DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

George B. Abercrombie
President & CEO
North American Pharmaceutical Operations
Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110

RE: NDA # 20-896
Xeloda® (capecitabine) Tablets
MACMIS ID# 11274

WARNING LETTER

Dear Mr. Abercrombie:

This Warning Letter objects to Hoffman-La Roche Inc. ("Roche")'s dissemination of a promotional professional sales aid and a patient-directed video[1] for Xeloda (capecitabine) Tablets. As part of its routine monitoring and surveillance program, the Food and Drug Administration ("FDA" or the "Agency")'s Division of Drug Marketing, Advertising, and Communications ("DDMAC") has reviewed the professional sales aid (18-039-111-201-0802) ("Sales Aid") and patient video "You and Your Xeloda Therapy" (18-029-111-136-0702) ("Video"), submitted to FDA on Form FDA 2253, and determined that they are in violation of the Federal Food, Drug, and Cosmetic Act (the "Act") and its implementing regulations. In addition, Roche representatives were observed disseminating the Sales Aid in the promotional exhibit area of the Twenty-Fifth Annual San Antonio Breast Cancer Symposium, held in San Antonio, Texas on December 11-14, 2002.

DDMAC has concluded that your Sales Aid is misleading because it fails to present risk information about Xeloda, which is associated with serious, potentially life-threatening risks. Your Video is misleading because it overstates the efficacy of Xeloda, minimizes the safety risks associated with the drug, and makes unsubstantiated superiority claims for Xeloda compared to other chemotherapy agents. Your Sales Aid and Video also omit material information about the limitations on the approved indications for Xeloda and therefore suggest uses for Xeloda as a cancer treatment that have not been shown to be safe and effective. Because these false or misleading claims and omissions have the potential to adversely affect the treatment of cancer patients, these promotional materials raise significant public health concerns.

[1] Roche distributes the video to healthcare professionals, who in turn provide it to patients.

Moreover, we remind you that DDMAC had previously objected, in an untitled letter dated January 9, 2002, to your dissemination of direct-to-consumer promotional materials for Xeloda that failed to present risk information about Xeloda, failed to appropriately communicate the indication for Xeloda, and made unsubstantiated efficacy claims. We are concerned that you are continuing to promote Xeloda in a way that fails to communicate its risks and that misrepresents its limited indications and limited proven efficacy.

I. Background

On April 30, 1998, April 30, 2001, and September 7, 2001, Xeloda was approved for certain limited indications in the treatment of colorectal cancer and breast cancer. Because Xeloda is associated with serious risks,[2] the approved product labeling ("PI") for Xeloda contains prominent warnings including a boxed warning that describes a potentially life-threatening drug interaction between Xeloda and the anticoagulant warfarin. The boxed warning states, in part:

> "Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking Xeloda concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. Postmarketing reports have shown clinically significant increases in prothrombin time (PT) and INR in patients who were stabilized on anticoagulants at the time Xeloda was introduced. These events occurred within several days and up to several months after initiating Xeloda therapy and, in a few cases, within one month after stopping Xeloda."

In its April 30, 2001, approval letter of the Supplemental New Drug Application ("SNDA"), FDA offered clear direction on how to present the proven safety profile of Xeloda in promotional materials, in direct and unequivocal language:

> "Furthermore, and as stated in the September 20, 2000 approvable letter, all promotional materials and activities must not present the differences in the safety profile between Xeloda and 5-FU/LV as an overall safety advantage for Xeloda. Any suggestions or implications that Xeloda is better tolerated or has fewer side effects overall would be misleading. Advertising must include the incidence of all grades and of all grade 3 and 4 adverse events in the two arms of the randomized trials. Presentation of trends in overall gastrointestinal toxicities in favor of Xeloda must be

[2] In addition to the boxed warning, the Warnings section of the Xeloda PI states that Xeloda can cause diarrhea, which can be serious, resulting in dehydration requiring aggressive therapy. The Precautions section of the PI states that treatment with Xeloda is associated with hand-and-foot syndrome, which can include numbness, tingling, swelling, and pain in the hands and/or feet, and in more serious cases, can affect the patient's ability to perform daily activities. In clinical trials reported in the Xeloda PI, over half of patients taking Xeloda experienced diarrhea and hand-and-foot syndrome. Other commonly reported adverse events associated with Xeloda are stomatitis, nausea, vomiting, and fatigue.

accompanied by the data that the incidence of grade 3 and 4 diarrhea, nausea and vomiting were similar between the arms."

