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Appendix -- Characteristics of Available Antiretroviral Drugs

Nucleoside Analogue Reverse Transcriptase Inhibitors * **

Didanosine (dideoxyinosine) (ddI), VIDEX (R)

Preparations: Pediatric powder for oral solution (when reconstituted as solution containing antacid): 10 mg/mL; Chewable tablets with buffers: 25, 50, 100, and 150 mg; Buffered powder for oral solution: 100, 167, and 250 mg

Dosage

Neonatal dose (infants aged <90 days): 50 mg per m² of body surface area every 12 hours.

Pediatric usual dose: In combination with other antiretrovirals: 90 mg per m² of body surface area every 12 hours.

Pediatric dosage range: 90 to 150 mg per m² of body surface area every 12 hours. (Note: may need higher dose in patients with central nervous system disease.)

Adolescent/Adult dose: Body weight \geq 60 kg: 200 mg twice daily. Body weight <60 kg: 125 mg twice daily.

Major toxicities

Most frequent: Diarrhea, abdominal pain, nausea, and vomiting. Unusual (more severe): Peripheral neuropathy (dose related), electrolyte abnormalities, and hyperuricemia.

Uncommon: Pancreatitis (dose related, less common in children than adults), increased liver enzymes, and retinal depigmentation.

Drug interactions

- Possible decrease in absorption of ketoconazole, itraconazole, and dapsone; administer at least 2 hours before or 2 hours after ddI.
- Tetracycline and fluoroquinolone antibiotic absorption significantly decreased (chelation of drug by antacid in pediatric powder and tablets); administer 2 hours before or 2 hours after ddI.

- Concomitant administration of ddI and delavirdine may decrease the absorption of these drugs; separate dosing by at least 2 hours.
- Administration with protease inhibitors: indinavir should be administered at least 1 hour before or after ddI on an empty stomach. Ritonavir should be administered at least 2 hours before or after ddI.

Special instructions

- ddI formulation contains buffering agents or antacids.
- Food decreases absorption; administer ddI on an empty stomach (1 hour before or 2 hours after a meal). Further evaluation in children regarding administration with meals is under study.
- For oral solution: shake well and keep refrigerated; admixture is stable for 30 days.
- When administering chewable tablets, at least two tablets should be administered to ensure adequate buffering capacity (e.g., if the child's dose is 50 mg, administer two 25-mg tablets and not one 50-mg tablet).

Lamivudine (3TC), EPIVIR (R)

Preparations: Solution: 10 mg/mL; Tablets: 150 mg

Dosage

Neonatal dose (infants aged <30 days): 2 mg per kg of body weight twice daily.

Pediatric dose: 4 mg per kg of body weight twice daily. Adolescent/Adult dose: Body weight ≥ 50 kg: 150 mg twice daily. Body weight <50 kg: 2 mg per kg body weight twice daily.

Major toxicities

Most frequent: Headache, fatigue, nausea, diarrhea, skin rash, and abdominal pain.

Unusual (more severe): Pancreatitis (primarily seen in children with advanced HIV infection receiving multiple other medications), peripheral neuropathy, decreased neutrophil count, and increased liver enzymes.

Drug interactions

- Trimethoprim/sulfamethoxazole (TMP/SMX) increases 3TC blood levels (possibly competes for renal tubular secretion); unknown significance.
- When used with zidovudine (ZDV) may prevent emergence of ZDV resistance, and for ZDV-resistant virus, reversion to phenotypic ZDV sensitivity may be observed.

Special instructions

- Can be administered with food.
- For oral solution: store at room temperature.

- Decrease dosage in patients with impaired renal function.

Stavudine (d4T), ZERIT (R)

Preparations: Solution: 1 mg/mL; Capsules: 15, 20, 30, and 40 mg

Dosage

Neonatal dose: Under evaluation in Pediatric AIDS Clinical Trial Group protocol 332.

Pediatric dose: 1 mg per kg of body weight every 12 hours (up to weight of 30 kg).

Adolescent/Adult dose: Body weight ≥ 60 kg: 40 mg twice daily. Body weight < 60 kg: 30 mg twice daily.

