Carboplatin

Biovinate®

10 mg/mL
(150 mg/15 mL and 450 mg/45 mL)
Solution for Intravenous Infusion
For Intravenous Use Only
Antineoplastic (Platinum Compound)

FORMULATIONS
Each 15 mL solution for intravenous infusion contains:
Carboplatin, BP……..150 mg
Each 45 mL solution for intravenous infusion contains:
Carboplatin, BP……..450 mg

PRODUCT DESCRIPTIONS
Carboplatin (Biovinate) is a clear, colorless sterile solution contained in a Type 1 amber glass vial.

CLINICAL PHARMACOLOGY
Pharmacodynamics / Mechanism of Action
Carboplatin is a platinum-containing antineoplastic agent. It is an analog of cisplatin but is less toxic. Like cisplatin, it contains a platinum atom surrounded in a plane by two ammonia groups and other ligands in the cis position. The other two ligands in carboplatin are present in a ring structure rather than as two chloride atoms in cisplatin. This difference makes carboplatin more stable and with less nephrotoxicity, neurotoxicity, ototoxicity, and emetogenicity.

Carboplatin's exact mechanism of action is not fully elucidated but it must undergo activation before antineoplastic activity occurs. The bidentate decarboxylate ligands of carboplatin are displaced by water (aquation) to form reactive platinum complexes which are believed to inhibit DNA synthesis by forming interstrand and intrastrand cross-linking of DNA molecules. The aquation of carboplatin occurs at a slower rate than that of cisplatin. Carboplatin is cell cycle-phase nonspecific.

Pharmacokinetics
In patients with creatinine clearance of about 60 mL/min or greater, plasma levels of intact carboplatin decay in a biphasic manner after a 30-minute IV infusion of 300 to 500 mg/m^2. Initial plasma $t_{1/2}$ (α) was found to be 1.1 to 2 hrs, and post distribution plasma $t_{1/2}$ (β) was found to be 2.6 to 5.9 hrs. Carboplatin's total body clearance, apparent volume of distribution and mean residence time were 4.4 L/hr, 16 L and 3.5 hrs, respectively. The C_{max} values and areas under the plasma concentration vs. time curves from 0 to infinity (AUC_{∞}) increased linearly with dose, although the increase was slightly more than dose proportional. Carboplatin, therefore, exhibited linear pharmacokinetics over the dosing range studied (300 to 500 mg/m^2).

Protein binding of carboplatin is low, with up to 29% of carboplatin bound during the first 4 hours. However, platinum from carboplatin is irreversibly bound to plasma proteins (85% to 89% bound by 24 hours) and is slowly eliminated with a minimum $t_{1/2}$ of 5 days.

The metabolism of carboplatin is not fully elucidated. There is no evidence that the drug undergoes enzymatic biotransformation; the bidentate decarboxylate ligands of carboplatin are believed to be displaced by water, forming positively charged platinum complexes that react with nucleophilic sites of DNA.

Carboplatin's major route of elimination is by renal excretion. Patients with creatinine clearances of approximately 60 mL/min or greater excreted 65% of the dose in the urine within 12 hours and 71% within 24 hours. All the platinum in the 24-hour urine was present as carboplatin. Only 3% to 5% of the administered platinum was excreted in the urine between 24 and 96 hrs. There were insufficient data to determine whether biliary, interstitial or fecal excretion occurs.

Pharmacokinetics in Patients with Renal Impairment
Renal clearance and total body clearance of platinum are reduced in patients with impaired renal function. In patients undergoing hemodialysis, the $t_{1/2\beta}$ of total and ultrafilterable platinum is increased compared with values reported in individuals with normal renal function. Doses should be adjusted in these patients.

INDICATIONS
- Initial treatment of advanced ovarian carcinoma of epithelial origin in established combinations with other approved chemotherapeutic agents
- For the palliative treatment of ovarian carcinoma of epithelial origin refractory to standard chemotherapy with or without cisplatin
- For the treatment of small cell lung carcinoma

DOSAGE AND ADMINISTRATION
NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency. Do not use needles or intravenous (IV) sets containing aluminum parts that may come in contact with the drug in the preparation or administration of carboplatin.

