Carpsol®
(Carboplatin)

1. NAME OF THE MEDICINAL PRODUCT

Carpsol®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Carboplatin is supplied in vials containing 50 mg in 5 mL & 150 mg/15 mL

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Carboplatin is a second generation cisplatin derivative which has shown to possess antitumor activity against a number of malignancies[1,5]. The drug is indicated for the treatment of the following solid tumors:

- *ovarian carcinoma* (including second-line/palliative treatment in patients who have previously received cisplatin-containing regimens)
- *small cell lung cancer*
- *cervical cancer*
- *head & neck cancer*

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Carboplatin can be administered either as a single agent or in combination with other anticancer agents. The drug is for intravenous (IV) use only and has to be administered by IV infusion over a period of at least 15 minutes.

There are two standards for dosing carboplatin: 1. Renal Function and 2. Body Surface Area (BSA)

1. Carboplatin dosing based on Renal Function[22-26]

Currently, the safest and most accepted therapeutic approach of dosing carboplatin is through renal function using the patient's glomerular filtration rate (GFR) and Calvert Formula to obtain a recommended AUC level, usually in the range of 4-8 mg/mL•min, depending on the respective protocol, pre-treatment status, concomitant radiation treatment or co-morbid circumstances that may affect a patient's renal function. This method compensates for variation in pre-treatment renal function that might otherwise result in underdosing patients with an above average renal function or overdosing patients with an impaired renal function. Dosing with this method is calculated in "mg" and not mg/m^2.

CALVERT FORMULA:

Total Dose (mg) = (target AUC) × (GFR + 25).

2. Carboplatin dosing based on BSA

Alternately, dosing may be based on the patient's body surface area (m^2). If the patient is obese or has severe fluid retention, the ideal body weight should be used to estimate dosage.

Single agent therapy: an initial single dose of 360 to 400 mg/m^2 is recommended.

Combination chemotherapy: in combination with other cytotoxic drugs carboplatin is recommended at the initial dosage of 300 mg/m^2.

As a general rule, carboplatin administration should be repeated at 4-week, cyclical intervals.

The therapeutic dosage of carboplatin may have to be adjusted according to the bone marrow status and to renal function as follows:

Bone marrow - Determination of the hematological nadirs during carboplatin treatment is recommended for dose adjustments. For patients in whom platelet and neutrophil counts remain above 1,00,000 and 2,000/mm^3, respectively, carboplatin dose may be increased by 25%. However, doses greater than 125% of the starting dose are not recommended. For patients whose platelet and neutrophil counts range from 1,00,000 to 50,000 and from 2,000 to 500/mm^3, respectively, dosage adjustments are not necessary. For patients who experience moderate to severe hematologic toxicity (i.e., platelet and neutrophil counts lower than 50,000 and 500/mm^3, respectively), consideration should be given to reducing the dosage - both in single agent or combination regimens - by 25%.[6]

In the presence of risk factors such as low performance status, extensive prior myelosuppressive therapies and/or age above 65 years, a 20 - 25% dose reduction is advisable; caution is also advised when giving carboplatin to patients who have previously received the nephrotoxic drug, cisplatin.

Carboplatin powder for injection has to be reconstituted immediately before use in Water for Injections, in 0.9% sodium chloride or in 5% dextrose; the solution must have a concentration of 10 mg/mL. The same solvents can similarly be used to achieve final, injectable concentrations as low as 0.5 mg/mL.

Aluminium reacts with carboplatin causing precipitate formation and loss of potency, therefore aluminium-containing equipment should not be used for preparation or administration of carboplatin.[9]

Prior to administration, carboplatin solutions should be inspected visually for particulate matter. Use the solution as soon as possible after preparation; infusion should be completed within 24 hours of preparation and any residue discarded. (see section **6.6. Special precautions for disposal and other handling**).

4.3. CONTRAINDICATIONS

Treatment with carboplatin is contraindicated in the following conditions:

- in patients with a history of hypersensitivity reactions to carboplatin or other platinum-containing compounds (e.g., cisplatin);
- in the presence of severe renal impairment;

- in the presence of severe bone marrow depression;
- in the presence of substantial bleeding.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The administration of carboplatin should be carried out under the supervision of physicians fully trained in the use of cytotoxic drugs. A close monitoring for toxicity is mandatory, particularly in the case of administration of high drug dosages.