Major toxicities

Most frequent: Headache, gastrointestinal disturbances, and skin rashes.

Uncommon (more severe): Peripheral neuropathy and pancreatitis. Other: Increased liver enzymes.

Drug interactions

- Drugs that decrease renal function could decrease clearance.
- Should not be administered in combination with zidovudine (poor antiretroviral effect).

Special instructions

- Can be administered with food.
- Need to decrease dose in patients with renal impairment.
- For oral solution: shake well and keep refrigerated; solution stable for 30 days.

Zalcitabine (ddC), HIVID (R)

Preparations: Syrup: 0.1 mg/mL (investigational); Tablets: 0.375 and 0.75 mg

Dosage

Neonatal dose: Unknown. Pediatric usual dose: 0.01 mg per kg of body weight every 8 hours. Pediatric dosage range: 0.005 to 0.01 mg per kg of body weight every 8 hours.

Adolescent/Adult dose: 0.75 mg three times a day.

Major toxicities

Most frequent: Headache, gastrointestinal disturbances, and malaise. Unusual (more severe): Peripheral neuropathy, pancreatitis, hepatic toxicity, oral ulcers, esophageal ulcers, hematologic toxicity, and skin rashes.

Drug interactions

- Cimetidine, amphotericin, foscarnet, and aminoglycosides may decrease renal clearance of ddC.
- Antacids decrease absorption of ddC.
- Concomitant use with ddI is not recommended because of the increased risk of peripheral neuropathy.
- Intravenous pentamidine increases the risk for pancreatitis; do not use concurrently.

Special instructions

- Administer on an empty stomach (1 hour before or 2 hours after a meal).
- Decrease dosage in patients with impaired renal function.

Zidovudine (ZDV, AZT), RETROVIR (R)

Preparations: Syrup: 10 mg/mL; Capsules: 100 mg; Tablets: 300 mg; Concentrate for injection/for intravenous infusion: 10 mg/mL

Dosage

Dose for premature infants: (Standard neonatal dose may be excessive in premature infants.) Under study in Pediatric AIDS Clinical Trial Group protocol 331: 1.5 mg per kg of body weight every 12 hours from birth to 2 weeks of age; then increase to 2 mg per kg of body weight every 8 hours after 2 weeks of age.

Neonatal dose: Oral: 2 mg per kg of body weight every 6 hours. Intravenous: 1.5 mg per kg of body weight every 6 hours.

Pediatric usual dose: Oral: 160 mg per m² of body surface area every 8 hours. Intravenous (intermittent infusion): 120 mg per m² of body surface area every 6 hours. Intravenous (continuous infusion): 20 mg per m² of body surface area per hour.

Pediatric dosage range: 90 mg per m² of body surface area to 180 mg per m² of body surface area every 6-8 hours.

Adolescent/Adult dose: 200 mg three times a day or 300 mg twice daily.

Major toxicities

Most frequent: Hematologic toxicity, including granulocytopenia and anemia, and headache.

Unusual: Myopathy, myositis, and liver toxicity.

Drug interactions

- Increased toxicity may be observed with concomitant administration of the following drugs (therefore, more intensive toxicity monitoring may be warranted): ganciclovir, interferon-alpha, TMP/SMX, acyclovir, and other drugs that can be associated with bone marrow suppression.

- The following drugs may increase ZDV concentration (and therefore potential toxicity): probenecid, atovaquone, methadone, valproic acid, and fluconazole.
- Decreased renal clearance may be observed with co-administration of cimetidine (may be significant in patients with renal impairment).
- ZDV metabolism may be increased with co-administration of rifampin and rifabutin (clinical significance unknown); clarithromycin may decrease concentrations of ZDV probably by interfering with absorption (preferably administer 4 hours apart).
- Ribavirin decreases the intracellular phosphorylation of ZDV (conversion to active metabolite).
- Phenytoin concentrations may increase or decrease.
- Should not be administered in combination with d4T (poor antiretroviral effect).