Dosage of carboplatin must be based on the clinical, renal and hematologic response and tolerance of the patient in order to obtain optimum therapeutic response with minimum adverse effects. While initial carboplatin dose can be based on body surface area, dose may be more accurately calculated using formula dosing methods based on patient's renal function (see **Formula Dosing**).

After dilution, carboplatin should be used by IV route only. No pre- or post-treatment hydration or forced diuresis is required.

Doses of carboplatin should generally not be repeated until neutrophil count is at least 2,000 cells/mm^3 and platelet count is at least 100,000 cells/mm^3.

As Monotherapy
The recommended initial dose of carboplatin in patients with normal renal function is:
- 360 mg/m^2 (previously treated recurrent ovarian carcinoma) **OR**
- 300 to 320 mg/m^2 (previously treated or have poor performance status) **OR**
- 400 mg/m^2 (previously untreated)

Administered as an IV infusion usually over 15 to 60 minutes on day 1 every 4 weeks (alternatively, see **Formula Dosing**).

Determination of the hematologic nadir by weekly blood count during the initial courses of carboplatin treatment is recommended for dosage adjustment for subsequent courses of therapy (see **Dosage Adjustments**).

In Combination with Cyclophosphamide
- For the treatment of advanced ovarian cancer for previously untreated patients, an initial carboplatin dose of 300 mg/m^2 as IV infusion usually over 15 to 60 minutes on day 1 every 4 weeks for 6 cycles (alternatively, see **Formula Dosing**).
- Cyclophosphamide 600 mg/m^2 is administered by IV infusion usually over 15 to 60 minutes on day 1 every 4 weeks for 6 cycles (please refer to cyclophosphamide package insert)

In Other Combination Regimens
When carboplatin is used as a component of a multiple-drug regimen, clinicians should consult published protocols for the dosage of each chemotherapeutic agent and the method and sequence of administration.

Formula Dosing
Carboplatin's initial dose may be calculated by using a mathematical formula based on the patient's renal function and desired platelet nadir. The use of Calvert's formula, as compared to empirical dose calculation based on body surface area, allows adjustment for patient variations in pretreatment renal function.

The formula is based on glomerular filtration rate (GFR in mL/min) and carboplatin AUC (in mg/mL · min). **The total dose is calculated in mg and not mg/m^2.**

Total Dose (mg) = target AUC x (GFR + 25)

Target AUCs providing the most appropriate dosage range are based on the treatment status of the patient:

Target AUC (mg/mL per minute)	Planned Chemotherapy	Patient Treatment Status
5 to 7	Carboplatin monotherapy	Previously untreated
4 to 6	Carboplatin monotherapy	Previously treated
4 to 6	Carboplatin plus cyclophosphamide	Previously untreated

Subsequent carboplatin dose should be adjusted according to hematologic tolerance to the previous dose (see **Dosage Adjustments**).

The Calvert formula is not sufficiently accurate to determine carboplatin dose for children or for adults with severe renal impairment (i.e., GFR <20 mL/min); this formula should not be used in such patients.

Dosage Adjustments
- Pretreatment platelet count and performance status are important prognostic factors for severity of myelosuppression in previously treated patients.
- Subsequent doses of carboplatin in single or combination therapy should be based on the hematologic response of the patient:

Platelets	Neutrophils	Adjust Dose (From Prior Course)
>100,000	>2,000	125%
50,000 to 100,000	500 to 2,000	100%
<50,000	<500	75%

No specific dosage adjustment data for children has been calculated.

Dose in Patients with Renal Impairment
The optional use of carboplatin in patients with impaired renal function requires adequate dosage adjustments and frequent monitoring of both hematologic nadirs and renal function. Patients with creatinine clearance values below 60 mL/min are at increased risk of severe bone marrow suppression. The initial dose of carboplatin in these patients may be based on the Calvert formula (see **Formula Dosing**) or on the creatinine clearance as follows:

Creatinine Clearance (mL/min)	Recommended Initial Dose (mg/m^2)
41 to 59	250
16 to 40	200

Subsequent doses should be adjusted according to the patient's tolerance to the previous dose and the acceptable level of myelosuppression.

