

IMPORTANT PRESCRIBING INFORMATION

September 2010

Dear Healthcare Provider:

Genentech, Inc. would like to inform you of an important update to the Valcyte® (valganciclovir hydrochloride) tablets and Valcyte® (valganciclovir hydrochloride) for oral solution Prescribing Information (PI) that pertains to pediatric dosing of Valcyte. Based upon an FDA analysis of the pediatric dosing algorithm, the *Dosing and Administration* section of the PI has been updated to include an upper limit on calculated creatinine clearance. **The change is being made to help avoid the potential of ganciclovir overexposure in pediatric patients with low body weight, low body surface area, and very low serum creatinine.**

When calculating the pediatric dose, as stated in the *Dosage and Administration* section of the PI, a maximum creatinine clearance value of 150 mL/min/1.73m² should be used, even when the calculated Schwartz creatinine clearance exceeds 150 mL/min/1.73m². All calculated doses should be rounded to the nearest 25 mg increment for the actual deliverable dose. If the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered. The revised language in *Section 2.3 Pediatric Patients* is as follows (new language underlined):

Prevention of CMV Disease: For pediatric patients 4 months to 16 years of age who have received a kidney or heart transplant, the recommended once daily dose of Valcyte starting within 10 days of transplantation until 100 days post-transplantation is based on body surface area (BSA) and creatinine clearance (CrCl) derived from a modified Schwartz formula, and is calculated using the equation below:

Pediatric Dose (mg) = 7 × BSA × CrCl (calculated using a modified Schwartz formula). If the calculated Schwartz creatinine clearance exceeds 150 mL/min/1.73m², then a maximum value of 150 mL/min/1.73m² should be used in the equation.

$$\text{Mosteller BSA (m}^2\text{)} = \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}}$$

$$\text{Schwartz Creatinine Clearance (mL/min/1.73m}^2\text{)} = \frac{k \times \text{Height (cm)}}{\text{Serum Creatinine (mg/dL)}}$$

where k =

0.45 for patients aged 4 months to <1 year,

0.45 for patients aged 1 to <2 years (note k value is 0.45 instead of the typical value of 0.55),

0.55 for boys aged 2 to <13 years and girls aged 2 to 16 years, and

0.7 for boys aged 13 to 16 years.

Valcyte for oral solution is the preferred formulation in pediatric patients since it provides the ability to administer a dose calculated according to the formula above; however, Valcyte tablets may be used if the calculated doses are within 10% of available tablet strength (450 mg).

We encourage you to become familiar with this revision. We have enclosed the revised Valcyte PI for your review. Should you need any further information on the dosing of Valcyte in high-risk pediatric kidney or heart transplant patients aged 4 months to 16 years, please contact our Medical Communications Department at 1-800-821-8590 or at the "Contact Us" section of the Genentech corporate website.

Healthcare professionals should report any serious adverse events suspected to be associated with the use of Valcyte to Genentech at 1-888-835-2555. Alternatively, this information may also be reported to the FDA's MedWatch reporting system by phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178), online (<https://www.accessdata.fda.gov/scripts/medwatch/>) or by mail, using the MedWatch form FDA 3500, to the FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787.

Please see reverse and accompanying full Prescribing Information, including Boxed WARNING, for important general dosing, product, and Safety Information for Valcyte.

INDICATION

Pediatric Patients: Valcyte® (valganciclovir hydrochloride) for oral solution and tablets are indicated for the prevention of CMV disease in kidney or heart transplant patients (4 months to 16 years of age) at high risk.

Limitations of Use:

- Valcyte is not indicated for use in either adult or pediatric liver transplant patients
- The safety and efficacy of Valcyte have not been established for:
 - Prevention of CMV disease in solid organ transplants other than those indicated
 - Prevention of CMV disease in pediatric solid organ transplant patients <4 months of age
 - Treatment of congenital CMV disease

IMPORTANT DOSING INFORMATION

- Valcyte should be taken with food
- The bioavailability of ganciclovir from Valcyte is significantly higher than from ganciclovir capsules. Therefore, Valcyte tablets cannot be substituted for ganciclovir capsules on a one-to-one basis
- Valcyte tablets should not be broken or crushed
- Valcyte for oral solution must be prepared by the pharmacist prior to dispensing to the patient

IMPORTANT SAFETY INFORMATION

WARNING: HEMATOLOGIC TOXICITY, CARCINOGENICITY, TERATOGENICITY, AND IMPAIRMENT OF FERTILITY

- **Clinical toxicity of Valcyte, which is metabolized to ganciclovir, includes granulocytopenia, anemia, and thrombocytopenia**
- **In animal studies, ganciclovir was carcinogenic, teratogenic, and caused aspermatogenesis**

CONTRAINDICATION

Valcyte is contraindicated in patients who have had a demonstrated clinically significant hypersensitivity reaction (eg, anaphylaxis) to valganciclovir, ganciclovir, or any component of the formulation.

WARNINGS AND PRECAUTIONS

- Severe leukopenia, neutropenia, anemia, thrombocytopenia, pancytopenia, bone marrow aplasia, and aplastic anemia have been observed in patients treated with Valcyte or ganciclovir
- **Do not administer if the absolute neutrophil count is <500 cells/ μ L, the platelet count is <25,000/ μ L, or the hemoglobin is <8 g/dL**
- Use with caution in patients with pre-existing cytopenias, or who have received or who are receiving myelosuppressive drugs or irradiation. Cytopenia may occur at any time during treatment and may worsen with continued dosing. Cell counts usually begin to recover within 3 to 7 days after discontinuing drug
- Advise women of childbearing potential to use effective contraception during treatment and for at least 30 days following treatment with Valcyte. Advise men to practice barrier contraception during and for at least 90 days following treatment with Valcyte
- Acute renal failure may occur in:
 - Elderly patients with or without reduced renal function. Caution should be exercised when administering Valcyte to geriatric patients and dosage reduction is recommended for those with impaired renal function
 - Patients receiving potential nephrotoxic drugs. Caution should be exercised when administering Valcyte to patients receiving potential nephrotoxic drugs
 - Patients without adequate hydration. Adequate hydration should be maintained for all patients

ADVERSE REACTIONS

Pediatric Patients: The most common adverse events and laboratory abnormalities reported in >10% of solid organ transplant recipients treated with Valcyte for oral solution or tablets are diarrhea, pyrexia, hypertension, upper respiratory tract infection, vomiting, anemia, neutropenia, constipation, nausea, and cough.

Please see accompanying full Prescribing Information, including Boxed WARNING, for additional Important Safety Information.

Sincerely,



Hal Barron, MD
Executive Vice President
Head, Global Development
Chief Medical Officer