Special instructions

- Can be administered with food (although the manufacturer recommends administration 30 minutes before or 1 hour after a meal).
- Decrease dosage in patients with severe renal impairment.
- Substantial granulocytopenia or anemia may necessitate interruption of therapy until marrow recovery is observed; use of erythropoietin, filgrastim, or reduced ZDV dosage may be necessary in some patients.
- Reduced dosage may be indicated in patients with substantial hepatic dysfunction.
- Infuse intravenous loading dose or intermittent infusion dose over 1 hour.
- For intravenous solution: dilute with 5% dextrose injection solution to concentration ≤ 4 mg/mL; refrigerated diluted solution is stable for 24 hours.
- Some experts in pediatric HIV infection use a dose of 180 mg per m² of body surface area every 12 hours when using in drug combinations with other antiretroviral compounds, but data on this dosing in children is limited.

Non-nucleoside Reverse Transcriptase Inhibitors* **

Delavirdine (DLV), RESCRIPTOR (R)

Preparations: Tablets: 100 mg

Dosage

Neonatal dose: Unknown. Pediatric dose: Unknown. Adolescent/Adult dose: 400 mg three times a day.

Major toxicities

Most frequent: Headache, fatigue, gastrointestinal complaints, and rash (may be severe).

Drug interactions

- Metabolized in part by hepatic cytochrome P450 3A (CYP3A). There could potentially be multiple drug interactions. ***
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- DLV decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. DLV is not recommended for concurrent use with antihistamines (e.g., astemizole or terfenadine); sedative-hypnotics (e.g., alprazolam, midazolam, or triazolam); calcium channel blockers (e.g., nifedipine); ergot alkaloid derivatives; amphetamines; cisapride; or warfarin.
- DLV clearance is increased, resulting in substantially reduced concentrations of DLV, with concurrent use of rifabutin, rifampin, or anticonvulsants (e.g., phenytoin, carbamazepine, or phenobarbital). Concurrent use is not recommended.
- Absorption of DLV is decreased if given with antacids or histamine₂ receptor antagonists.
- Increased trough concentrations of DLV if given with ketoconazole or fluoxetine; increased levels of both drugs if DLV is given with clarithromycin.
- DLV increases levels of dapsone and quinidine.
- Administration with protease inhibitors: decreases metabolism of saquinavir and indinavir, resulting in a significant increase in saquinavir and indinavir concentrations and a slight decrease in DLV concentrations.

Special instructions

- Can be administered with food.
- Should be taken 1 hour before or 1 hour after ddI or antacids.
- Tablets can be dissolved in water and the resulting dispersion taken promptly.

Nevirapine (NVP), VIRAMUNE (R)

Preparations: Suspension: 10 mg/mL (investigational); Tablets: 200 mg

Dosage

Neonatal dose (through age 3 months): Under study in Pediatric AIDS Clinical Trial Group protocol 356: 5 mg per kg of body weight once daily for 14 days, followed by 120 mg per m² of body surface area every 12 hours for 14 days, followed by 200 mg per m² of body surface area every 12 hours.

Pediatric dose: 120 to 200 mg per m² of body surface area every 12 hours. Note: Initiate therapy with 120 mg per m² of body surface area administered once daily for 14 days. Increase to full dose administered every 12 hours if there are no rash or other untoward effects.

Adolescent/Adult dose: 200 mg every 12 hours. Note: Initiate therapy at half dose for the first 14 days.

Increase to full dose if there is no rash or other untoward effects.

Major toxicities

Most frequent: Skin rash (some severe and life-threatening, including Stevens-Johnson syndrome), sedative effect, headache, diarrhea, and nausea.

Unusual: Elevated liver enzymes and, rarely, hepatitis.

Drug interactions

- Induces hepatic cytochrome P450 3A (CYP3A); autoinduction of metabolism occurs in 2-4 weeks with a 1.5-fold to twofold increase in clearance. There could potentially be multiple drug interactions. ***
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Drugs having suspected interactions and should be used only with careful monitoring: rifampin and rifabutin; oral contraceptives (alternative or additional methods of birth control should be used if co-administering with hormonal methods of birth control); sedative- hypnotics (e.g., triazolam or midazolam); oral anticoagulants; digoxin; phenytoin; or theophylline.
- Administration with protease inhibitors: indinavir and saquinavir concentrations are decreased significantly, and ritonavir concentration may be decreased. Whether increased doses of protease inhibitors are needed is unknown.