Limited data are available for patients with severely impaired renal function (creatinine clearance <15) to permit treatment recommendation.

Geriatric Dosing
Because renal function is often reduced in geriatric patients, dosing formulas incorporating estimates of GFR should be used to provide predictable plasma carboplatin AUCs and minimize the risk of toxicity.

Preparation of Intravenous Infusion
Vials of carboplatin may be further diluted with 5% dextrose or 0.9% sodium chloride solution for injection to concentrations as low as 0.5 mg/mL.

Prior to administration, carboplatin solutions should be inspected visually for particulate matter and discoloration.

Stability
Diluted solutions are stable for 24 hours when stored at 15°C to 25°C in glass or plastic containers, and in dark storage condition. Discard unused portion after 24 hours.

Diluted solutions are stable for 48 hours under refrigeration (2°C to 8°C) from the time of initial dilution, after which time the unused portion should be discarded.

Special Handling Precautions
Preparation and Handling
- Procedures for proper handling and disposal of anti-cancer drugs should be considered to minimize exposure to carboplatin.
- Personnel should be trained in good techniques for reconstitution and handling.
- Pregnant staff should be excluded from working with carboplatin.
- As for all antineoplastic agents, personnel handling carboplatin should wear impervious gloves, safety glasses and protective clothing such as gowns and masks.
- Preparation of antineoplastics should be performed in a designated area, preferably a vertical laminar flow hood. The work surface should be covered with disposable plastic-backed absorbent paper.
- It is recommended that lock fittings are used in the assembly of syringes and administration sets to avoid leakage.
- Professional staff administering antineoplastic agents should exercise particular care to prevent spillage and contact with the drug.
- Avoid inhalation of particles and contact with skin and mucous membranes. If skin contact occurs, the area should be vigorously washed with soap and water. If carboplatin comes into contact with mucous membranes, the membranes should be flushed immediately and thoroughly with water. Seek immediate medical attention if the drug is ingested, inhaled or comes in contact with eyes.
- Personnel regularly involved in the preparation and handling of cytotoxic agents should have bi-annual blood examinations.
- Discard any unused carboplatin solution for infusion properly.

Spillage/Contamination
- In the event of spillage, personnel wearing protective clothing should sponge up the spilled material.
- The area should be rinsed twice with water. All solutions, and contaminated clothing and sponges put into a plastic bag and sealed. The bag should be disposed of properly.

Disposal
- Adequate care and precaution should be taken in the disposal of items that come in contact with carboplatin.
- All materials that have come in contact with cytotoxic agents including needles, syringes, vials, absorbent materials, and other materials should be placed in a thick plastic bag or other impervious container and incinerated at 1000°C. Excreta should be similarly treated.

CONTRAINDICATIONS
- Hypersensitivity to carboplatin, cisplatin or other platinum-containing compounds
- Hypersensitivity to mannitol
- Pre-existing severe renal impairment (creatinine clearance of <20 mL/min)
- Severe myelosuppression
- Significant bleeding
- Pregnant or breastfeeding women

WARNINGS AND PRECAUTIONS
Bone marrow suppression is dose-related and may be severe, resulting in infection and/or bleeding. Anemia may be cumulative and may require transfusion support. Vomiting is another frequent drug-related adverse effect.

Anaphylactic-like reactions to carboplatin have been reported and may occur within minutes of carboplatin administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms.

General
Carboplatin is a highly toxic drug with a narrow therapeutic index and a therapeutic effect is unlikely to occur without some evidence of toxicity. Carboplatin should only be administered under the supervision of a qualified physician experienced in cancer chemotherapeutic drugs. Blood counts as well as renal and hepatic function tests must be done regularly. Diagnostic and treatment facilities should be readily available for appropriate management of therapy and possible complications.

