SUMMARY OF PRODUCT CHARACTERISTICS

CARBOPLATIN VIANEX
Carboplatin
Solution for Infusion 50mg, 150mg and 450mg per vial

1. NAME OF THE MEDICINAL PRODUCT
CARBOPLATIN VIANEX

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5ml vial contains carboplatin 50mg.
Each 15ml contains carboplatin 150mg.
Each 45ml contains carboplatin 450mg.

3. PHARMACEUTICAL FORM
Solution for infusion.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications
Carboplatin is indicated for the treatment of the following neoplasms:

- Advanced ovarian carcinoma of epithelial origin
- Small cell lung carcinoma
- Non small cell lung carcinoma
- Epidermogenic carcinoma of the head and neck of the cervix
- Urine bladder carcinoma from transitional epithelium (combined with other cytostatic drugs)

Remarkable responses have been observed when carboplatin was used in the treatment of cervix uteri carcinoma.

4.2. Posology and Method of Administration
Carboplatin is administered by intravenous route only.
In previously untreated adult patients with normal renal function, the recommended dosage is 400 mg/m^2 of body surface as a single dose administered by intravenous infusion (of 15 to 60 minutes duration).

The therapy should not be repeated until four weeks after the previous carboplatin course or/and until the neutrophil and platelet counts are above of 2,000 and 100,000 per mm³, respectively. Reduction of the initial dosage by 20-25% is recommended for patients with risk factors such as prior myelosuppressive therapy and poor performance status (ECOG-Zubrod 2-4 or Karnofsky below 80). In patients older than 65 years, the dosage adjustment, initially or subsequently, may be necessary, dependent on the physical status of the patient.

Determination of hematological nadir by weekly blood counts during the initial courses of treatment with carboplatin is necessary for future dosage adjustment.

Impaired renal function: Patients with creatinine clearance values below 60ml/min, have a higher risk of severe myelosuppression. The frequency of severe leucopenia, neutropenia or thrombocytopenia is maintained at levels of about 25% with the following dose schedules:

- 250 mg/m^2 carboplatin intravenously the 1st day in patients with initial creatinine clearance values of 41-59ml/min.
- 200 mg/m^2 carboplatin intravenously the 1st day in patients with initial creatinine clearance values of 16-40ml/min.

Apart from the above empirical way of the initial dose calculation, the initial dose may be calculated by a mathematical formula, as well, proposed by Calvert. This formula is:

Dose (mg) = (target AUC*) X (GFR + 25)

GFR: Glomerular Filtration Rate (ml/min).
AUC: Estimated values under the curve of carboplatin concentrations toward time (mg/ml•min).

Note: With the above mentioned formula, the total dose of carboplatin is calculated in mg and not in mg/m^2.

*** Target AUC**	**Planned Chemotherapy**	**Patient treatment status**
5-7 mg/ml•min	Single agent carboplatin	Previously untreated
4-6 mg/ml•min	Single agent carboplatin	Previously treated
4-6 mg/ml•min	Therapy with carboplatin plus cyclophosphamide	Previously untreated

In patients who in the past have had an intensive** therapy and to whom a monotherapy with carboplatin is administered, when the target is to achieve a particular platelet nadir, Egorin formula may be used:

$$\text{Dose (mg/m}^2\text{)} = 86 + \left[\frac{\text{Creatinine clearance (ml/min)}}{\text{Body Surface (m}^2\text{)}}\right] \times 0.091 \times \left[\frac{\text{Platelet count before therapy} - \text{Desirable platelet nadir}}{\text{Platelet count before therapy}} \times 100\right] - 17$$

** Patients who received an intensive therapy in the past are those who were treated with: mitomycin C, nitrosourea, a combination chemotherapy with doxorubicin, cyclophosphamide and cisplatin, a combination chemotherapy with 5 different products or radiotherapy $\geq$ 4500 rads in a radiation area 20 x 20 cm or more than one therapeutic area.

There are no data for the use of carboplatin in patients with creatinine clearance $\leq$15ml/min.

All the above dosage recommendations are valid for the initial therapy. The dosage which will follow has to be adjusted (more or less) according to patient tolerance and the acceptable myelosuppression level.

Combination Therapy: When carboplatin is used in combination with other myelosuppressive agents, dosage adjustments are required according to the regimen and schedule to be adopted.