Special instructions

- Can be administered with food.
- May be administered concurrently with ddI.
- NVP-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase dose until rash resolves. NVP should be discontinued immediately in patients who develop severe rash or a rash accompanied by constitutional symptoms (i.e., fever, oral lesions, conjunctivitis, or blistering).
- For investigational suspension: Must be shaken well; store at room temperature.

Protease Inhibitors* ** *****

Indinavir , CRIXIVAN (R)

Preparations: Capsules: 200 and 400 mg

Dosage

Neonatal Dose: Unknown. Due to side effect of hyperbilirubinemia, should not be given to neonates until further information is available.

Pediatric Dose: Under study in clinical trials: 500 mg per m² of body surface area every 8 hours.

Adolescent/Adult dose: 800 mg every 8 hours.

Major toxicities

Most frequent: Nausea, abdominal pain, headache, metallic taste, dizziness, and asymptomatic hyperbilirubinemia (10%).

Unusual (more severe): Nephrolithiasis (4%) and exacerbation of chronic liver disease.

Rare: Spontaneous bleeding episodes in hemophiliacs, hyperglycemia, keto-acidosis, diabetes, and hemolytic anemia.

Drug interactions

- Cytochrome P450 3A4 (CYP3A4) responsible for metabolism. There could potentially be multiple drug interactions. ***
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Indinavir decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. Indinavir is not recommended for concurrent use with antihistamines (e.g., astemizole or terfenadine); cisapride; ergot alkaloid derivatives; or sedative- hypnotics (e.g., triazolam or midazolam).
- Indinavir levels are significantly reduced with concurrent use of rifampin. Concurrent use is not recommended.
- Rifabutin concentrations are increased, therefore a dose reduction of rifabutin to half the usual daily dose is recommended.
- Ketoconazole and itraconazole cause an increase in indinavir concentrations (consider reducing adolescent/adult indinavir dose to 600 mg every 8 hours).
- Co-administration of clarithromycin increases serum concentration of both drugs (dosing modification not needed).
- Co-administration of nevirapine may decrease indinavir serum concentration.
- Administration with other protease inhibitors: co-administration with nelfinavir increases concentration of both drugs; co-administration with saquinavir increases concentration of saquinavir.

Special instructions

- Administer on an empty stomach 1 hour before or 2 hours after a meal (or can take with a light meal).
- Adequate hydration required to minimize risk of nephrolithiasis (at least 48 oz of fluid daily in adult patients).
- If co-administered with ddI, give at least 1 hour apart on an empty stomach.

- Decrease dose in patients with hepatic insufficiency.
- Capsules are sensitive to moisture and should be stored in original container with desiccant.

Nelfinavir , VIRACEPT (R)

Preparations: Powder for oral suspension: 50 mg per 1 level gram scoopful (200 mg per 1 level teaspoon); Tablets: 250 mg tablet

Dosage

Neonatal dose: Under study in Pediatric AIDS Clinical Trial Group protocol 353: 10 mg per kg of body weight three times a day. (Note: no preliminary data available, investigational.)

Pediatric dose: 20 to 30 mg per kg of body weight three times a day. Adolescent/Adult dose: 750 mg three times a day.

Major toxicities

Most frequent: Diarrhea. Less common: Asthenia, abdominal pain, rash, and exacerbation of chronic liver disease.

Rare: Spontaneous bleeding episodes in hemophiliacs, hyperglycemia, keto-acidosis, and diabetes.