Generally, carboplatin courses should not be administered more frequently than every 4 weeks to ensure that the nadir in blood counts has occurred and that there has been recovery to a satisfactory level.

Discontinue carboplatin therapy if severe myelosuppression or abnormal renal or hepatic function is observed.

Hematologic Toxicity (see **Boxed Warning**)
Bone marrow suppression (leukopenia, neutropenia, and thrombocytopenia) is dose-dependent and is also the dose-limiting toxicity. Frequently monitor peripheral blood counts during carboplatin treatment and when appropriate until recovery is achieved. Median nadir occurs at day 21 in patients receiving single agent carboplatin. Do not repeat single intermittent courses of carboplatin until leukocyte, neutrophil and platelet counts have normalized. This recovery usually takes 5 to 6 weeks. Since anemia is cumulative, transfusions may be needed during treatment with carboplatin, particularly in patients receiving prolonged therapy (i.e., more than 6 cycles).

Myelosuppression is increased in patients who received prior antineoplastic therapy (especially cisplatin-containing regimens), who are receiving concurrently or received recently other myelosuppressive drugs or radiation therapy, and those with renal impairment. Initial carboplatin doses in these patients should be appropriately reduced (see **Dosage and Administration**) and blood counts should be carefully monitored between courses.

Nephrotoxicity
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. Adjust doses in patients with impaired renal function (see **Dosage and Administration**). Although carboplatin has limited nephrotoxic potential, previous therapy with cisplatin or concomitant administration with other nephrotoxic drugs may increase the risk of nephrotoxicity.

Gastrointestinal
Carboplatin can induce emesis, which can be more severe in patients previously receiving emetogenic therapy. Nausea and/or vomiting, which are generally mild to moderate in severity, may occur within 6 to 12 hours after carboplatin administration and may persist up to 24 hours or longer. Incidence and intensity of emesis have been reduced by using premedication with antiemetics. Although no conclusive efficacy data exist with carboplatin's schedules, lengthening the duration of single IV administration to 24 hours or dividing the total dose over 5 consecutive daily pulse doses has resulted in reduced emesis.

Neurotoxicity
Although peripheral neurotoxicity is infrequent, its incidence is increased in patients older than 65 years old and in patients previously treated with cisplatin. Pre-existing cisplatin-induced neurotoxicity does not worsen in about 70% of patients receiving carboplatin as secondary treatment.

Anaphylaxis (see **Boxed Warning**)
Patients receiving carboplatin should be observed closely for possible hypersensitivity reactions, and appropriate equipment for maintenance of an adequate airway and other supportive measures and agents for the treatment of such reactions (e.g., antihistamines, epinephrine, oxygen, corticosteroids) should be readily available whenever carboplatin is administered. Patients with prior exposure to other platinum-containing compounds are at increased risk for carboplatin-induced allergic reactions, including anaphylaxis.

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 attenuated vaccine should be avoided in patients receiving carboplatin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Others
Loss of vision, which can be complete for light and colors, has been reported after use of carboplatin doses higher than those recommended. Vision appears to recover totally or to a significant extent within weeks of stopping these high doses.

Carcinogenicity, Mutagenicity and Impairment of Fertility
Carboplatin's carcinogenic potential has not been studied, but compounds with similar mechanism of action and mutagenicity profiles have been reported to be carcinogenic. Carboplatin has been shown to be mutagenic both *in vitro* and *in vivo*. It has also been shown to be embryotoxic and teratogenic in rats receiving the drug during organogenesis. Secondary malignancies (e.g., acute myelogenous leukemia and myelodysplastic syndrome) have been rarely reported with carboplatin treatment, mostly when given in combination with other potentially leukemogenic agents.

Most forms of chemotherapy have been associated with reduction of oogenesis and spermatogenesis and patients receiving carboplatin should be warned of this potential. Although not reported with carboplatin, this has been reported with other platinum agents. Recovery of fertility after exposure can occur but is not guaranteed.

