Carpsol®
(Carboplatin)

1. NAME OF THE MEDICINAL PRODUCT

Carpsol Injection 10mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL of concentrate for solution for infusion contains 10 mg of carboplatin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentration for solution for infusion in vials.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Carboplatin is indicated for the treatment of:

- Advanced ovarian carcinoma of epithelial origin, as:
  (a) first-line treatment
  (b) second-line treatment, after the failure of other treatments.

- Small cell carcinoma of the lung associated with other antineoplastic agents.
- Advanced squamous cell carcinoma of the head and neck in a polychemotherapy regimen.
- Neoadjuvant treatment of invasive bladder carcinoma (Jewett stages B and C) and of the advanced disease, forming part of polychemotherapy regimens.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Posology
Carboplatin must be administered exclusively by the intravenous route.

The starting dose of carboplatin as a single agent recommended for previously untreated patients with normal kidney function is 360-400 mg/m^2 administered as a single intravenous dose by infusion for 15 to 60 minutes. The treatment must not be repeated until 4 weeks after the previous administration of carboplatin 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.

For patients who do not experience haematologic toxicity (i.e. the platelet and neutrophil counts remain above 100,000 and 2,000/mm^3, respectively) with the previous dose, the carboplatin dose can be increased by 25% in a single treatment or in combination (e.g. cyclophosphamide).

A reduction of 20% to 25% from the starting dose is recommended for those patients with risk factors such as previous myelosuppressive treatment and poor general condition (ECOG-Zubrod 2-4 or Karnofsky less than 80).

Determine the haematological nadir by weekly blood counts during the initial cycles of treatment with carboplatin to adjust the dose in subsequent treatment cycles.

Alternatively, the starting dose can be calculated using the Calvert formula. This is based on kidney function (glomerular filtration rate). This reduces the risk of administering an insufficient dose or an overdose given individual differences in kidney function.
Calvert formula: total dose (mg) = (target AUC*) × (glomerular filtration rate + 25)
Note: With Calvert's formula, the total dose of carboplatin is calculated in mg, not in mg/m^2.

*** Target AUC**	**Planned chemotherapy**	**Previous treatments**
5-7 mg/mL min	Carboplatin only	No previous treatment
4-6 mg/mL min	Carboplatin only	Previous treatment
4-6 mg/mL min	Carboplatin plus cyclophosphamide	No previous treatment

The Calvert formula must not be used in patients who previously received intensive treatment, who have been given one of the following treatments:
- mitomycin C
- nitrosourea
- doxorubicin/cyclophosphamide/cisplatin combined chemotherapy
- combined therapy including 5 or more cytostatic agents
- radiation therapy ≥ 4,500 rad in one 20 × 20-cm area or in multiple areas.

Treatment in combination with other chemotherapy agents
In combination with other myelosuppressive chemotherapy agents, a dose adjustment is required according to the treatment regimen and schedule to be followed.

Kidney failure
Patients with creatinine clearance below 60 mL/min have a high risk of experiencing severe myelosuppression. The frequency of leukopenia, neutropenia or severe thrombocytopenia has been kept at 25% using the following dose recommendations:

Creatinine clearance	Starting dose (Day 1)
41-59 mL/min	250 mg/m^2
16-40 mL/min	200 mg/m^2

In patients with creatinine clearance of 15 mL/min or lower, there is insufficient data to recommend treatment with carboplatin.

The recommended doses included above are indicated for the initial treatment cycles. The following doses must be adjusted based on the patient's tolerance and on acceptable levels of myelosuppression.

The optimal use of carboplatin in patients with kidney impairment requires frequent monitoring of haematological nadirs, electrolytes and kidney function.

Paediatric population
There is insufficient information available to recommend a dose in the paediatric population.

Patients of advanced age
In patients age 65 years and older, the carboplatin dose must be adjusted during the first cycle and subsequent treatment cycles.

Method of administration
Carboplatin must be administered exclusively by the intravenous route.

Needles or devices for intravenous administration that include aluminium parts that could come into contact with the carboplatin must not be used for preparation or administration. Carboplatin interacts with aluminium, causing the formation of a precipitate and/or a loss of potency.