Xeloda's PI states the indications for Xeloda as follows:

"XELODA is indicated as first-line treatment of patients with metastatic colorectal carcinoma **when treatment with fluoropyrimidine therapy alone is preferred. Combination chemotherapy has shown a survival benefit compared to 5-FU/LV alone. A survival benefit over 5-FU/LV has not been demonstrated with XELODA monotherapy. Use of XELODA instead of 5-FU/LV in combinations has not been adequately studied to assure safety or preservation of the survival advantage.**" [Emphasis added.]

"XELODA in combination with docetaxel is indicated for the treatment of patients with metastatic breast cancer **after failure of prior anthracycline-containing chemotherapy.**" [Emphasis added.]

"XELODA monotherapy is also indicated for the treatment of patients with metastatic breast cancer **resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated, eg, patients who have received cumulative doses of 400 mg/m^2 of doxorubicin or doxorubicin equivalents. Resistance is defined as progressive disease while on treatment, with or without an initial response, or relapse within 6 months of completing treatment with an anthracycline-containing adjuvant regimen.**" [Emphasis added.]

Significantly, in its April 30, 2001, approval letter, FDA informed Roche of the need for promotional materials to clearly communicate these limitations on Xeloda's indications. The letter also offered clear direction on how to present the proven efficacy profile of Xeloda in promotional materials (e.g., the importance of communicating the survival endpoints), especially as compared with other treatments. Specifically, the approval letter stated, in direct and unequivocal language:

"All promotional materials and activities regarding the efficacy or use of Xeloda for first-line metastatic colorectal cancer must include the entire language of the indication section in the approved product labeling."

"Similarly, when promoting the efficacy and use of Xeloda in metastatic colorectal cancer, all promotional materials and activities must include information on the endpoint of survival. Survival is the

primary endpoint of interest in first-line colorectal cancer and the primary basis of approval of this sNDA. Selective presentation of surrogate endpoints such as response rate and/or time to progression would be false and misleading. Moreover, minimization of the survival data could represent a public health and safety issue. In addition, please note that physicians and patients must be made aware that treatment exists that has demonstrated survival superior to the five-day regimen of 5-FU/LV. This information must be prominently presented in your promotional materials and activities."

II. Omission or Minimization of Important Risk Information and Misleading Comparative Safety and Tolerability Claims

Your Sales Aid and Video for Xeloda fail to properly communicate the safety and tolerability issues associated with Xeloda therapy, thereby overstating its safety profile.

A. Sales Aid

Your Sales Aid fails to provide <u>any</u> risk information about Xeloda. Your Sales Aid promotes the efficacy of Xeloda against a wide variety of cancer types, and thus suggests broad use of the drug, but fails to warn of the potentially fatal drug interaction with warfarin, as well as the other important safety and tolerability issues associated with Xeloda treatment.

B. Video

Your Video downplays the adverse events associated with Xeloda and makes unsubstantiated claims that Xeloda has a better safety and tolerability profile than other chemotherapy drugs. The Video is narrated by an oncology nurse ("Nurse") and features two patients taking Xeloda, a younger woman ("Female Patient") and an older man ("Male Patient"). Although the Video notes the common adverse events associated with taking Xeloda, the patient testimonials minimize their severity and importance. The Male Patient states that compared to other chemotherapy drugs, taking Xeloda is "duck soup." The Female Patient states that Xeloda, unlike other chemotherapy drugs, does not make you feel "too tired" or "too sick" to do your daily activities. We are unaware of any data to substantiate these superiority claims and, moreover, these claims are in stark contrast to the high incidence of reported adverse events with Xeloda that would make a patient feel tired and sick, such as diarrhea, nausea, vomiting, stomatitis, hand-and-foot syndrome, and fatigue.

The patient testimonials specifically downplay two very common and potentially serious adverse events associated with Xeloda, namely, diarrhea and hand-and-foot syndrome. The Warnings section of the PI describes diarrhea associated with Xeloda therapy as sometimes severe, resulting in dehydration requiring aggressive therapy.

The Male Patient, however, only describes having "some looseness of bowels, not quite diarrhea—what I call looseness of bowels." The Precautions section of the Xeloda PI states that the symptoms of hand-and-foot syndrome may range from numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort that does not disrupt a patient's normal activities to moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or to perform activities of daily living. The Female Patient, however, describes hand-and-foot syndrome as merely "… dryness of the palms of your hands and bottoms of the feet" and notes that her doctor "offered some suggestions for some lotions to use." Therefore, the testimonials promote the misleading message to patients that the adverse events described in the PI are more serious than those actually experienced by patients.

