Roche

Pharmaceuticals

November 2000

Dear Doctor,

Roche Laboratories would like to inform you of important safety-related changes to the prescribing information concerning the use of Xeloda in patients with renal impairment at baseline. A copy of the complete revised labeling is included with this letter.

A recently completed clinical pharmacology study evaluated the effects of renal impairment in patients with cancer on the pharmacokinetics of Xeloda. Based on this study and a subsequent safety analysis of the clinical database, the Xeloda labeling has been revised to contraindicate the use of Xeloda in patients with severe renal impairment (calculated creatinine clearance below 30 mL/min). In addition, for patients with moderate renal impairment (calculated creatinine clearance 30-50 mL/min) at baseline, the starting dose of Xeloda should be reduced to 75% of the recommended starting dose (i.e., from 2500 mg/m^2/day for 14 days followed by a week rest to 1900 mg/m^2/day for 14 days followed by a week rest). Patients with mild renal impairment should be treated with the standard recommended dose of Xeloda with close monitoring. The creatinine clearance was calculated according to the formula of Cockroft and Gault in the majority of patients, and not measured via a 24-hour urine collection.

The analyses of clinical pharmacology study and overall clinical safety data indicated that:

- Patients with severe renal impairment (calculated CrCl <30 mL/min) had a high rate of grade 3-4 and serious adverse events and shorter treatment duration.
- Patients with moderate renal impairment (calculated CrCl 30-50 mL/min) had a greater overall incidence of treatment-related grade 3-4 and serious adverse events relative to patients with normal renal function. The increased incidence of undesirable effects did not impact negatively on the overall benefit for these patients when treated with Xeloda since the tumor response rate was maintained.
- Patients with mild renal impairment (calculated CrCl 51-80 mL/min), although experiencing slightly more serious adverse events and withdrawals due to adverse events than the patients with normal renal function, maintained their overall benefit/risk ratio.

The following lists the labeling changes.

CONTRAINDICATIONS:

Xeloda is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min [Cockroft and Gault]).

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WARNINGS:
Renal Insufficiency: In patients with moderate renal impairment (creatinine clearance 30-50 mL/min [Cockroft and Gault]) at baseline, a dose reduction to 75% of the Xeloda starting dose is recommended. In patients with mild renal impairment (creatinine clearance 51-80 mL/min) no adjustment in starting dose is recommended. Careful monitoring and prompt treatment interruption is recommended if the patient develops a grade 2, 3, or 4 adverse event with subsequent dose adjustments as outlined in the table in DOSAGE AND ADMINISTRATION.

DOSAGE AND ADMINISTRATION/*Adjustment of Starting Dose in Special Population/ Renal Impairment*:
In patients with moderate renal impairment (creatinine clearance 30-50 mL/min [Cockroft and Gault, as shown below]) at baseline, a dose reduction to 75% of the Xeloda starting dose (from 2500 mg/m^2/day to 1900 mg/m^2/day) is recommended. In patients with mild renal impairment (creatinine clearance 51-80 mL/min) no adjustment in starting dose is recommended. Careful monitoring and prompt treatment interruption is recommended if the patient develops a grade 2, 3, or 4 adverse event with subsequent dose adjustments as outlined in the table above. Xeloda is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min [Cockroft and Gault]).

Cockroft and Gault Equation:

$$\text{Creatinine clearance for males} = \frac{(140 - \text{age [yrs]})\ (\text{body wt [kg]})}{(72)\ (\text{serum creatinine [mg/dL]})}$$

Creatinine clearance for females = 0.85 x male value

PATIENT PACKAGE INSERT/Who should not take Xeloda:

- Patients with severe renal impairment. Please inform your doctor if you know of any renal impairment that you may have. Your doctor may either prescribe a different drug or reduce the Xeloda dose.

Please see the accompanying full prescribing information.

Roche Laboratories is committed to providing you with the most up-to-date and accurate information regarding its products. Should you have any questions or require additional information, please contact Roche Professional Product Information at 1-800-526-6367.

Sincerely,

Ted P. Szatrowski, M.D.
Medical Director