaxis	- Hiccups~~,~~ ~~chest pain,~~ - Pulmonary embolism		- Interstitial lung disease~~,~~ sometimes fatal~~,~~ - Pulmonary fibrosis***~~*~~	
Gastrointestinal disorders*	- Diarrhoea, Nausea~~,~~ - Diarrhoea - Vomiting~~,~~ - Stomatitis/ Mucositis~~,~~ - Abdominal pain~~,~~ - Constipation~~.~~	- Dyspepsia~~,~~ - Gastro-esophageal reflux~~,~~ - Gastrointestinal haemorrhage~~,~~ - Rectal haemorrhage	- Ileus~~,~~ - Intestinal obstruction	- Colitis including *Clostridium difficile* diarrh~~o~~ea~~,~~ - Pancreatitis	
Renal and urinary disorders		- Haematuria~~,~~ - Dysuria~~, abnormal~~ - Micturition frequency abnormal			~~Acute tubular necrosis, acute interstitial nephritis and acute renal failure[1]~~
Skin and subcutaneous tissue disorders	- Skin disorder - Alopecia	- Skin exfoliation (i.e. Hand & Foot syndrome) - Rash erythematous - Rash - Hyperhidrosis - Nail disorder			
Musculoskeletal and connective tissue disorders	- Back pain	- Arthralgia - Bone pain			

MedDRA Organ System Classes	Very Common	Common	Uncommon	Rare	~~Very rare[1]/ Unknown[2]~~
Metabolism and nutrition disorders	- Anorexia~~,~~ ~~glycaemic abnormalities~~ - Hyperglycemia - Hypokalaemia~~,~~ ~~natraemia abnormalities~~ - Hypernatraemia	- Dehydration - Hypocalcemia	- Metabolic acidosis		
Infections and infestations*	- Infection	- Rhinitis~~,~~ - Upper respiratory tract infection~~,~~ - Neutropenic sepsis, including fatal outcomes	- Sepsis, including fatal outcomes		
Vascular disorders		- Haemorrhage ~~NOS (Not Otherwise Specified),~~ - Flushing~~,~~ - Deep vein thrombosis~~,~~ - Hypertension		- Disseminated intravascular coagulation (DIC), including fatal outcomes (see section 4.4)	
~~**Hepato-biliary disorders**~~					~~Liver sinusoidal obstruction syndrome[+] *~~
General disorders and administration site conditions	- Fatigue - Fever[++]~~, fatigue,~~ - Asthenia~~,~~ - Pain~~,~~ - Injection site reaction[+++]				
Immune system disorders*	- Allergy/allergic reaction[+]				
Psychiatric disorders		- Depression~~,~~ - Insomnia	- Nervousness		

....
Post-marketing experience with frequency unknown
• intestinal ischaemia, including fatal outcomes (see section 4.4).
• duodenal ulcer, and complications, such as duodenal ulcer haemorrhage or perforation, which can be fatal (see section 4.4).
..

Renal and urinary disorders
Very rare (<1/10,000):
Acute tubular necrosis, acute interstitial nephritis and acute renal failure.

Cardiac disorders
Post-marketing experience with frequency unknown
QT prolongation, which may lead to ventricular arrhythmias including Torsade de Pointes, which may be fatal (see section 4.4).

Respiratory, thoracic and mediastinal disorders
Post-marketing experience with frequency unknown
Laryngospasm

Musculoskeletal and connective tissue disorders
Post-marketing experience with frequency unknown
Rhabdomyolysis, including fatal outcomes (see section 4.4).

Combined therapy of oxaliplatin with leucovorin, irinotecan and 5-fluorouracil (FOLFIRINOX) - Grade 3 and 4 adverse reactions:
- *Blood and lymph system disorders*
Very common: Neutropenia (45.7%)
Common: Thrombocytopenia (9.1%), Anemia (7.8%), Febrile neutropenia (5.4%)

- *Vascular disorders*
Common: Thromboembolism (6.6%)

- *Metabolic and nutritional disorders*
Very common: Fatigue (23.6%)

- *Gastrointestinal disorders*
Very common: Vomiting (14.5%), Diarrhea (12.7%)

- *Nervous system disorders*
Common: Sensory neuropathy (9%)

- *Hepatobiliary disorders*
Common: Increased ALAT (7.3%)

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