In addition to the unsupported tolerability claims discussed above, the Video makes misleading claims that Xeloda is safer and has fewer toxicities than intravenous (or "IV") chemotherapy drugs. The Video contains an animated depiction comparing Xeloda to IV chemotherapy drugs. The Nurse narrates as follows:

> "As you can see, IV drugs reach the tumor, but they also travel everywhere throughout the body. A challenge with IV delivery is giving a dose that's high enough to kill the cancer cells but not so high that it harms the patient. In contrast, Xeloda is inactive as a pill, and remains inactive initially after being swallowed. As it goes through the digestive system, Xeloda is absorbed into the bloodstream and travels throughout the body. When Xeloda comes in contact with a naturally occurring protein called thymidine phosphorylase, or TP, it is transformed into 5-FU, a powerful cell-killing drug."

The Video thus suggests that Xeloda is safer and less toxic than IV chemotherapy drugs because it is targeted to kill tumor cells and would not harm normal cells to the same extent. FDA is not aware of substantial evidence or substantial clinical experience showing Xeloda to be safer or less toxic than IV chemotherapy drugs.

III. Misleading Claims About Impact on Daily Activities and Comparative Efficacy to Other Chemotherapy Drugs

A. Video

Your Video misrepresents the typical patient experience while taking Xeloda, in particular, by minimizing the likely impact Xeloda will have on a patient's daily activities. In addition, the Video suggests that Xeloda is more effective than, to our knowledge, has been demonstrated by substantial evidence or substantial clinical experience.

Specifically, the testimonials in your Video imply that patients on Xeloda do not experience the adverse impact on their daily activities normally associated with chemotherapy. The Video presents the following misleading claims:

> "They [patients] have more time to do the things they want to do," *Nurse*
>
> "It gives me freedom, I feel stronger, I mean I go to the gym now—work out," *Male Patient*
>
> "I can do anything that I want to do… I can do all the daily things that sometimes when you are on other chemotherapy and you're out of the house and you're too tired or too sick, you can't clean your house… It's good to be empowered enough that you can do things on your own and be self-sufficient and not have to ask people to come help you," *Female Patient*

Although your "disclaimer" at the beginning of the Video states that the patients in the Video are describing their own experiences while on Xeloda and the viewer's experiences may be different, the Nurse follows up these patient testimonials by stating that these experiences "are not unusual," thus reinforcing the message that patients can expect this type of experience with Xeloda therapy. FDA is not aware of substantial evidence or substantial clinical experience to support the claims of improved functioning and strength, ability to resume all activities of daily living, ability to be "self-sufficient," and superiority over other chemotherapy agents with respect to these outcomes. Your claims can mislead patients about the benefits of treatment with Xeloda and its comparative benefits over other chemotherapy drugs with respect to how they will be able to function in their daily activities. To suggest that Xeloda patients will not feel "too tired or too sick" to do all of their daily activities is contrary to the high percentages of adverse events reported by patients in clinical trials, including hand-and-foot syndrome which, according to the Xeloda PI, in its more severe cases "causes the patient to be unable to work or perform activities of daily living."

Your Video also makes misleading claims that Xeloda more effectively targets cancer cells and therefore is more effective than IV chemotherapy drugs. The animated depiction comparing Xeloda to IV chemotherapy drugs notes that IV drugs reach the tumor, but also travel elsewhere throughout the body. In contrast, the Video notes the following about Xeloda:

> "When Xeloda comes in contact with a naturally occurring protein called thymidine phosphorylase, or TP, it is transformed into 5-FU, a powerful cell-killing drug. Since many tumors have a higher level of TP than normal tissue, they receive a higher concentration of 5-FU, which then acts against the cancer cells. Research has shown that Xeloda has a higher response rate than intravenous 5-FU in patients with colorectal cancer."

The Nurse concludes that Xeloda is "extremely effective." In totality, these claims misleadingly suggest that Xeloda, as an oral formulation, is more effective than intravenous chemotherapy drugs due to its selective distribution. FDA is not aware of substantial evidence or substantial clinical experience to support this comparative efficacy claim. Even more concerning, you use response rate to suggest Xeloda has superior efficacy over intravenous 5-FU and you fail to discuss the survival data. As the Agency clearly informed Roche in the approval letter for Xeloda discussed above, promotional material that selectively presents surrogate endpoints such as response rate, and fails to provide information on the endpoint of survival, is false or misleading.