Carboplatin is a highly toxic drug with a narrow therapeutic index and a therapeutic effect is unlikely to occur without some evidence of toxicity.

Bone Marrow Function

Bone marrow suppression (leukopenia, neutropenia and thrombocytopenia) is dose-dependent and is the dose-limiting toxicity of carboplatin. Peripheral blood cell counts should be performed at frequent intervals (e.g., on a weekly basis) in patients receiving carboplatin. Although at the recommended drug doses the hematologic toxicity of carboplatin is usually moderate and reversible, severe myelosuppression (especially thrombocytopenia) may occur in patients with renal impairment and in patients who are concurrently receiving (or have received) other myelosuppressive drugs or radiation therapy. Dose adjustment criteria for patients who experience myelosuppression following a dose of carboplatin are provided in section **4.2. Posology and method of administration**; as an alternative to dosage reduction, administration of the full therapeutic dose of the drug may be delayed until recovery of neutrophil and platelet counts (values ≥ 2,000/mm^3 and 1,00,000/mm^3, respectively). Treatment of severe hematologic toxicity may consist of supportive care, anti-infective agents for complicating infections, transfusions of blood products, autologous bone marrow rescue, peripheral stem cell transplantation and hematopoietic agents (colony-stimulating factors).

Blood and Lymphatic System Disorders

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

Hemolytic-uremic syndrome (HUS) is a potentially life-threatening side effect. Carboplatin should be discontinued at the first sign of any evidence of microangiopathic hemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or lactate dehydrogenase (LDH). Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

Secondary Leukemia

Acute promyelocytic leukaemia (APL) and myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) have been reported years after therapy with carboplatin and other antineoplastic treatments.[29]

Hepatobiliary Disease

Cases of hepatic veno-occlusive disease (sinusoidal obstructive syndrome) have been reported. Some of them were fatal.

Renal Function

Carboplatin is excreted primarily in the urine and renal function must be monitored in patients receiving the drug. Creatinine clearance appears to be the most sensitive measure of kidney function in patients receiving carboplatin. Dose adjustment criteria for patients with impaired renal function are provided in section **4.2. Posology and method of administration**. Unlike cisplatin, pre- and post-treatment hydration is not necessary with carboplatin as the drug has a relatively low nephrotoxic potential, however, previous therapy with cisplatin or concomitant administration of other nephrotoxic drugs (e.g., aminoglycoside antibiotics) may increase the risk of nephrotoxicity (see section **4.5. Interaction with other medicinal products and other forms of interaction**).

Central Nervous System (CNS)/Hearing Functions

Routine neurologic examination is advisable during carboplatin therapy, particularly in patients previously treated with cisplatin and in patients over 65 years of age. Carboplatin may produce cumulative ototoxicity. Audiograms should be performed prior to initiating therapy and during treatment or when auditory symptoms occur. Clinically important deterioration of auditive function may require dosage modifications or discontinuation of therapy. The risk of ototoxicity may be increased by concomitant administration of other ototoxic drugs (e.g., aminoglycosides) (see section **4.5. Interaction with other medicinal products and other forms of interaction**).[30]

Delayed onset hearing loss has been reported in pediatric patients. Long-term audiometric follow-up in this population is recommended.[30]

GI Effects

Carboplatin can induce emesis. The incidence and severity of emesis may be reduced by pretreatment with antiemetics or by carboplatin administration as a continuous IV infusion over 24 hours, or as IV administration of divided doses over 5 consecutive days rather than as a single infusion. Selective inhibitors of type 3 (5-HT3), serotonergic receptors (e.g., ondansetron) or substituted benzamides (e.g., metoclopramide) may be particularly effective antiemetics, and combination therapy may be considered for patients experiencing severe or refractory emetogenic effects.

Tumour Lysis Syndrome (TLS)

Patients 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.[29]

Hypersensitivity Reactions

As in the case of other platinum complexed compounds, allergic reactions to carboplatin have been reported. Patients should be monitored for possible anaphylactoid reactions and appropriate equipment and medication should be readily available to treat such reactions (e.g., antihistamines, corticosteroids, epinephrine, oxygen) whenever carboplatin is administered.

Immunosuppressant Effects/Increased Susceptibility to Infections

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[22].