During the preparation and administration of carboplatin, take appropriate safety measures for cytotoxic drugs. Carboplatin must be prepared by trained staff members wearing protective gloves, masks and protective clothing (see section 6.6).

4.3. CONTRAINDICATIONS

- Hypersensitivity to the active substance or to other compounds that contain platinum or any of the excipients listed in section 6.1.
- Patients with severe pre-existing kidney failure (creatinine clearance < 30 mL/min) unless, in the doctor's opinion, the potential benefits of the treatment outweigh the risks.
- Patients with severe myelosuppression.
- Patients with tumours with major bleeding.
- Concomitant treatment with the yellow fever vaccine (see section 4.5).

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Administer carboplatin only under the constant supervision of doctors experienced in therapy with cytotoxic agents and only when the potential benefit of treatment with carboplatin surpasses the possible risks. The appropriate facilities for adequate treatment of possible complications must be available.

Closely monitor for toxicity, particularly in cases where high doses of the drug are administered. Carboplatin is a highly toxic drug with a narrow therapeutic window, and its therapeutic effect is generally associated with some evidence of toxicity. Perform blood counts and liver and kidney function tests regularly. The treatment must be discontinued if abnormal myelosuppression or abnormal kidney or liver function is observed.

Haematologic toxicity
Myelosuppression (leukopenia, neutropenia and thrombocytopenia) is dose-dependent and is the dose-limiting toxic effect of the carboplatin dose (see section 4.2).

Perform periodic (typically weekly) peripheral blood counts in patients under treatment with carboplatin and, in case of toxicity, repeat these counts until normal values are recovered.

The lowest (nadir) values are reached on day 21 (on average) in patients receiving carboplatin as a single agent and on day 15 (on average) in patients receiving carboplatin in combination with other chemotherapy agents. In general, cycles of carboplatin as a single agent must not be repeated until the leukocyte, neutrophil and platelet counts have recovered to normal levels. Do not repeat treatment until 4 weeks have passed since the administration of a cycle with carboplatin 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.

Although anaemia is common and cumulative, it rarely requires transfusion.

In patients who have received previous treatment (particularly with cisplatin) or radiation, the severity of the myelosuppression and/or the severity of impaired kidney function are increased. Reduce the starting dose of carboplatin in these patients appropriately (see section 4.2), and monitor adverse effects using blood counts between cycles. Carefully plan the doses and administration times for carboplatin in combination with other myelosuppressive drugs to minimise adverse effects.

In cases of severe haematologic toxicity, supportive measures, the administration of antibiotics in complicated infections, blood transfusions, rescue with autologous bone marrow transplant, transplantation of peripheral blood stem cells and haematopoietic agents (colony-stimulating factors) may be necessary.

The myelosuppressive effects may be additive to those of the concomitant chemotherapy. Patients with severe and persistent myelosuppression have a high risk of infectious complications that include fatal cases (see section 4.8). Stop carboplatin treatment if any of these adverse reactions occurs.

Blood and Lymphatic System Disorders
Cases of haemolytic anaemia with the presence of serologic drug-induced antibodies have been reported in patients treated with carboplatin. This event can be fatal.

Haemolytic uraemic syndrome (HUS)
Haemolytic uraemic syndrome (HUS) is a life-threatening adverse reaction. Stop carboplatin as soon as the first sign of microangiopathic haemolytic anaemia appears, such as a rapid reduction in haemoglobin together with thrombocytopenia, or raised serum bilirubin, serum creatinine, blood urea nitrogen or lactate dehydrogenase (LDH). Kidney failure may not be reversible on suspending the treatment, and dialysis may be required.

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

Hepatic veno-occlusive disease
Cases of hepatic veno-occlusive disease (sinusoidal obstruction syndrome) have been reported, some of which were fatal. Monitor patients for signs and symptoms of abnormal liver function or portal hypertension that do not obviously result from liver metastases.

Liver function

There is insufficient information to recommend a posology in patients with liver failure. However, stop treatment if liver failure is observed.