IV. Omission of Material Facts About Approved Indications and Promotion for Uses Beyond Those Proven Safe and Effective

A. Sales Aid

The Sales Aid fails to convey the specific indications for Xeloda, and suggests that Xeloda is effective in the treatment of a broader range of cancer patients than has been proven safe and effective by substantial evidence or substantial clinical experience. The Sales Aid contains claims regarding the mechanism of action of Xeloda, including a prominently featured bar graph that depicts the distribution of thymidine phosphorylase (TP) in human normal and tumor tissues. This bar graph lists various tissue types, including colorectal, gastric, breast, cervical, uterine, ovarian, renal, bladder, thyroid, and liver. Additionally, presented immediately above the bar graph is the statement "Because TP activity is higher in most tumor tissue than in normal tissue, final conversion of capecitabine to 5-FU occurs preferentially in the tumor."

In this context, this presentation suggests that Xeloda is effective against gastric, cervical, uterine, ovarian, renal, bladder, thyroid, and liver cancers. FDA is not aware of substantial evidence or substantial clinical experience to support the claim that Xeloda is effective (or safe) for treating gastric, cervical, uterine, ovarian, renal, bladder, thyroid or liver cancer. In addition, a relationship between the mechanism of action of Xeloda, and clinical efficacy and safety outcomes has not been demonstrated by substantial evidence or substantial clinical experience. To suggest that Xeloda is effective against such a broad range of cancers based on the mechanism of action illustrated, without substantiating clinical evidence, is misleading and especially concerning because there are other available treatments with proven efficacy and established safety profiles and, in some cases, proven survival benefits, for these types of cancers.

Furthermore, as noted above, Xeloda's proven efficacy in the treatment of colorectal and breast cancer is limited, as reflected in its approved indications. However, your Sales Aid omits any information about the approved indications for Xeloda. Without this context, the presentation suggests that Xeloda is effective as first-line monotherapy for all colorectal and breast cancer patients. Patients with metastatic colorectal and metastatic breast cancers have available to them other approved therapies with a demonstrated survival benefit, including anthracycline combination

regimens. Xeloda offers minimal proven survival benefits in patients with newly-diagnosed metastatic colorectal or metastatic breast cancers and carries the potential for increased toxicity with its use. These important facts are not communicated in your Sales Aid.

B. Video

The Video also promotes Xeloda as an effective treatment for breast cancer and colorectal cancer, without communicating the limitations on its indication or its limited proven survival benefits. Specifically, the Video promotes that "Xeloda is used in the treatment of metastatic breast and metastatic colorectal cancers" and "In addition, your oncologist may combine other chemotherapy agents, such as Taxotere, with your Xeloda therapy." This misleadingly suggests that Xeloda can be used as first-line therapy in any patient with metastatic breast cancer or metastatic colorectal cancers, and that Xeloda can be used with Taxotere (docetaxel) and other chemotherapy agents as first line therapy for both metastatic breast cancer and metastatic colorectal cancers. Xeloda is not approved as first-line treatment for metastatic breast cancer. Xeloda is indicated in combination with Taxotere only for patients with metastatic breast cancer after they have failed prior anthracycline-containing chemotherapy. Similarly, Xeloda monotherapy has not demonstrated a survival benefit in metastatic colorectal cancer in contrast to existing combination treatments. This important information is not disclosed in your Video. Therefore, your Video fails to properly communicate Xeloda's approved indications and overstates Xeloda's proven efficacy.

V. Conclusions and Requested Actions

You have disseminated a professional sales aid and a patient video that omit or minimize material facts regarding the safety profile of Xeloda, make misleading efficacy claims for Xeloda, make unsubstantiated superiority claims over other cancer therapies and omit material facts about the approved indications for Xeloda. These claims have the potential to misguide physicians in making prescribing and treatment decisions, and, therefore, jeopardize patient safety. We request that you immediately cease dissemination of them, and of all promotional materials that contain the same or similar violations outlined in this letter, and that you provide a detailed response to the issues raised in this Warning Letter. This response should include:

1) The date on which you ceased the dissemination of these materials, and all promotional materials that contain the same or similar violations outlined in this letter.

2) A plan of action to disseminate accurate and complete information to the audience(s) that received the violative promotional materials.

3) A written statement of your intent to comply with "1" and "2."

Please submit a written response to DDMAC by June 12, 2003, describing Roche's intent and plans to comply with DDMAC's request. If you have any questions or comments, please contact Joseph A. Grillo, Pharm.D., Carol H. Barstow, JD, or Jean-Ah Kang, Pharm.D. by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857.