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Carboplatin is mostly used in combination with antineoplastic drugs having similar cytotoxic effects. In these circumstances additive toxicity is likely to occur. Concomitant use of carboplatin and other myelosuppressive agents or radiation therapy may potentiate the hematologic toxicity.

- An increased incidence of emesis has been reported when carboplatin and other emetogenic drugs are given concurrently or carboplatin is administered to patients who previously received emetogenic therapy[9].

- Concomitant administration of carboplatin and aminoglycosides results in an increased risk of nephrotoxicity and/or ototoxicity, and the drugs should be used concurrently with caution. The use of other nephrotoxic drugs results in a potentiation of renal effects by carboplatin[9].

- Carboplatin interacts with aluminium to form a black precipitate of platinum and loss of potency. Aluminium-containing IV sets, needles, catheters and syringes should not be used for administration[9].

A decrease in phenytoin serum levels has been observed with concurrent administration of carboplatin and phenytoin/fosphenytoin. This may lead to exacerbation of seizures.[30]

4.6. FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential

Women of childbearing potential should be advised to avoid becoming pregnant while receiving carboplatin and to use effective contraception during treatment with carboplatin and for at least six months after the last dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment with carboplatin and for at least three months after the last dose.[30]

Pregnancy

Carboplatin may cause harm to the fetus when administered to pregnant women. The drug should be used during pregnancy only in life-threatening situations or for disease for which safer drugs cannot be used or are ineffective.

If the drug is administered during pregnancy or if the patient becomes pregnant while receiving carboplatin, the patient should be informed of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during carboplatin therapy.

Lactation

It is not clearly established whether carboplatin or its platinum-containing metabolites are distributed into human milk. However, because of the potential for serious adverse reactions in infants should the drug pass into the milk, nursing should be discontinued during therapy.

Fertility

Male and female fertility may be impacted by treatment with carboplatin (see section **5.3. Preclinical safety data**). Both men and women should seek advice for fertility preservation before treatment with carboplatin.[30]

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of carboplatin on the ability to drive or use machinery has not been systematically evaluated.

4.8. UNDESIRABLE EFFECTS

Many side effects of carboplatin therapy are unavoidable due to the pharmacological actions of the drug. However, the adverse effects are generally reversible if detected early.

Adverse reactions as reported for the various organ systems are as follows.

Neoplasms benign, malignant and unspecified

There have been rare reports of acute myelogenous leukemias and myelodysplastic syndromes arising in patients who have been treated with carboplatin, mostly when given in combination with other potentially leukemogenic agents[22].

Blood and lymphatic system disorders

The major and dose-limiting toxicity of carboplatin is bone marrow suppression, which is manifested by thrombocytopenia, leukopenia, neutropenia and/or anemia[9-12]. Myelosuppression is dose-related. Platelet and leukocyte/granulocyte nadirs usually occur two to three weeks from drug administration. Recovery is generally adequate to allow the administration of the subsequent carboplatin dose four weeks after a previous administration. Anemia (hemoglobin less than 11 g/dL), which may be symptomatic, occurs in a substantial proportion of patients. This effect may be cumulative and transfusions may be needed particularly in patients receiving prolonged therapy (e.g., more than 6 cycles).

Hemolytic anemia (sometimes fatal) has also been reported.[30]

Clinical sequelae of bone marrow/hematologic toxicity such as fever, infections, sepsis/septic shock and hemorrhage may be expected.

Hemolytic uremic syndrome (HUS) has been reported.[30]

Metabolism and nutrition disorders

Electrolyte abnormalities (hypokalemia, hypocalcemia, hyponatremia and/or hypomagnesemia)[9].

Nervous system disorders

Peripheral neuropathies may occur, mainly in the form of paraesthesias and decreased deep tendon reflexes[9,11]. The effect, more common in patients over 65 years of age, appears to be cumulative, occurring mainly in patients receiving prolonged therapy and/or in those who have received prior cisplatin therapy. CNS effects may also

occur. In some cases the neurotoxicity seen with carboplatin may be the result of a combination with some delayed effect of prior cisplatin therapy. Dysgeusia has been reported in patients taking carboplatin.[30]

Eye disorders

Visual abnormalities, such as transient sight loss (which can be complete for light and colors) or other disturbances may occur in patients treated with carboplatin. Improvement and/or total recovery of vision usually occurs within weeks after the drug is discontinued. Cortical blindness has been reported in patients with impaired renal function receiving high-dose carboplatin[13].