Pediatric patients: The data are insufficient to establish dosage recommendations in pediatric population.

4.3 Contraindications

Carboplatin is contraindicated in patients with pre-existing severe renal impairment unless, based on physician's and patient's judgment the potential benefits outweigh therapy risks (see section 4.2).

Carboplatin should not be used in patients with severe myelosuppression and/or in patients with bleeding neoplastic sites. Carboplatin is also contraindicated in patients with a history of allergic reactions to carboplatin or other platinum containing compounds.

4.4 Special warnings and precautions for use

Carboplatin is a cytostatic drug and should be only administered by physicians experienced in the use of anti-neoplastic chemotherapeutic agents. Hematological blood counts as well as renal and hepatic function should be monitored regularly. The drug should be discontinued if pathologic bone marrow suppression or renal or hepatic function pathologic changes are observed.

The myelosuppression (leucopenia, neutropenia and thrombocytopenia) depends on the dosage level and limits the dosage. Frequent monitoring of peripheral blood counts is recommended during treatment with carboplatin and in case of toxic impact, until the patient's recovery.

The average number of days for nadir is the 21st day in patients who are treated with carboplatin as monotherapy and the 15th day in patients who are treated with carboplatin in combination with other chemotherapeutic agents. In general, the intermittent therapeutic regimens with carboplatin should not be repeated until the leucocyte, neutrophil and platelet counts become normal again.

Transfusion support is frequently required during carboplatin therapy, especially in patients who receive a prolonged therapy, due to the fact that anemia is frequent and additive. Myelosuppression is increased in patients previously treated (especially with cisplatin) or and with impaired renal function. The initial dosages of carboplatin for the above patient groups should be decreased accordingly (see section 4.2) and the effects should be carefully monitored with frequent peripheral blood counts between the therapy courses.

The combination therapy with carboplatin and other myelosuppressive therapies must be planned very carefully with respect to dosages and timing of administration in order to minimize additive effects.

Although carboplatin has a limited nephrotoxicity potential, the concurrent administration with aminoglycosides led to episodes of increased nephrotoxicity and ototoxicity. At higher than the recommended doses, in combination with other ototoxic agents, clinically significant hearing loss has been reported in pediatric patients.

Carboplatin may cause nausea and vomiting which may be more intense in patients who had previously been treated (especially with cisplatin). Preventive administration of antiemetics and prolongation of carboplatin administration time (with continuous drop infusion or within 5 consecutive days) were reported to be useful in reducing the incidence and intensity of this adverse event.

Although the neurotoxicity in the peripheral nervous system is in general rare and mild, the incidence may increase in patients older than 65 years and/or in patients who have already been treated with cisplatin. The stabilization or the improvement of preexisting neurotoxicity due to cisplatin therapy has been observed in about 50% of the patients who received a complementary therapy with carboplatin.

As with other platinum containing compounds, allergic reactions to carboplatin have been reported. These reactions can occur within few minutes after administration and should be managed with the appropriate supportive therapy. There is an increased risk of allergic reactions, including anaphylaxis, in patients previously treated with platinum (see sections 4.3 and 4.8).

In patients with renal impairment and after the use of carboplatin at doses higher than the recommended ones, visual disturbances including visual loss have been rarely reported. Vision is restored completely or at a high degree within weeks after the discontinuation of the high doses.

Very high doses of carboplatin (up to five times the recommended dose of the drug in monotherapy) lead to severe abnormalities of the hepatic and renal function.

Pediatric use: The safety and efficacy in children have not been established.

Elderly patients: In studies including combination therapy with carboplatin and cyclophosphamide, the elderly patients receiving carboplatin were more likely to develop thrombocytopenia than younger patients. In studies with carboplatin as monotherapy for various tumor types, adverse events were similar between the young and the elderly patients. However, a greater sensitivity of the elderly persons cannot be excluded. Renal function should be taken into consideration when dosage is determined, since this is often reduced in the elderly.

4.5. Interactions with other medicinal products and other forms of interaction
The use of carboplatin with other nephrotoxic agents is not recommended.