Renal function
Carboplatin is primarily excreted in urine. Monitor the kidney function of patients under treatment with carboplatin. Creatinine clearance has been shown to be the most sensitive parameter for measuring kidney function in patients who receive carboplatin. In patients with kidney failure, the effect of carboplatin on the haematopoietic system is more pronounced and of longer duration than in patients with normal kidney function. The recommendations for dose adjustment in these patients are found in section 4.2.

Unlike cisplatin, carboplatin has low nephrotoxic potential, so hydration before and after treatment is not required. However, previous treatment with cisplatin or concomitant administration with other nephrotoxic medicinal products (e.g. aminoglycosides) can increase the risk of nephrotoxicity (see section 4.5).

Central nervous system/auditory function
During treatment with carboplatin, a neurological examination is recommended, particularly in patients who have received previous treatment with cisplatin and in patients aged over 65 years.

Carboplatin can cause cumulative ototoxicity. Perform audiograms before starting and during treatment, or when auditory symptoms appear. Clinically-significant impairment of hearing function may require changing the dose or stopping the treatment. The risk of ototoxicity may be increased by concomitant administration of other ototoxic drugs (e.g., aminoglycosides) (see section 4.5).

Ototoxicity may be more pronounced in children. Delayed onset hearing loss have been reported in paediatric patients. In this population, long-term audiometric follow-up is recommended.

Although neurological toxicity is generally common, moderate and limited to paraesthesia and reduced deep tendon reflexes, its frequency increases in patients aged over 65 years and/or in patients previously treated with cisplatin. Monitor patients and perform regular neurological exams.

Cases of visual disturbances have been reported in patients with kidney failure, including loss of sight, after the administration of carboplatin at doses higher than recommended. Vision is fully or mostly recovered weeks after stopping the treatment with high doses.

Gastrointestinal effects
Carboplatin can cause vomiting. The incidence and severity of vomiting can be reduced by administering antiemetics before treatment or during the administration of carboplatin treatment by continuous intravenous infusion over 24 hours, or by intravenous fractionated doses divided over 5 consecutive days instead of a single dose. Type 3 selective serotonin receptor inhibitors (e.g. ondansetron) or substituted benzamides (e.g. metoclopramide) can be effective antiemetics, and combined therapy can be considered in patients who experience severe vomiting or in patients who do not respond to the treatment.

Hypersensitivity reactions
As with other compounds that contain platinum, cases of allergic reactions to carboplatin have been reported. Therefore, the patient must be monitored to detect possible anaphylactoid reactions, and the appropriate equipment and suitable medication must be available (e.g. antihistamines, corticosteroids, adrenaline, oxygen) for treating these reactions.

There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8). Kounis syndrome can develop in patients with and without cardiac risk factors, and may be presented with a combination of cardiac and allergic symptoms, or as standalone. Coronary vasospasm may be treated with steroids and antihistamines in addition to spasmolytics treatment.

Immunosuppression effect/increased susceptibility to infections
The administration of live or attenuated virus vaccines in patients who are immunocompromised by the use of chemotherapy agents, including carboplatin, can cause severe or fatal infections.

In patients under treatment with carboplatin, do not administer live virus vaccines. Killed or inactivated vaccines may be administered, although the response may be reduced (see section 4.5).

Reversible posterior leukoencephalopathy syndrome (RPLS)
Cases of reversible posterior leukoencephalopathy syndrome (RPLS) have been reported in patients treated with carboplatin in combination with chemotherapy. RPLS is a rare neurological condition that is reversible after stopping treatment, progresses rapidly, and may include seizures, hypertension, headache, confusion, blindness and other visual and neurological disturbances (see section 4.8). The diagnosis of RPLS is based on confirmation by brain imaging tests, preferably Magnetic Resonance.

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. Closely monitor patients at high risk of developing TLS, such as patients with a high proliferative index, high tumour burden and high sensitivity to cytotoxic agents, and take appropriate precautions.

Use in elderly patients
In studies that included combined treatment with carboplatin and cyclophosphamide, elderly patients treated with carboplatin developed severe thrombocytopenia more frequently than young patients. As kidney function is often reduced in elderly patients, kidney function must be taken into account when determining the dose (see section 4.2).

