יולי 2019

רופא/ה, רוקח/ת נכבד/ה,

הנדון: <u>Oxaliplatin medac 50 mg - אוקסליפלטין מדאק 50 מ"ג</u>
<u>Oxaliplatin medac 100 mg - אוקסליפלטין מדאק 100 מ"ג</u>
<u>Oxaliplatin medac 150 mg - אוקסליפלטין מדאק 150 מ"ג</u>

<u>מרכיב פעיל</u>:

Oxaliplatin medac 50 mg: 50 mg Oxaliplatin
Oxaliplatin medac 100 mg: 100 mg Oxaliplatin
Oxaliplatin medac 150 mg: 150 mg Oxaliplatin

<u>צורת מינון</u>:

Powder For Solution For Infusion

<u>התוויות מאושרות</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 primary tumor.

•Treatment of metastatic colorectal cancer.

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

חברת צמל ביו-פארמה בע"מ מבקשת להודיעכם על העדכונים הבאים בעלון לרופא של התכשיר.

בעקבות אימוץ כלשונו של עלון תכשיר המקור Eloxatin עודכן סעיף ההתוויות וסעיף המינון אופן המתן של התכשיר ונוספו החמרות. ההחמרה מסומנת באמצעות <u>קו תחתי</u>, שמשמעותו היא תוספת מידע הקשור להחמרה.

4.1 Therapeutic indications

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 primary tumour
• 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 NCCN guidelines, version 2.2014).

4.2 Posology and method of administration

Posology

FOR ADULTS ONLY

The recommended dose for oxaliplatin in adjuvant setting is 85 mg/m^2 intravenously, repeated every two weeks for 12 cycles (6 months).

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).

Oxaliplatin should always be administered before fluoropyrimidines – i.e. 5-fluorouracil.

Oxaliplatin is administered as a 2- to 6-hour intravenous infusion in 250 to 500 ml of 5% glucose solution to give a concentration between 0.2 mg/ml and 0.7 mg/ml; 0.70 mg/ml is the highest concentration in clinical practice for an oxaliplatin dose of 85 mg/m^2.

Oxaliplatin was mainly used in combination with continuous infusion 5-fluorouracil based regimens. For the two-weekly treatment schedule 5-fluorouracil regimens combining bolus and continuous infusion were used.

Oxaliplatin in combination with leucovorin, irinotecan and 5-fluorouracil should only be administered to patients less than 76 years-old, with ECOG performance status (Eastern Cooperative Oncology Group) 0-1, who have no cardiac ischemia, and normal or nearly normal level of bilirubin.

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).

- Hepatic insufficiency:

In a phase I study including patients with several levels of hepatic impairment, frequency and severity of hepato-biliary disorders appeared to be related to progressive disease and impaired liver function tests at baseline. No specific dose adjustment for patients with abnormal liver function tests was performed during clinical development.

- Elderly subjects:

No increase in severe toxicities was observed when oxaliplatin was used as a single agent or in combination with 5-fluorouracil in patients over the age of 65. In consequence, no specific dose adaption is required for elderly patients.

- Paediatric patients:

There is no relevant indication for use of oxaliplatin in children. The effectiveness of oxaliplatin single agent in the paediatric populations with solid tumors has not been established (see section 5.1).

Method of administration

Oxaliplatin is administered by intravenous infusion.

The administration of oxaliplatin does not require hyperhydration.

Oxaliplatin diluted in 250 to 500 ml of 5% glucose solution to give a concentration not less than 0.2 mg/ml must be infused via a central venous line or a peripheral vein over 2 to 6 hours. Oxaliplatin infusion must always precede the administration of 5-fluorouracil.

In the event of extravasation, administration must be discontinued immediately.

Instructions for use

Oxaliplatin must be diluted before use. Only 5% glucose diluent is to be used to dilute the concentrate for solution for infusion product. (see section 6.6).

החמרות בעלון לרופא:

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.

Nausea, vomiting, diarrhoea, dehydration and haematological changes
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).
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 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).

If grade 4 diarrhoea, grade 3-4 neutropenia (neutrophils < 1.0x109/l), febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count < 1.0x109/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 < 50x109/l) occur, Oxaliplatin must be discontinued until improvement or resolution, and the dose of Oxaliplatin should be reduced by 25% at subsequent cycles, in addition to any 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 Interaction 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).

4.8 Undesirable effects

Metabolism and nutrition disorders

Common – Hypocalcemia

Infections and infestations*
Common …including fatal outcomes
Uncommon- Sepsis, including fatal outcomes

Post-marketing experience with frequency unknown
Infections and infestations
Septic shock, including fatal outcomes.

Gastrointestinal disorders….
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).

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 המאושר נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלו מודפס על ידי פנייה לבעל הרישום, צמל ביו-פארמה בע"מ, טלפון: 073-7151111.

בברכה,

צמל ביו-פארמה בע"מ