Ear and labyrinth disorders

Tinnitus and hearing loss has been reported in patients receiving carboplatin.

Cardiac disorders

Cardiac failure[9]; Ischaemic coronary artery disorders (e.g., Myocardial infarction, Cardiac arrest, Angina, Myocardial ischaemia)[28]; Kounis syndrome[30]

Vascular disorders

Cerebrovascular events[9]

Gastrointestinal disorders

Nausea and/or vomiting, which generally are mild to moderate in severity, may occur within 6-12 hours after carboplatin administration, and may persist up to 24 hours or longer[9,11]. Other GI effects such as mucositis, stomatitis,[30] diarrhea, constipation and abdominal pain have also been reported.

Hepatobiliary disorders

Mild and usually transient elevations of serum alkaline phosphatase, aspartate aminotransferase or bilirubin concentrations may occur[9]. Substantial abnormalities in liver function test have been reported in patients treated with carboplatin at high doses and autologous bone marrow transplantation[9].

Immune system disorders

Allergic reactions to carboplatin have been reported[9]. These include anaphylaxis/anaphylactoid reactions, hypotension, bronchospasm, and pyrexia. Hypersensitivity reactions may occur within a few minutes after IV administration of carboplatin.

Skin and subcutaneous tissue disorders

Exfoliative dermatitis may rarely occur. Erythematous rash, pruritus, urticaria, and alopecia have also been reported in association with carboplatin[9].

Musculoskeletal and connective tissue disorders

Myalgia/arthralgia[9]

Renal and urinary disorders

Acute renal failure has been reported rarely. Mild and transient elevations of serum creatinine and of blood urea nitrogen concentrations may occur[9,14,15]. Risk of carboplatin-induced nephrotoxicity (e.g., impaired creatinine clearance) becomes more prominent at relatively high dosages or in patients previously treated with cisplatin.

General disorders and administration site conditions

Asthenia, flu like symptoms, reactions at injection site.[9]

4.9. OVERDOSE

There are no known antidotes for carboplatin overdosage, thus every possible measure should be taken to avoid an overdose; this includes full awareness of the potential danger of an overdose, careful calculation of the dose to be administered and availability of adequate diagnostic and treatment facilities. Acute overdosage with carboplatin may result in an enhancement of its expected toxic effects (e.g., severe myelosuppression, intractable nausea and vomiting, severe neurosensorial toxicities, liver failure, kidney failure, etc.). Death may follow. Hemodialysis is only effective, even then partially, up to 3 hours after administration because of the rapid and extensive binding of platinum to plasma proteins. Signs and symptoms of overdosage should be managed with supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacodynamic group: Antineoplastic agent, platinum compound.

Mechanism of action

Carboplatin binds to DNA and causes a cross binding of the two DNA strands. This will change the helix configuration and inhibit the DNA synthesis. The effect is probably independent of the cycle.

Pharmacodynamic properties: Carboplatin is a platinum compound, cis-diammine (1,1-cyclobutane-dicarboxyl) platinum, with anti-tumor effect. The biochemical properties are similar to those of cisplatin.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

Following a single dose by IV infusion over 60 minutes, the plasma concentration of total platinum and free platinum (ultra filtrate) will fall biphasically according to first order kinetics. Initial half life of free platinum is in the order of magnitude 1 – 2 hours and the terminal half life 3 – 6 hours. Total platinum has the same initial half life, while the terminal half life is lower (approx. 24 hours). An approximately linear relationship between the dose (in the area 300 – 500 mg/m^2) and plasma AUC of the total and the free platinum is achieved. Repeated doses of carboplatin during four continuous days do not cause accumulations of platinum in plasma. Twenty-four hours after administration of the dose, 85% of the plasma platinum will be protein bound.

Distribution

The volume of distribution for carboplatin is 16 liters.

Elimination

Carboplatin is mainly excreted through the urine, in which 30% of the dose is secreted unconverted. In patients with creatinine clearance of 60 mL/min or higher, 65% and 70% of the dose is retrieved after 12 and 24 hours respectively. Total clearance for carboplatin is 4.4 liters/hour.