4.6 Pregnancy and lactation
Use during Pregnancy
Carboplatin can be harmful to the foetus when administered to a pregnant woman. Carboplatin has been shown to be embryotoxic and teratogenic in rats during organogenesis. There are no controlled studies in pregnant women. If this drug is to

be used in pregnant women or if the patient is becoming pregnant during the therapy, the patient should be informed on the potential hazard to the foetus. Women of child-bearing potential should be advised to avoid becoming pregnant when carboplatin is administered.

Use during lactation
It is not known whether carboplatin is excreted in human milk. Since many medicinal products are excreted in human milk and due to the potential of carboplatin induced serious adverse events to the breast-feeding infant, lactation should be discontinued or therapy to be discontinued taking into consideration the significance of the drug administration to the mother.

4.7. Effects on ability to drive and use machines
No effect has been reported. The possibility of visual and oto-toxicity as well as the physical status of the patient should be taken into consideration.

4.8 Undesirable effects
The incidence of undesirable effects reported hereunder is based on cumulative data obtained from 1,893 patients to whom carboplatin was administered as monotherapy and on the post-marketing experience.

Haematological toxicity
Myelosuppression is the dose-limiting toxic reaction of carboplatin. In patients with normal baseline values, thrombocytopenia with platelet counts less than 50,000/mm^3 is observed in 25% of the patients, neutropenia with neutrophil counts less than 1,000/mm^3 in 18% of the patients and leucopenia with leucocyte counts less than 2,000/mm^3 in 14% of the patients. The nadir is usually observed the 21st day (or the 15th day in patients who receive a combined therapy with carboplatin and other anti-neoplastic drugs). Until the 28th day, a recovery is already observed in platelet counts of more than 100,000/mm^3 in 90% of the patients, in neutrophil counts of more than 2,000/mm^3 in 74% and of leukocyte counts of more than 4,000/mm^3 in 67% of the patients. Febrile neutropenia has been reported post-marketing. Thrombocytopenia, neutropenia and leucopenia are more severe in patients who were previously treated (especially with cisplatin) and in patients with impaired renal function. In patients with poor general physical status, leucopenia and thrombocytopenia are observed at a higher degree. The above mentioned reactions, although usually reversible, resulted in virulent and hemorrhagic complications in 4% and 5% of the patients to whom carboplatin was administered, respectively. The above complications resulted in death due to toxicity in less than 1% of the patients. Anemia with hemoglobin levels below 11g/dl has been observed in 71% of the patients with normal baseline values. The more the body is exposed to carboplatin, the more frequent the anemia is. Transfusion support was applied in 26% of the patients to whom carboplatin was administered. Myelosuppression can be also exacerbated by combined therapy of carboplatin with other myelosuppressive compounds or therapies.

Gastrointestinal toxicity
Vomiting has been observed in 65% of the patients. About one third of these patients suffer severe emesis. Nausea occurs in a further 15% of patients. The patients who

were previously treated (especially with cisplatin), present a greater tendency of vomiting.
Nausea and/or vomiting usually disappear within 24 hours after administration and usually respond to or are prevented by the use of antiemetics. It seems that the prolonged administration of carboplatin (with continuous drop intravenous infusion or within 5 consecutive days) can cause less vomiting than the simple repeated therapeutic dose schedule. Vomiting increases when carboplatin is administered in combination with other emetogenic drugs. Other gastrointestinal side effects were pain in 17% of patients, diarrhea in 6% and constipation also in 6% of patients. Cases of anorexia have been reported post-marketing of the drug. The real involvement of carboplatin in the above phenomena is not clear.

Neurotoxicity
Peripheral neuropathy has been noted in 4% of the patients who received carboplatin expressed mainly with paraesthesias. Patients older than 65 years and those who in the past had been treated with cisplatin and those who were treated with carboplatin in prolonged therapy, seem to have a higher risk of developing peripheral neuropathy. Further exacerbation of symptoms is not observed in half of the patients who had already shown peripheral neurotoxicity due to cisplatin administration before the start of carboplatin therapy.

Clinically significant ototoxicity and other sensory disorders (such as visual disorders and taste alteration) have been observed in only 1% of the patients. Symptoms from the central nervous system have been reported in 5% of the patients and it seems that are often related to the use of antiemetics.
Even though the total occurrence of neurological side effects seems to increase in patients who receive carboplatin in combination with other drugs, this might be related to the prolonged duration of therapy in the patients to whom these observations have been made.

