תאריך: מאי 2020

רופא/ה, רוקח/ת נכבד/ה

חברת טבע מודיעה על העדכונים הבאים בעלון לרופא של התכשיר:

Carboplatin Teva, concentrate for solution for infusion

קרבופלטין טבע, תמיסה מרוכזת להכנת תמיסה לעירוי

Contains: Carboplatin 10 mg/ml

עדכונים בעלון לרופא

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

- Advanced ovarian carcinoma in initial treatment and secondary treatment.
- Metastatic small cell carcinoma of the lung.

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

4.3 Contraindications

[...]

- Concomitant use with yellow fever vaccine (see section 4.5).

4.4 Special warnings and precautions for use

Hematologic Toxicity

Leukopenia, neutropenia, and thrombocytopenia are dose-dependent and dose-limiting. Peripheral blood counts should be monitored during carboplatin treatment frequently and, in case of toxicity, until recovery is achieved. Median day of nadir is day 21 in patients receiving single agent carboplatin and day 15 in patients receiving carboplatin in combination with other chemotherapeutic agents. In general, single intermittent courses of carboplatin should not be repeated until leukocyte, neutrophil, and platelet counts have returned to normal.

Therapy should not be repeated until 4 weeks after the previous carboplatin course and/or until the neutrophil count is at least 2,000 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3.

Anemia is frequent and cumulative requiring very rarely a transfusion.

Hemolytic anemia with the presence of serologic drug-induced antibodies has been reported in patients treated with carboplatin. This event can be fatal.

Severity of myelosuppression is increased in patients with prior treatment (in particular with cisplatin) and/or impaired kidney function. Initial carboplatin dosages in these groups of patients should be appropriately reduced (see section 4.2) and the effects carefully monitored through frequent blood counts between courses.
Carboplatin combination therapy with other myelosuppressive forms of treatment must be planned very carefully with respect to dosages and timing in order to minimise additive effects.

Myelosuppressive effects may be additive to those of concomitant chemotherapy. Patient with severe and persistent myelosuppression are at high risk of infectious complications including fatal outcomes (see section 4.8). If any of these events occurs, carboplatin dosing should be interrupted and dose modification or discontinuation should be considered.

Acute promyelocytic leukaemia and myelodysplastic syndrome (MDS)/ acute myeloid leukemia (AML) have been reported years after therapy with carboplatin and other antineoplastic treatments.

Haemolytic-uraemic syndrome (HUS)
Haemolytic-uraemic syndrome (HUS) is a life-threatening side effect. Carboplatin should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopaenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

Allergic Reactions
As with other platinum-based drugs, allergic reactions appearing most often during perfusion may occur and necessitate discontinuation of the perfusion and an appropriate symptomatic treatment. Cross reactions, sometimes fatal, have been reported with all the platinum compounds (see section 4.3 and section 4.8).

Neurologic Toxicity
Although peripheral neurologic toxicity is generally common and mild, limited to paresthesia and decrease of osteotendinous reflexes, its frequency is increased in patients older than 65 years and/or in patients previously treated with cisplatin. Monitoring and neurological examinations should be carried out at regular intervals.
Visual disturbances, including loss of vision, have been reported after the use of carboplatin in doses higher than those recommended in patients with renal impairment. Vision appears to recover totally or to a significant extent within weeks of stopping these high doses.

Geriatric Use
In studies involving combination therapy with carboplatin and cyclophosphamide, elderly patients treated with carboplatin were more likely to develop severe thrombocytopenia than younger patients. Because renal function is often decreased in the elderly, renal function should be considered when determining dosage (see section 4.2).

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
Cases of Reversible Posterior Leukoencephalopathy Syndrome (RPLS) have been reported in patients receiving carboplatin in combination chemotherapy. RPLS is a rare, reversible after

treatment discontinuation, rapidly evolving neurological condition, which can include seizure, hypertension, headache, confusion, blindness, and other visual and neurological disturbances (see section 4.8). Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI (Magnetic Resonance Imaging).

Other
Auditory defects have been reported during carboplatin therapy. Ototoxicity may be more pronounced in children. Cases of hearing loss with a delayed onset have been reported in paediatric patients. A long-term audiometric follow-up in this population is recommended.