Other
Both male and female patients must use contraceptive methods to prevent conception and/or reproduction during and after treatment with carboplatin. Genetic counselling is recommended if the patient wants to have children after completing the treatment (see section 4.6).

Do not use equipment containing aluminium during preparation and administration (see section 6.2).

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

Carboplatin is generally used in combination with other antineoplastic drugs with similar cytotoxic effects. In these cases, additive toxicity is likely to occur.

The concomitant administration of carboplatin with other myelosuppressive drugs or radiation therapy can potentiate haematologic toxicity.

An increased incidence of vomiting has been reported after the concomitant administration of carboplatin with other emetic drugs or after administering carboplatin to patients who have previously received treatment with emetic drugs.

Considering the increased thrombotic risk in tumour diseases, the use of oral anticoagulants is common. If it is decided to treat the patient with oral anticoagulants, monitor INR more frequently due to the high intra-individual variability of coagulation in these diseases and possible interactions between the oral anticoagulants and the chemotherapy treatments.

Contraindicated concomitant use:
- Yellow fever vaccine: risk of fatal generalised vaccine disease (see section 6.3).

Concomitant use not recommended:
- Attenuated live vaccines (except yellow fever): risk of systemic disease, which may be fatal. This risk is increased in individuals who are immunosuppressed due to an underlying disease. An inactivated vaccine must be administered when available (poliomyelitis).

- Phenytoin, fosphenytoin: a decrease in phenytoin serum levels has been observed with concurrent administration of carboplatin and phenytoin/fosphenytoin. Risk of exacerbation of seizures due to reduced digestive absorption of phenytoin due to the cytotoxic medicinal product, or risk of exacerbated toxicity or loss of efficacy of the cytotoxic medicinal product due to the hepatic metabolism of phenytoin.

Concomitant use that must be evaluated:
- Cyclosporine (and by extrapolation, tacrolimus and sirolimus): increased immunosuppression with risk of lymphoproliferation.

- Aminoglycosides: the concomitant administration of carboplatin with aminoglycoside antibiotics must be considered, particularly in patients with kidney failure, due to the risk of cumulative nephrotoxicity and ototoxicity.

- Loop diuretics: the concomitant administration of carboplatin with loop diuretics must be considered due to cumulative nephrotoxicity and ototoxicity.

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 7 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 4 months after the last dose.

Pregnancy

Carboplatin can harm the foetus if it is administered to pregnant women. In rats, the administration of intravenous carboplatin during organogenesis has been shown to be embryotoxic and teratogenic. No controlled studies have been conducted in pregnant women.
If used during pregnancy, or if the patient becomes pregnant during treatment, warn them of the potential danger to the foetus. Advise women of fertile age to take measures to prevent conception during and after treatment with carboplatin.

Carboplatin will only be administered during pregnancy in situations that are life-threatening for the mother or for diseases in which safer medicinal products cannot be used or have been ineffective.

Lactation

Carboplatin and its active metabolites have been identified in human milk of treated mothers. Due to the risk of serious adverse effects of carboplatin, breast-feeding must be discontinued during treatment and for 1 month following last dose or discontinue treatment with Carboplatin Pharmacia 10mg/ml concentrate for solution for infusion, taking into account the importance of the drug to the mother.

Fertility

Male and female fertility may be impacted by treatment with carboplatin (see section 5.3). Both men and women should seek advice for fertility preservation before treatment with carboplatin.

In patients who are receiving chemotherapy treatments, gonadal suppression resulting in amenorrhoea and azoospermia may appear. These effects appear to be related to the dose and duration of the treatment and may be irreversible. It is difficult to predict the degree of impairment of ovarian or testicular function, as combinations of multiple antineoplastic agents are commonly used, making it difficult to evaluate the effects of these medicinal products separately.