Nephrotoxicity
Alteration of renal function is unusual after administration of the usual doses although carboplatin was administered without high volume fluid hydration or and reinforced diuresis. A rise in serum creatinine was seen in 6%, in blood urea in 14% and in uric acid in 5% of the patients. These reactions were usually mild and reversible in 50% of the patients. Creatinine clearance was proven to be the most sensitive control parameter of renal function in patients receiving carboplatin and the most useful as far as the appearance of the relation between the drug clearance and myelosuppression is concerned. 27% of the patients with baseline value higher than or equal to 60ml/min, showed a decrease below this value during carboplatin treatment.

Electrolytes
Decreases in serum electrolyte levels have been reported for sodium in 29%, potassium in 20%, calcium in 22% and magnesium in 29% of the patients. No additional administration of electrolytes with carboplatin has been given. The combination chemotherapy did not increase the incidence of these electrolyte disorders.
Several types of early hyponatraemia have been reported. While carboplatin contribution is not clear if other contributing factors are considered (diuresis, respiratory disorders, malignancy etc.) the hyponatraemic potential should be

considered especially for those patients with other risk factors, such as the concurrent therapy with diuretics. Sodium administration or water limitation generally reverted the hyponatraemia.

Hepatic toxicity
There has been increase of total bilirubin in 5%, SGOT in 15% and alkaline phosphatase in 24% of the patients with normal baseline values. These changes were generally mild and reversible in half of the patients approximately.

In limited number of patients to whom very high doses of carboplatin were administered and who underwent autologous bone marrow transplantation, a great increase of the values of liver function tests has been noted.

Allergic reactions
Hypersensitivity to carboplatin has been reported in 2% of the patients. Anaphylactic-like reactions occurred in a few minutes after administration. These allergic reactions, similar to those reported after treatment with other platinum containing compounds (rash, urticaria, erythema, pruritus, rarely bronchospasm and hypotension) have been successfully treated with the usual therapy with adrenalin, corticosteroids and antihistamines.

Other rare events
Secondary malignancies have been considered relevant to combination therapy with multiple drugs. Nevertheless, the relation to carboplatin is not clear. Side effects of the respiratory system, cardiovascular system, mucosa, urogenital system, skin and musculoskeletal system were observed in ≤5% of patients. Although death as a result of cardiovascular disorders (heart failure, embolism, stroke) was reported in ≤1% of the patients, it is not obvious whether death was due to chemotherapy or to the general pathological condition of the patient. Arterial hypertension has been reported post-marketing of the drug.

Among various side effects, the most common reactions were asthenia (8%) and alopecia (3%). Their incidence was very increased in patients treated with carboplatin in combination with other drugs.

Haemolytic-uremic syndrome was rarely reported. Malaise, dehydration, stomatitis as well as injection site reactions, including redness, swelling and pain, have been reported post-approval and marketing of the drug. Necrosis associated with extravasation has also been reported.

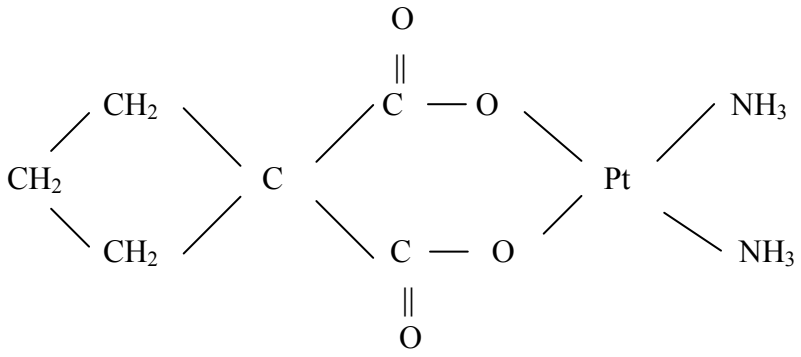
4.9 Overdose
There is not any known antidote for carboplatin overdose. The anticipated complications of overdose are myelosuppression as well as impairment of hepatic and renal function. The use of doses higher than the recommended is related with visual loss (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The active ingredient [Cis-Diamine (1,1-cyclobutane-dicarboxylato)platinum] is a platinum compound with antineoplastic action. Carboplatin is a crystalline powder with molecular formula $C_6H_{12}N_2O_4Pt$ and molecular weight 371.25. It is soluble in water at a concentration of 14 mg/ml, and the 1% solution pH is 5-7. It is virtually insoluble in ethanol, acetone and dimethylacetamide.