INTERACTIONS WITH OTHER MEDICAMENTS

Myelosuppressive Agents or Radiation Therapy: Concomitant use with carboplatin may potentiate the hematologic toxicity of the other agents and vice versa.

Nephrotoxic or Ototoxic Agents (e.g., aminoglycosides, vancomycin, capreomycin, and diuretics): Concomitant administration may increase carboplatin's nephrotoxicity and ototoxicity risks.

Emetogenic Agents: 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.

Vaccines (See **Warnings and Precautions**)

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy and Lactation

Pregnancy Category D
There is positive evidence of human fetal risk and use in pregnancy is not recommended. If carboplatin is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be informed of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Breastfeeding: It is not known whether carboplatin is excreted in human milk. Because there is a possibility of toxicity in nursing infants secondary to carboplatin treatment of the mother, it is recommended that breastfeeding be discontinued if the mother is treated with carboplatin.

Pediatric
Safety and effectiveness in children have not been established.

Geriatric
For patients 65 years old and above, dosage adjustment, initially or subsequently, may be necessary, depending on the physical condition of the patient.
Severe thrombocytopenia associated with carboplatin therapy occurred more frequently in geriatric patients than in younger patients. In addition, carboplatin-induced peripheral neuropathy appears to be more common in adults older than 65 years old than in younger patients. Among a total of 1942 patients (21% of whom were ≥65 years old) receiving carboplatin monotherapy in different tumor types, a similar incidence of adverse effects was observed in younger and older patients. Other reported clinical experience has not identified differences between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Because renal function was often decreased in the elderly, consider renal function in the selection of carboplatin dosage.

UNDESIRABLE EFFECTS (see **Warnings and Precautions**)
Hematologic Effects: Leukopenia, neutropenia, anemia and thrombocytopenia. Myelosuppression is usually more severe in patients with impaired renal function. Patients with poor performance status also experienced a higher incidence of severe leukopenia and thrombocytopenia. Hematologic effects, although usually reversible, have resulted in infectious or hemorrhagic complications (e.g., bleeding) in 5% of the patients treated with carboplatin, with drug-related death occurring in <1% of the patients. Fever has also been reported in patients with neutropenia.

Gastrointestinal Effects: Nausea and/or vomiting; carboplatin is significantly less emetogenic than cisplatin. However, patients previously treated with emetogenic agents, especially cisplatin, appear to be more prone to vomiting. Less frequent effects are abdominal pain, cramps, constipation, diarrhea, anorexia, and mucositis (i.e., oral ulceration).

Neurological Effects: Carboplatin produced significantly fewer and less severe neurological effects than cisplatin. Neurotoxicity associated with carboplatin is usually characterized by peripheral neuropathy, which is generally sensory in nature (e.g., paresthesia, decreased deep tendon reflexes). Carboplatin-induced peripheral neuropathy appears to be more common in patients older than 65 years old than in younger adults. It also appears to be cumulative, occurring most commonly in patients receiving prolonged therapy and/or those who have received prior cisplatin therapy; in some cases, neurotoxicity may be a delayed effect of cisplatin rather than secondary to carboplatin. Dysgeusia has been reported very rarely. Central nervous system symptoms have been reported in 5% of patients and appeared to be most often related to antiemetic use.

Sensory Effects: Clinical ototoxicity and other sensory abnormalities such as visual disturbances and change in taste were reported in only 1% of patients. Ototoxicity may be dose-limiting at carboplatin doses of ≥2 g/m^2 and may manifest as tinnitus. Hearing loss has occurred in pediatric patients receiving carboplatin at higher than recommended doses in combination with other ototoxic agents. Visual abnormalities and loss of vision have been rarely reported; improvement and/or total recovery of vision occurred within weeks after carboplatin discontinuation.

Nephrologic Effects: Carboplatin's nephrotoxic effects are less common and less severe than with cisplatin. Concomitant IV hydration and diuresis are generally not needed with carboplatin therapy. Mild and transient elevations of serum creatinine (6%) and blood urea nitrogen (14%) concentrations are uncommon. Most of these reported abnormalities have been mild and about half of them were reversible. Increases in uric acid have been reported. Acute renal failure and hemolytic uremic syndrome have occurred rarely. Risk and severity of nephrotoxicity were increased with high dose carboplatin regimen, especially when given concurrently with other nephrotoxic chemotherapeutic agents.