Advise male patients under treatment with carboplatin to use effective contraceptive measures during treatment and for up to 4 months after completing it, and to seek counselling about sperm storage before starting treatment, due to the possibility of developing irreversible infertility due to the carboplatin treatment.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies have been conducted on the effect of carboplatin on the ability to drive and use machines. However, as carboplatin can cause nausea, vomiting, visual disturbances and ototoxicity, it is not recommended to drive vehicles or use machines after the administration of the medicinal product.

4.8. UNDESIRABLE EFFECTS

Many of the adverse reactions to carboplatin are related to the pharmacological action of the medicinal product. In general, if these adverse reactions are detected promptly, they are reversible. The adverse reactions reported are based on the cumulative data on 1,893 patients who received an injection of carboplatin as a single agent and on post-marketing experience.

The adverse reactions are listed below by system organ class, MedDRA preferred term and frequency, using the following frequency ranges: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to

< 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000), frequency not known (cannot be estimated from the available data).

System organ class	Frequency	MedDRA term
Neoplasms, benign, malignant and unspecified (including cysts and polyps)	Not known	Treatment-induced secondary malignancies
Infections and infestations	Common	Infections NEC*
	Not known	Pneumonia
Blood and lymphatic system disorders	Very common	Thrombocytopenias, neutropenias, leukopenias, anaemias NEC
	Common	Haemorrhage*
	Not known	Bone marrow failure, febrile neutropenia, haemolytic uraemic syndrome, hemolytic anemia
Immune system disorders	Common	Hypersensitivity, anaphylactoid reactions
Metabolism and nutrition disorders	Not known	Dehydration, anorexia, hyponatraemia Tumour lysis syndrome
Nervous system disorders	Common	Peripheral neuropathy, paraesthesia, tendon reflex decreased, sensory disturbance, dysgeusia
	Not known	Stroke*, Reversible posterior leukoencephalopathy syndrome (RPLS)
Eye disorders	Common	Visual disturbances, rare cases of loss of vision
Ear and labyrinth disorders	Common	Ototoxicity
Cardiac disorders	Common	Heart disorder*
	Not known	Heart failure, Kounis syndrome
Vascular disorders	Not known	Embolism*, hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	Common	Respiratory disorders, 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
Investigations	Very common	Creatinine 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% including heart failure, embolism and stroke

Cardiac disorders
Cases of heart failure and ischaemic coronary artery disorders (e.g. myocardial infarction, cardiac arrest, angina pectoris, myocardial ischaemia) have been reported.

Blood and lymphatic system disorders
Myelosuppression is the major dose-limiting toxicity of carboplatin, which appears as thrombocytopenia, leukopenia, neutropenia and/or anaemia. The myelosuppression is dose-related.
In patients with normal baseline values, thrombocytopenia appears with platelet counts below 50,000 cells/mm^3 in 25% of patients, neutropenia with a granulocyte count below 1,000 cells/mm^3 in 18% of patients and leukopenia with a white cell count below 2,000 cells/mm^3 in 14% of patients. The nadir is usually reached on day 21 after administering carboplatin. The myelosuppression may be worse with the combination of carboplatin and other myelosuppressive agents or treatments.
Myelosuppression is more severe in patients with previous treatment, in patients treated with cisplatin and in patients with kidney failure. Patients with poor general condition usually experience leukopenia and thrombocytopenia. These reactions, although reversible, have caused infections and haemorrhagic complications in 4% and 5% of patients, respectively, after the administration of an injection of carboplatin. These complications have resulted in death in less than 1% of patients.

Anaemia has been observed with haemoglobin values of 8 g/dL in 15% of patients with normal baseline values. The incidence of anaemia increases as exposure to carboplatin increases. This adverse reaction may be cumulative and may require transfusions, particularly in patients who receive long-term treatment (after more than 6 cycles). Fever, infections, sepsis/septic shock and bleeding may appear as a result of the carboplatin-induced haematologic toxicity and myelosuppression.
Hemolytic anemia (sometimes fatal) has also been reported.