Drug interactions

- Nelfinavir is in part metabolized by cytochrome P450 3A4 (CYP3A4). There could potentially be multiple drug interactions. ***
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Nelfinavir decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. Nelfinavir is not recommended for concurrent use with antihistamines (e.g., astemizole or terfenadine); cisapride; ergot alkaloid derivatives; certain cardiac drugs (e.g., quinidine or amiodarone); or sedative-hypnotics (e.g., triazolam or midazolam).
- Nelfinavir levels are greatly reduced with concurrent use of rifampin. Concurrent use is not recommended.
- Rifabutin causes less decline in nelfinavir concentrations; if co-administered with nelfinavir, rifabutin should be reduced to one half the usual dose.
- Estradiol levels are reduced by nelfinavir, and alternative or additional methods of birth control should be used if co-administering with hormonal methods of birth control.
- Co-administration with delavirdine (DLV) increases nelfinavir concentrations twofold and decreases DLV concentrations by 50%. There are no data on co-administration with nevirapine, but some experts use higher doses of nelfinavir if used in combination with nevirapine.
- Administration with other protease inhibitors: co-administration with indinavir increases

concentration of both drugs; co-administration with saquinavir increases concentration of saquinavir with little change in nelfinavir concentration; co-administration with ritonavir increases concentration of nelfinavir without change in ritonavir concentration.

Special instructions

- Administer with meal or light snack.
- If co-administered with ddI, nelfinavir should be administered 2 hours before or 1 hour after ddI.
- For oral solution: powder may be mixed with water, milk, pudding, ice cream, or formula (for up to 6 hours).
- Do not mix with any acidic food or juice because of resulting poor taste.
- Do not add water to bottles of oral powder; a special scoop is provided with oral powder for measuring purposes.
- Tablets readily dissolve in water and produce a dispersion that can be mixed with milk or chocolate milk; tablets also can be crushed and administered with pudding.

Ritonavir , NORVIR (R)

Preparations: Oral solution: 80 mg/mL; Capsules: 100 mg

Dosage

Neonatal dose: Under study in Pediatric AIDS Clinical Trial Group protocol 354 (single dose pharmacokinetics).

Pediatric usual dose: 400 mg per m² of body surface area every 12 hours. To minimize nausea/vomiting, initiate therapy starting at 250 mg per m² of body surface area every 12 hours and increase stepwise to full dose over 5 days as tolerated.

Pediatric dosage range: 350 to 400 mg per m² of body surface area every 12 hours.

Adolescent/Adult dose: 600 mg twice daily. To minimize nausea/vomiting, initiate therapy starting at 300 mg twice daily and increase stepwise to full dose over 5 days as tolerated.

Major toxicities

Most frequent: Nausea, vomiting, diarrhea, headache, abdominal pain, and anorexia.

Less common: Circumoral paresthesias and increase in liver enzymes. Rare: Spontaneous bleeding episodes in hemophiliacs, pancreatitis, increased levels of triglycerides and cholesterol, hyperglycemia, ketoacidosis, diabetes, and hepatitis.

Drug interactions

- Ritonavir is extensively metabolized by hepatic cytochrome P450 3A (CYP3A). There could potentially be multiple drug interactions. ***

- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Not recommended for concurrent use with analgesics (e.g., meperidine, piroxicam, or propoxyphene); antihistamines (e.g., astemizole or terfenadine); certain cardiac drugs (e.g., amiodarone, bepridil hydrochloride, encainide hydrochloride, flecainide acetate, propafenone, or quinidine); ergot alkaloid derivatives; cisapride; sedative-hypnotics (e.g., alprazolam, clorazepate, diazepam, estazolam, flurazepam hydrochloride, midazolam, triazolam, or zolpidem tartrate); certain psychotropic drugs (e.g., bupropion hydrochloride, clozapine, or pimozide); rifampin; or rifabutin.
- Estradiol levels are reduced by ritonavir, and alternative or additional methods of birth control should be used if co-administering with hormonal methods of birth control.
- Ritonavir increases metabolism of theophylline (levels should be monitored, and dose may need to be increased).
- Ritonavir increases levels of clarithromycin (dose adjustment may be necessary in patients with impaired renal function); desipramine (dose adjustment may be necessary); and warfarin (monitoring of anticoagulant effect is necessary).
- Ritonavir may increase or decrease digoxin levels (monitoring of levels is recommended).
- Drugs that increase CYP3A activity can lead to increased clearance and therefore lower levels of ritonavir include carbamazepine, dexamethasone, phenobarbital, and phenytoin (anticonvulsant levels should be monitored because ritonavir can affect the metabolism of these drugs as well).
- Administration with other protease inhibitors: co-administration with saquinavir and nelfinavir increases concentration of these drugs with little change in ritonavir concentration.