The syntactical formula of carboplatin is the following:



Carboplatin has biochemical properties similar to those of cisplatin and causes predominantly interstrand DNA crosslinks.

Pediatric patients: the safety and efficacy have not been established in children.

5.2 Pharmacokinetic properties

When carboplatin is administered at doses 300-500 mg/m^2 in patients with creatinine clearance of about and more than 60ml/min, carboplatin plasma concentrations decrease biphasically with average half lives in a and b phase 1.6 and 3.0 hours, respectively.

The total clearance, the apparent volume of distribution and the average time of carboplatin presence are 73ml/min, 16lt, and 3.5 hours respectively. The Cmax and AUC show a linear relationship with the dose. Consequently, above the range of doses of the drug that have been studied, carboplatin demonstrates a linear pharmacokinetic behavior in patients with creatinine clearance $\geq$60ml/min.

Significant quantities of free ultrafilterable substance containing other platinum compounds except carboplatin are not found in plasma, but platinum originated from carboplatin is protein bound and is slowly excreted with a minimum half life of 5 days.

The main route of carboplatin excretion is via kidneys. Patients with creatinine clearance of about and more than 60ml/min excrete 70% of carboplatin dose in the urine, mostly within 12-16 hours. All platinum in the 24 hours' urine is carboplatin and only 3-5% of the administered platinum is excreted between 24 to 96 hours.

In patients with creatinine clearance below 60ml/min, the renal and total clearance of carboplatin decrease when creatinine clearance decreases.

Consequently, carboplatin doses should be decreased in patients with creatinine clearance <60ml/min. There are not any sufficient data to prove whether excretion takes place through the bile or the intestine.

It has been reported that carboplatin clearance ranges from 3 up to 4 times the values, in pediatric patients. As in adult patients, the bibliographic data show that the renal function possibly contributes to the range of carboplatin clearance.

5.3 Preclinical safety data
Carboplatin has been shown to be embryotoxic and teratogenic in rats when administered during organogenesis. Carboplatin has been shown to be mutagenic *in vitro* and *in vivo*. Although the carcinogenic potential of carboplatin has not been studied, compounds with similar mechanism of action and mutagenic action have been reported to be carcinogenic. Carboplatin can be harmful to the foetus if administered during pregnancy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Water for injections.

6.2 Incompatibilities
Aluminum reacts with carboplatin causing sediment formation and/or decrease of potency. For this reason, needles or intravenous sets containing aluminum parts that may come into contact with carboplatin should not be used.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
The unopened vials are stable until the date mentioned on the package when stored ≤ 25°C protected from light.

6.5 Nature and contents of container
Glass vials containing 5 ml (50 mg), 15 ml (150 mg), 45 ml (450 mg) of carboplatin solution 10 mg/ml. The solution is colorless to light yellow.

6.6 Special precautions for use and handling
The product may be diluted in Glucose 5% or Sodium Chloride 0.9%, in concentrations not lower than 0.5mg/ml.

When diluted as directed with Glucose 5%, Carboplatin Vianex solutions are stable for 8 hours at temperature ≤25°C or for 24 hours at 2° – 8° C.
When diluted as directed with Sodium Chloride 0.9%, Carboplatin Vianex solutions are stable for 1 hour at temperature ≤25°C.

Precautions for the safe handling of the drug
Note: During the preparation or administration, needles or intravenous sets containing aluminum parts that may come into contact with carboplatin should not be used. Aluminum reacts with carboplatin causing sediment formation and/or decrease of potency.

The procedures for the appropriate use and disposal of anticancer drugs should be taken into consideration. Several guidelines have been published for this issue. There is no agreement that the recommended guidelines are all necessary or generalized.

To minimize the skin exposure during vial handling, you should always wear impermeable gloves. This includes all handling in clinical practice, pharmacy, warehouses and use at home, including handling during de-packaging and control, transport within the same premises and preparation of the dose for administration.

7. MARKETING AUTHORIZATION HOLDER
VIANEX S.A. – Tatoiou Str., 146 71 Nea Erythrea, Greece

8. MARKETING AUTHORIZATION NUMBER

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

June 18, 2009