Nervous system disorders
Peripheral neuropathies have appeared in 4% of patients, primarily in the form of paraesthesia and decreased deep tendon reflexes. These effects, which are more common in patients aged over 65 years, appear to be cumulative and primarily occur in patients who receive extended treatment with carboplatin and/or in those who have previously been treated with cisplatin.
In 1% of patients, clinically significant sensory abnormalities appeared (e.g. visual disturbances and dysgeusia).
In general, the frequency of neurological adverse effects is increased after receiving carboplatin in combination with other drugs. This may also be related to cumulative dose exposure.

Eye disorders
In patients treated with carboplatin, visual abnormalities such as transient loss of vision (which can be complete for light and colours) and other disorders have been observed. Improvement and/or total recovery of vision

usually occurs weeks after the end of treatment. Cases of cortical blindness have been reported in patients with kidney disorders who receive high doses of carboplatin.

Ear and labyrinth disorders
In a series of analysed audiometry tests, hearing disorders outside the conversational range were found, with deficiencies in the high-frequency range (4,000-8,000 Hz) at a frequency of 15%. There have been very rare reports of hypoacusis. During treatment with carboplatin, exacerbation of ear damage due to previous treatment with cisplatin has occurred.
Cases of tinnitus and hearing loss have been reported in patients treated with carboplatin.

Gastrointestinal disorders
In 65% of cases, vomiting occurs, which is severe in one third. Nausea appears in an additional 15%. Previously treated patients (particularly patients treated with cisplatin) appear to be more susceptible to vomiting. These reactions usually disappear within 24 hours after treatment and, generally, there is a response to antiemetic treatment, including preventive treatment. Vomiting is more common when carboplatin is administered in combination with other emetic drugs.
Mild to moderate nausea and/or vomiting can occur 6 to 12 hours after the administration of carboplatin and may last for 24 hours or more.

Cases of mucositis, diarrhoea and constipation have also been reported in 6% of patients, and abdominal pain in 8% of patients.

Renal and urinary disorders
After administering standard doses of carboplatin, the development of impaired kidney function has been uncommon, even if the carboplatin injection is given without hydration with a large fluid volume and/or without forced diuresis. Increased serum creatinine occurs in 6% of patients, increased blood urea nitrogen in 14% of patients, and increased uric acid levels in 5% of patients. Typically, in one half of all affected patients, these increases are moderate and reversible. Creatinine clearance has been shown to be the most sensitive parameter for measuring kidney function in patients who receive carboplatin. Twenty-seven percent (27%) of patients with baseline creatinine clearance values of 60 mL/min or higher experience a reduction during treatment with carboplatin. The risk of carboplatin-induced nephrotoxicity (altered creatinine clearance) is more likely at high doses or in patients who have previously been treated with cisplatin.

Skin and subcutaneous tissue disorders
Some cases of exfoliative dermatitis have been reported. Cases of erythematous rash, pruritus, urticaria and alopecia have also been reported.

Musculoskeletal and connective tissue disorders
Cases of myalgia/arthralgia have been reported.

Metabolism and nutrition disorders
Decreases in sodium, potassium, calcium and/or magnesium levels have been observed in 29%, 20%, 22% and 29% of patients, respectively. In particular, cases of early hyponatraemia have been reported. Electrolyte losses are minor and most cases occur without clinical symptoms.

Neoplasms, benign, malignant and unspecified (including cysts and polyps)

Some cases of acute myelogenic leukaemia and myelodysplastic syndromes have been reported in patients treated with carboplatin, particularly when carboplatin is administered in combination with other leukaemogenic agents.

Vascular disorders
Cases of cerebrovascular events have been reported.

General disorders and administration site conditions
Cases of asthenia, flu-like symptoms and injection site reactions have been reported.

Immune system disorders
After administering carboplatin, occasionally fatal anaphylactoid reactions have been reported, which may appear a few minutes after the administration of carboplatin with the following symptoms: oedema, dyspnoea, tachycardia, hypotension, urticaria, anaphylactic shock, bronchospasm and pyrexia.