5.3. PRECLINICAL SAFETY DATA

LD_{50} for IV carboplatin is for mice and rats respectively 150 and 61 mg/kg, and above 31.1 mg/kg for dogs. The main target organs following single administration were the hemolymphopoietic system, the kidneys and the gastrointestinal tract. Toxic effects following repeated dosing were investigated in mice, rats and dogs. The main target organs were the hemolymphopoietic system, the gastrointestinal tract, kidneys, liver and reproductive organs of both females and males.

Treatment of rats, males and females, with carboplatin IV prior to mating and up to implantation caused increased fetal lethality and fewer live fetuses. Treatment of pregnant rats with carboplatin IV during the organogenesis (days 7 – 17) caused delayed fetal development and growth, and slower postnatal growth. Treatment of rats from day 17 of the pregnancy through the breastfeeding period up to weaning did not cause any effects on birth or viability or on the development of the offspring.

Carboplatin is genotoxic in most *in vitro* and *in vivo* tests which have been conducted. Toxicity studies have shown that extravasal injection will cause tissue necrosis.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Water for injection
Nitrogen

6.2. INCOMPATIBILITIES

Information not available.

6.3. SHELF LIFE

Product as packaged for sale:	24 months at 25°C protected from light.[27]
Product after first opening the container:	Vials are prepared for single use only; any unused portion must be discarded after use.[27]
Product after reconstitution or dilution:	Infusion should be completed within 24 hours of preparation and any residue discarded[27].

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

Do not freeze. Protect from light.

6.5. NATURE AND CONTENTS OF CONTAINER

Carpsol Injection: 50 mg in 5 mL, 150 mg in 15 mL, 1's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

The usual precautions for handling and preparing cytotoxic drugs should be observed when reconstituting or administering carboplatin.

Special precautions for prolonged IV infusion: Carboplatin diluted in 0.9% sodium chloride and stored at 25°C undergoes about 5% degradation of the initial concentration over 24 hours[7]. In addition, 0.9% sodium chloride solutions are considered not suitable for carboplatin infusion not only because of the loss of active drug but also given the possibility that conversion to cisplatin may occur, with a risk of increased toxicity[7]. Therefore it is recommended not to dilute carboplatin in 0.9% sodium chloride when intended for prolonged IV infusion[8].

Personnel should be trained in good technique for reconstitution and handling. Pregnant staff should be excluded from working with carboplatin.

Preparation should be performed in a designated area ideally in a vertical laminar flow hood, with the work surface covered with disposable plastic-backed absorbent paper.

Care should be taken to prevent inhaling particles and exposing the skin to carboplatin.

Adequate protective clothing should be worn, such as PVC gloves, safety glasses, disposable gowns and masks.

It is recommended that lock fittings are used in the assembly of syringes and giving sets to avoid leakage.

In the event of contact with the eyes, wash with water or saline. If the skin comes into contact with the drug wash thoroughly with water and in both cases seek medical advice. Seek immediate medical attention if the drug is ingested or inhaled.

All used material, needles, syringes, vials and other items which have come into contact with cytotoxic drugs should be incinerated. Excreta should be similarly treated. Contaminated surfaces should be washed with copious amounts of water.

Carpsol/LPD/PK-02
According to CDS V 5.0 Dated 10 July 2019; Supersedes CDS V 4.0 Dated 11 August 2017

Marketed by:
Pfizer Pakistan Limited
B-2, S.I.T.E., Karachi

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7. REFERENCES

1. Cannera R, Bragman K, *et al*. Carboplatin: current status and future prospects. *Cancer Treat. Rev*., 15: 17-32, 1988.

2. Albert DS. Clinical pharmacology of carboplatin. *Semin. Oncol*., 17: 6-8, 1990.

3. Muggia FM. Overview of carboplatin: replacing, complementing, and extending the therapeutic horizons of cisplatin. *Sem. Oncol.*, 16: 7-13, 1989.

4. Alberts DS, Mason-Liddil N. Carboplatin in the treatment of ovarian cancer. *Sem. Oncol.*, 16: 19-26, 1989.

5. Raghavan D, Perez R, *et al*. Carboplatin for small cell lung cancer: progress toward greater efficacy and reduced toxicity. *Sem. Oncol.*, 21: 1-8, 1994.