Venoocclusive liver disease
Cases of hepatic venoocclusive disease (sinusoidal obstruction syndrome) have been reported, some of which were fatal. Patients should be monitored for signs and symptoms of abnormal liver function or portal hypertension which do not obviously result from liver metastases.

Tumour lysis syndrome (TLS)
In post marketing experience tumour lysis syndrome (TLS) has been reported in patients following the use of carboplatin alone or in combination with other chemotherapeutic agents.
Patient at high risk of TLS, such as patients with high proliferative rate, high tumor burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken.

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including carboplatin, may result in serious or fatal infections.
Vaccination with a live vaccine should be avoided in patients receiving carboplatin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

[...]

4.5 Interaction with other medicinal products and other forms of interaction
Due to the increase of thrombotic risk in case of tumoral diseases, the use of anticoagulative treatment is frequent. The high intra-individual variability of the coagulability during diseases, and the eventuality of interaction between oral anticoagulants and anticancer chemotherapy, require, if it is decided to treat the patient with oral anticoagulants, to increase frequency of the control of the INR monitoring.

Concomitant use contraindicated
- Yellow fever vaccine: risk of generalised vaccinal disease mortal (see section 4.3).

Concomitant use not recommended
- Live attenuated vaccines (except yellow fever): risk of systemic, possible fatal disease. This risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where this exist (poliomyelitis).
- Phenytoin, fosphenytoin: Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by the cytotoxic drug or risk of toxicity enhancement or lose of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin.

[...]

Concomitant use to take into consideration

- Cyclosporin (and by extrapolation tacrolimus and sirolimus): Excessive immunosuppression with risk of lymphoproliferation.

[...]

4.6 Fertility, pregnancy and lactation

Fertility

Gonadal suppression resulting in amenorrhea or azospermia may occur in patients receiving antineoplastic therapy. These effects appear to be related to dose and length of therapy and may be irreversible. Prediction of the degree of testicular or ovarian function impairment is complicated by the common use of combinations of several antineoplastics, which makes it difficult to assess the effects of individual agents.

[...]

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. However,

Carboplatin may cause nausea, vomiting, vision abnormalities and ototoxicity, therefore patients should be warned on the potential effect of these events on the ability to drive or to use machines.

4.8 Undesirable effects

The frequency of adverse reactions reported is based on a cumulative database of 1,893 patients receiving single agent carboplatin and post-marketing experience.

The list is presented by system organ class, MedDRA preferred term, and frequency using the following frequency categories: very common (≥1/10), common (≥1/100 to < 1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data).

System Organ Class	Frequency	MedDRA Term
Infections and infestations	Common	Infections*
	Not known	Pneumonia
Neoplasms, benign, malignant and unspecified (incl. cysts and polyps)	Not known	Treatment related secondary malignancy
Blood and lymphatic system disorders	Very common	Thrombocytopenia, neutropenia, leukopenia, anaemia
	Common	Haemorrhage*
	Not known	Bone marrow failure, febrile neutropenia, haemolytic-uraemic syndrome
Immune system disorders	Common	Hypersensitivity, anaphylactoid type reaction
Metabolism and nutrition disorders	Not known	Dehydration, anorexia, hyponatraemia, tumor lysis syndrome
Nervous system disorders	Common	Neuropathy peripheral, paraesthesia, decrease of osteotendinous reflexes, sensory disturbance, dysgeusia

	Not known	Cerebrovascular accident*, Reversible Posterior Leukoencephalopathy Syndrome (RPLS)#
Eye disorders	Common	Visual disturbance, Rare cases of loss of vision
Ear and labyrinth disorders	Common	Ototoxicity
Cardiac disorders	Common	Cardiovascular disorder*
	Not known	Cardiac failure*
Vascular disorders	Not known	Embolism*, hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	Common	Respiratory disorder, interstitial lung disease, bronchospasm
Gastrointestinal disorders	Very common	Vomiting, nausea, abdominal pain
	Common	Diarrhoea, constipation, mucous membrane disorder
	Not known	Stomatitis, pancreatitis#
Skin and subcutaneous tissue disorders	Common	Alopecia, skin disorder
	Not known	Urticaria, rash, erythema, pruritus
Musculoskeletal and connective tissue disorders	Common	Musculoskeletal disorder
Renal and urinary disorders	Common	Urogenital disorder
General disorders and administration site conditions	Common	Asthenia
	Not known	Injection site necrosis, injection site reaction, injection site extravasation, injection site erythema, malaise
Investigation	Very common	Creatinine renal clearance decreased, blood urea increased, blood alkaline phosphatase increased, aspartate aminotransferase increased, liver function test abnormal, blood sodium decreased, blood potassium decreased, blood calcium decreased, blood magnesium decreased.
	Common	Blood bilirubin increased, blood creatinine increased, blood uric acid increased