Hepatobiliary disorders
Abnormal liver function test results have been observed in patients with normal baseline levels, including total bilirubin increased in 5% of patients, AST increased in 15% of patients and alkaline phosphatase increased in 24% of patients. These changes were generally moderate and reversible in half of patients.
Moderate and generally transient elevations may occur in plasma levels of alkaline phosphatase, aspartate aminotransferase or bilirubin.
In a limited number of patients, significant abnormalities in liver function tests have been reported in patients treated with high doses of carboplatin and with autologous bone marrow transplants. Severe cases of fulminant liver necrosis have been reported after the administration of high doses of carboplatin.

General disorders and administration site conditions
Injection site reactions (burning sensation, pain, redness, swelling, urticaria, extravasation-related necrosis injection site) have been reported.

Other adverse reactions
Secondary malignancies have been reported after the administration of carboplatin in combination with other cytotoxic drugs.

Occasionally, cases of alopecia, fever, chills, mucositis, asthenia, malaise and dysgeusia have been observed.

Haemolytic uraemic syndrome has occurred in isolated cases.

Isolated cases of cardiovascular disorders (heart failure, embolism) have been reported, as well as isolated cases of stroke.

Cases of hypertension have been reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9. OVERDOSE

There are no known antidotes for the treatment of carboplatin overdose. Therefore, the appropriate measures must be taken to prevent a possible overdose of the medicinal product. These measures include careful calculation of the dose, as well as the availability of suitable means for diagnosis and treatment. An acute carboplatin overdose can cause an increase in the incidence or severity of some of the known adverse reactions to the medicinal product (e.g. severe myelosuppression, nausea and vomiting that are difficult to treat, acute neurosensory toxicity, hearing function disorders, liver and kidney failure). Death may also occur. The use of carboplatin doses that are higher than recommended has been associated with loss of vision (see section 4.4).
Haemodialysis is partially effective if performed within the first 3 hours after administering the drug, as platinum is rapidly and widely bound to plasma proteins.
The signs and symptoms of overdose must be managed with appropriate supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents – Other antineoplastic agents, platinum compounds, ATC code: L01XA02.

Mechanism of action: Carboplatin is a platinum compound with antineoplastic properties, of which only the cis-diamine (1,1 cyclobutane-dicarboxyl) platinum isomer is active. It has biochemical properties similar to those of cisplatin. It appears to be bound to DNA to produce intra- and intercaternary bridging structures that modify the structure of DNA and inhibit DNA synthesis.

Paediatric population: The safety and efficacy of carboplatin have not been established in children.

5.2 Pharmacokinetic properties

Absorption:
After IV infusion of a single dose of carboplatin over 60 minutes, the plasma concentration of total platinum and free (ultrafiltrable) platinum decreases according to a two-phase curve that follows first-order reaction kinetics. The initial half-life of free platinum is on the order of magnitude of 1 to 2 hours, and the terminal half-life is 3 to 6 hours. The initial half-life of total platinum is the same, while a terminal half-life approximately 5 days for total platinum in plasma. An approximately linear relationship between the dose (in the area of 300-500 mg/m^2) and the area under the curve is achieved for plasma total and free platinum. The administration of repeated doses over four consecutive days did not produce platinum accumulation in plasma. Eighty-five percent (85%) of platinum in plasma is bound to proteins within 24 hours after administration.

Distribution:
The volume of distribution of carboplatin is 16 litres.

Elimination
Carboplatin is primarily excreted in urine; 30% of the administered dose is excreted in unaltered form. In patients with creatinine clearance of 60 mL/min or more, 65% and 70% of the administered dose are recovered after 12 and 24 hours, respectively. Total carboplatin clearance is 4.4 litres/hour.

5.3 Preclinical safety data

Carboplatin has been shown to be embryotoxic and teratogenic in rats. It is mutagenic *in vivo* and *in vitro* and, although the carcinogenic potential of carboplatin has not been studied, it has been reported that compounds with similar mechanisms of action and mutagenicity are carcinogenic.
Toxicity studies have shown that the extravascular administration of carboplatin causes tissue necrosis.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Water for injection

6.2. INCOMPATIBILITIES

Carboplatin interacts with aluminium, causing the formation of a black platinum precipitate.
During the preparation or administration of carboplatin, do not use needles, syringes, catheters or any other device used in intravenous administration that contains aluminium that could come into contact with the carboplatin. The precipitation can cause a reduction in antineoplastic activity.