6. Van Der Wall E, Beijnen JH, Rodenhuis S. High dose chemotherapy regimens for solid tumors. *Cancer Treat. Rev.*, 21: 105-132, 1995.

7. Cheung, YW, *et al*. Stability of cisplatin, iproplatin, carboplatin and tetraplatin in commonly used intravenous solutions. *Am. J. Hosp. Pharm*., 44: 124-130, 1987.

8. Allsopp MA, *et al*. The degradation of carboplatin in aqueous solutions containing chloride or other selected nucleophiles. *Int. J. Pharmaceutics*, 69: 197-210, 1991.

9. McEnvoy GK ed. *American Hospital Formulary Service* 2008 – Drug Information.

10. Beale PJ, Kelland LR, Judson IR. Platinum agents in the treatment of cancer. *Exp. Opin. Invest. Drugs*, 5: 681-693, 1996.

11. Canetta R, *et al*. Carboplatin: the clinical spectrum to date. *Cancer Treat. Rev*., 12: 125-136, 1985.

12. Ten Bokkel Huinink WM. Current status of chemotherapy for ovarian carcinoma. *Eur. J. Cancer Clin. Oncol.*, 24: 583-585, 1987.

13. O'Brien MER, *et al*. Blindness associated with high-dose carboplatin. *Lancet*, 339: 558, 1992.

14. Reed E, Jacob J. Carboplatin and renal dysfunction. *Ann. Intern. Med*., 110: 409, 1989.

15. Smit EF, *et al*. Carboplatin and renal function. *Ann. Intern. Med*., 110: 1034, 1989.

16. Harrap KR. Preclinical studies identifying carboplatin as a viable cisplatin alternative. *Cancer Treat. Rev.*, 12: 21-33, 1985.

17. Rose WC, Schurig JE. Preclinical antitumor and toxicologic profile of carboplatin. *Cancer Treat. Rev.*, 12: 1-19, 1985.

18. Van Echo DA, Egorin MJ, Aisner J. The pharmacology of cisplatin. *Sem. Oncol*., 16: 1-6, 1989.

19. CBDCA Clinical Brochure – Division of Cancer Treatment, 1981.

20. Physicians' Desk Reference, 48th Ed., p. 664, 1994.

21. Reynolds JEF ed. Martindale – The extra pharmacopeia. The Pharmaceutical Press, 13th edition, London 1993.

Reference 22-27: *CDS Revision Date September 15, 2008*

22. Lincoff A, Racanelli T. Carboplatin. Clinical Expert Report to support revisions to the Core Data Sheet. Safety and Risk Management, Pfizer Inc. September 2008.

23. Calvert AH, Newell DR, Gumbrell LA, *et al*. Carboplatin dosage: prospective evaluation of a simple formula based on renal function *J Clin Oncol* 1989; 7:1748-1756.

24. Jodrell DI, Egorin MJ, Canetta RM, *et al*. Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian-cancer. *J Clin Oncol* 1992; 10:520–528.

25. Reyno LM, Egorin MJ, Canetta RM, *et al*. Impact of cyclophosphamide on relationships between carboplatin exposure and response or toxicity when used in the treatment of advanced ovarian cancer. *J Clin Oncol* 1993; 11:1156–1164.

26. Ghazal-Aswad S, Tilby MJ, Lind M, *et al*. Pharmacokinetically guided dose escalation of carboplatin in epithelial ovarian cancer: Effect on drug-plasma AUC and peripheral blood drug-DNA adduct levels. *Annals of Oncology* 1999; 10:329-334.

27. Carboplatin Injection. Module 3.2.P.8.1 Stability Summary and Conclusions. CTDP-8100-00-00. August 2007.

Reference 28: *CDS Revision Date October 2009*

28. Lincoff A, Carboplatin. Clinical Expert Report to support revisions to the Core Data Sheet. Safety and Risk Management, Pfizer Inc. October 2009.

Reference 29: *CDS Revision Date August 11, 2017*

29. 2.5 Clinical Overview to support updates to section 4.4 special warnings and precautions for use of the Core Data Sheet, August 2017.

Reference 30: *CDS Revision Date July 2019*

30. 2.5 Clinical Overview to Support Updates to Sections 4.2, 4.4, 4.5, 4.6 and 4.8 of the Core Data Sheet, July 2019.