Hepatic Effects: Mild and usually transient elevations of serum alkaline phosphatase, aspartate aminotransferase, or bilirubin concentrations have been reported. These abnormalities have generally been mild and reversible in about half of the cases, although the role of metastatic liver tumor may complicate the assessment in many patients. Severe abnormalities of liver function tests occurred in a few patients at carboplatin doses of more than 4 times the recommended dose.

Metabolic Effects: Carboplatin may cause electrolyte abnormalities, principally hyponatremia, hypokalemia, hypocalcemia, and/or hypomagnesemia. Such electrolyte changes are usually not symptomatic and do not require administration of supplemental electrolytes. Dehydration has also been reported.

Hypersensitivity: Anaphylaxis, angioedema, and anaphylactoid reactions have been reported (see **Boxed Warnings**). Rash, perioral tingling, urticaria, erythema, pruritus, bronchospasm, facial edema, hypotension, and hypoxia have occurred within a few minutes after IV administration of carboplatin in patients who have previously received a platinum-containing antineoplastic agent. Exfoliative dermatitis, tachycardia, wheezing, and facial flushing have been reported rarely. In addition, some reactions may be caused by mannitol rather than by carboplatin.

Cardiovascular Effects: Although not attributed to antineoplastic therapy, adverse cardiovascular effects including cardiac failure, embolism, ischemic coronary artery disorders (e.g., myocardial infarction, cardiac arrest, angina, myocardial ischemia), and cerebrovascular accident have been reported. Fatalities associated with cardiovascular events occurred in less than 1% of patients. Hypertension has also been reported.

Respiratory Effects: Pulmonary fibrosis, manifested by chest tightness and dyspnea, has been reported very rarely. This should be considered if a pulmonary hypersensitivity state is excluded.

Local Effects: Injection site reactions, including redness, swelling, pain and extravasation have been reported. Necrosis associated with extravasation has also been reported.

Others: Pain and asthenia were the most frequently reported miscellaneous adverse effects; they were most likely related to tumor size and anemia. Alopecia and influenza-like syndrome were rarely reported. Malaise has also been reported. Myalgias/arthralgias were reported in patients receiving carboplatin with paclitaxel; these effects were cumulative with repeated cycles.

OVERDOSE AND TREATMENT
Limited information is available on the acute toxicity of carboplatin. Overdosage of the drug would produce expected complications secondary to bone marrow suppression and/or hepatotoxicity. In addition, typical nonhematologic toxicity associated with platinum-containing antineoplastic agents (e.g., nephrotoxicity, neurotoxicity, ototoxicity) would be expected to become prominent with carboplatin overdosage. Death may also follow.

Currently, there is no specific antidote for carboplatin overdose. Management of overdose consists principally in discontinuance of the drug and initiation of supportive measures for the type of toxicity observed. The use of colony-stimulating factors (CSFs), platelet transfusions, and/or red blood cell transfusions should be considered in patients experiencing substantial myelosuppression.

Although carboplatin is removed by hemodialysis, it is not known whether this procedure would enhance elimination of the drug following overdosage. Furthermore, hemodialysis is only effective up to 3 hours after administration because of the rapid and extensive binding of platinum to plasma proteins. Plasmapheresis has been used effectively in the management of cisplatin overdosage, and the possibility that it may be useful in the management of massive carboplatin overdosage should be considered.

STORAGE CONDITIONS
Store the vial in the original carton at temperatures not exceeding 30°C.
Do not refrigerate. Protect from light and free from contact with metals.

AVAILABILITY
Biovinate 150 mg Solution for Infusion - Amber glass vial (Type 1) - 15 mL (Box of 1's) DR-XY41717
Biovinate 450 mg Solution for Infusion - Amber glass vial (Type 1) - 45 mL (Box of 1's) DR-XY41716

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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