* Fatal in <1%, fatal cardiovascular events in <1% included cardiac failure, embolism, and cerebrovascular accident combined.
# based on the post-marketing experience

Description of selected adverse reactions

Blood and lymphatic system disorders

Myelosuppression is the dose-limiting toxicity of carboplatin. In patients with normal baseline values, thrombocytopenia with platelet counts below 50,000/mm^3 occurs in 25% of patients, neutropenia with granulocyte counts below 1,000/mm^3 in 18% of patients, and leukopenia with WBC counts below 2,000/mm^3 in 14% of patients. The nadir usually occurs on day 21. Myelosuppression can be worsened by combination of carboplatin with other myelosuppressive compounds or forms of treatment.

Myelotoxicity is more severe in previously treated patients, in particular in patients previously treated with cisplatin and in patients with impaired kidney function. Patients with poor performance status have also experienced increased leukopenia and thrombocytopenia. These effects, although usually reversible, have resulted in infectious and hemorrhagic complications in 4% and 5% of patients given carboplatin, respectively. These complications have led to death in less than 1% of patients.
Anaemia with haemoglobin values below 8 g/dL has been observed in 15% of patients with normal baseline values. The incidence of anaemia is increased with increasing exposure to carboplatin.

Gastrointestinal disorders
[...]
The other gastro-intestinal complaints corresponded to pain in 8% of patients, diarrhoea, and constipation in 6 % of patients.

Nervous system disorders
Peripheral neuropathy (mainly paresthesias and decrease of osteotendinous reflexes) has occurred in 4% of patients administered carboplatin. Patients older than 65 years and patients previously treated with cisplatin, as well as those receiving prolonged treatment with carboplatin, appear to be at increased risk.
Clinically significant sensory disturbances (i.e., visual disturbances and taste modifications) have occurred in 1% of patients.
The overall frequency of neurologic side effects seems to be increased in patients receiving carboplatin in combination. This may also be related to longer cumulative exposure.

Ear and labyrinth disorders
Auditory defects out of the speech range with impairments in the high-frequency range (4,000-8,000 Hz) were found in serial audiometric investigations with a frequency of 15%. Very rare cases of hypoacusia have been reported.
In patients with a hearing organ predamaged due to cisplatin, a further exacerbation in the hearing function sometimes occurs during treatment with carboplatin.

Renal and urinary disorders
When given in usual doses, development of abnormal renal function has been uncommon, despite the fact that carboplatin has been administered without high-volume fluid hydration and/or forced diuresis. Elevation of serum creatinine occurs in 6% of patients, elevation of blood urea nitrogen in 14%, and of uric acid in 5% of patients. These are usually mild and are reversible in about one-half the patients. Creatinine clearance has proven to be the most sensitive renal function measure in patients receiving carboplatin. Twenty-seven percent (27%) of patients who have a baseline value of 60 mL/min or greater, experience a reduction in creatinine clearance during carboplatin therapy.

Electrolytes
Decreases in serum sodium, potassium, calcium, and magnesium occur in 29%, 20%, 22%, and 29% of patients, respectively. In particular, cases of early hyponatraemia have been reported. The electrolyte losses are minor and mostly take a course without any clinical symptoms.

Hepatobiliary disorders
Modification of liver function in patients with normal baseline values was observed, including elevation of total bilirubin in 5%, SGOT in 15%, and alkaline phosphatase in 24% of patients.

These modifications were generally mild and reversible in about one-half the patients. In a limited series of patients receiving very high dosages of carboplatin and autologous bone marrow transplantation, severe elevation of liver function tests has occurred.
Cases of an acute, fulminant liver cell necrosis occurred after high-dosed administration of carboplatin.

[...]

4.9 Overdose

No overdosage occurred during clinical trials. The anticipated complications of overdosage would be related to myelosuppression as well as impairment of hepatic and renal and auditory function. Use of higher than recommended doses of carboplatin has been associated with loss of vision (see section 4.4).

[...]