6.3. SHELF LIFE

2 years.

After first opening the product:
The vials are for single use. Discard the unused portion.

After reconstitution/dilution:
After reconstitution/dilution, the product must be infused within 24 hours. Discard the unused portion.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.
Keep in the outer packaging to protect from light.
After dilution: For storage conditions after diluting the medicinal product, see section 6.3.

6.5. NATURE AND CONTENTS OF CONTAINER

The container closure system for Carboplatin Injection 10 mg/mL consists of a Type I clear glass vial, an elastomeric closure, and an aluminium seal with a plastic flip-off top.

Package sizes:
50mg/5ml and 150mg/15ml - Carton with 1 vial

Not all pack sizes may be marketed.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

Carpsol does not contain any preservative or bacteriostatic agent. Therefore, vials of this product are for single use. Discard any remaining solution for infusion.

Instructions for dilution:
Carboplatin can be diluted before infusion with 0.9% saline solution for injection or with 5% glucose solution to obtain a concentration of 0.5 mg/mL (500 micrograms/mL).
To reduce microbiological risk, prepare the dilution immediately before use. Visually inspect the solution before administration to check that the solution is free from particles. The infusion must be completed within 24 hours after its preparation and the unused portion must be discarded

The use of Luer-Lock syringes and large-bore needles is recommended so as to minimise pressure and possible aerosol formation. Use of a vented needle during the preparation can also reduce aerosols.

Precautions for administration by long-duration infusion of the concentrate for solution for infusion: when dissolving Carboplatin concentrate for solution for infusion in 0.9% saline solution and storing it for 24 hours at 25 °C, the active substance degrades by 5% from the initial concentration. Therefore, dissolving Carboplatin in 0.9% saline solution is not considered appropriate for long-duration infusions because, in addition to the loss of active substance, carboplatin may be converted into cisplatin, increasing the risk of toxicity.

Guidelines for safe handling of antineoplastic agents:
- Carboplatin must be handled by health personnel who are trained in the use of chemotherapy agents.
- Pregnant women must avoid handling this medicinal product.
- The trained health personnel who handle carboplatin must wear protective gear: safety goggles, gown, gloves and disposable masks.
- Prepare the dilution in a designated area (preferably under a laminar flow hood). Protect the work surface with absorbent, plastic-lined disposable paper.
- All material used for reconstitution, administration or cleaning must be disposed of in high-risk waste material bags for destruction by incineration at high temperatures.
- Any spill or leak must be treated with diluted sodium hypochlorite solution (1% available chlorine), preferably by soaking, and then with water.
- All cleaning materials must be disposed of as indicated above.
- In case of accidental contact with the eyes or skin, wash immediately with plenty of water, soap and water or sodium bicarbonate solution and seek medical attention. A mild cream may be used to treat temporary itching of the skin. If the eyes are affected, see a doctor.
- Always wash your hands after taking off gloves.

Disposal:
The unused medicinal product and all materials that have been in contact with it shall be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS

Please see pack for specifications.

7. REGISTRATION HOLDER / MARKETING AUTHORIZATION HOLDER:

According to Spain Approved SmPC dated Feb 15, 2024 & approved information in Pakistan

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

Name of Manufacturing site	Address of site	Manufacturing step
M/s Bridgewest Perth Pharma Pty Limited	15 Brodie Hall Drive, Technology Park, Bentley, Western Australia, 6102, Australia.	Manufacturing
Pfizer Pakistan Limited	B-2, SITE, Karachi	Packaging & Batch Release

8. REGISTRATION / MARKETING AUTHORIZATION NUMBER:

013966

9. DATE FROM WHICH MARKETING IS AUTHORIZED:

30-Jan-1993

10. DATE OF REVISION OF THE TEXT:

15-Feb-2024

Carpsol/LPD/PK-02
According to Spain Approved SmPC dated Feb 15, 2024 & approved information in Pakistan

*Please visit our website **www.pfizerpro.com.pk** for latest version of Product leaflet.*