Special instructions

- Administration with food increases absorption.
- If ritonavir is prescribed with ddI, there should be 2 hours between taking each of the drugs.
- Oral solution must be kept refrigerated and stored in original container; can be kept at room temperature if used within 30 days.
- To minimize nausea, therapy should be initiated at a low dose and increased to full dose over 5 days as tolerated.
- Techniques to increase tolerance in children: a) mixing oral solution with milk, chocolate milk, or vanilla or chocolate pudding or ice cream; b) dulling the taste buds before administration by chewing ice, giving popsicles or spoonfuls of partially frozen orange or grape juice concentrates; c) coating the mouth by giving peanut butter to eat before the dose; or d) administration of strong-tasting foods such as maple syrup, cheese, or strong-flavored chewing gum immediately after dose.

Saquinavir , INVIRASE (TM) (TM) (hard gel capsule) and FORTOVASE (TM) (soft gel capsule)

Preparations: Hard gel capsules: 200 mg; Soft gel capsules: 200 mg

Dosage

Neonatal dose: Unknown. Pediatric dose: Unknown (will be studied in Pediatric AIDS Clinical Trials Group protocol 397).

Adolescent/Adult dose: Hard gel capsules: 600 mg three times a day; Soft gel capsules: 1200 mg three times a day.

Major toxicities

Most frequent: Diarrhea, abdominal discomfort, headache, nausea, paresthesias, and skin rash.

Less common: Exacerbation of chronic liver disease. Rare: Spontaneous bleeding episodes in hemophiliacs, hyperglycemia, keto-acidosis, and diabetes.

Drug interactions

- Saquinavir is metabolized by the cytochrome P450 3A4 (CYP 3A4) system in the liver, and there are numerous potential drug interactions. ***
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Saquinavir decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. Saquinavir is not recommended for concurrent use with antihistamines (e.g., astemizole or terfenadine); cisapride; ergot alkaloid derivatives, or sedative- hypnotics (e.g., midazolam or triazolam).
- Saquinavir levels are significantly reduced with concurrent use of rifampin (decreases saquinavir levels by 80%), rifabutin (decreases saquinavir levels by 40%), and nevirapine (decreases saquinavir levels by 25%).
- Saquinavir levels are decreased by carbamazepine, dexamethasone, phenobarbital, and phenytoin.
- Saquinavir levels are increased by delvirdine and ketoconazole.
- Saquinavir may increase levels of calcium channel blockers, clindamycin, dapsone, and quinidine. If used concurrently, patients should be closely monitored for toxicity.
- Administration with other protease inhibitors: co-administration with indinavir, ritonavir, or nelfinavir increases concentration of saquinavir with little change in concentration of the other drug.

Special instructions

- Administer within 2 hours of a full meal to increase absorption.
- Concurrent administration of grapefruit juice increases saquinavir concentration.
- Sun exposure can cause photosensitivity reactions, therefore sunscreen or protective clothing is recommended.

Information in this appendix is not all inclusive. Complete and detailed prescribing and toxicity information on these drugs is available from the drug companies and should be reviewed by the health-care provider before prescribing these drugs.

** Adolescents in early puberty (Tanner I-II) should be dosed using pediatric schedules, whereas those in late puberty (Tanner Stage V) should be dosed using adult schedules. Youth who are in the midst of their growth spurt (Tanner III females and Tanner IV males) should be closely monitored for medication efficacy and toxicity when choosing adult or pediatric dosing guidelines.

*** Drugs metabolized by the hepatic cytochrome P450 enzyme system have the potential for significant interactions with multiple drugs, some of which may be life-threatening. These interactions are outlined in detail in prescribing information available from the drug companies. These interactions will not be reiterated in this document, and the health-care provider should review those documents for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be carefully reviewed for potential drug interactions.

**** Data in children is limited, and doses may change as more information is obtained about the pharmacokinetics of these drugs in children.

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