We remind you that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID #11274 in addition to the NDA number.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of your promotional campaign for Xeloda, and may determine that additional remedial messages will be necessary to fully correct the false and misleading messages resulting from your violative conduct.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Abrams

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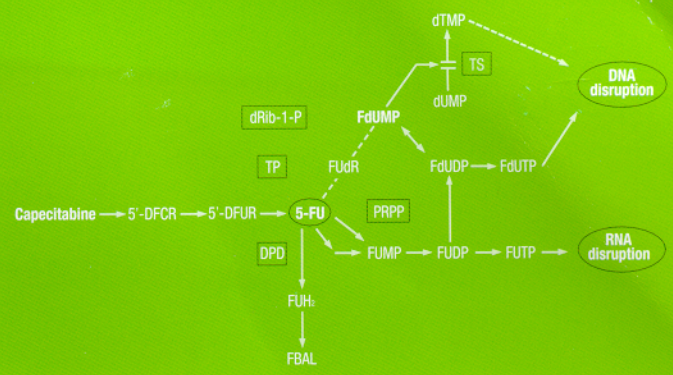
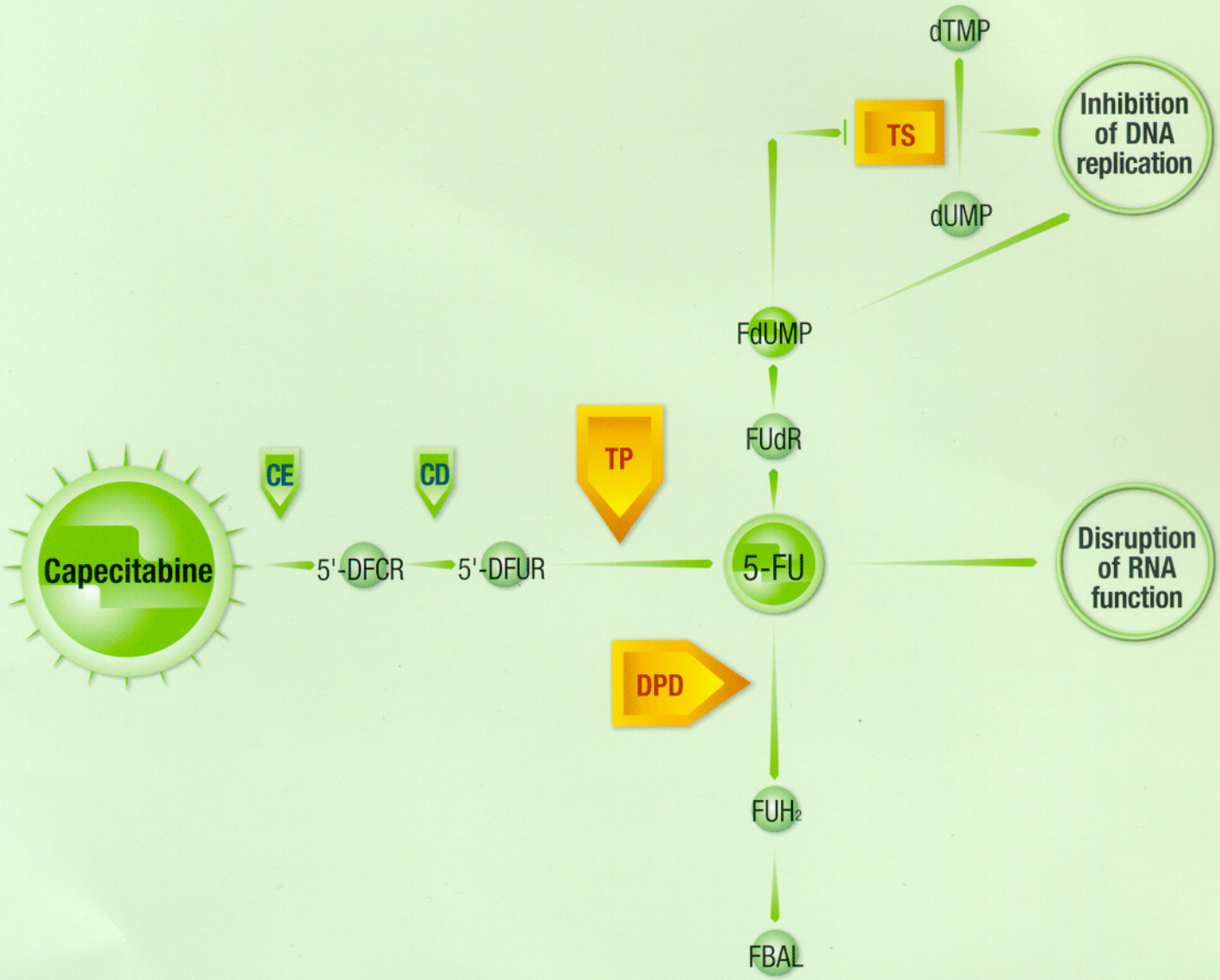
CAPECITABINE:
ENZYMATIC BIOACTIVATION AND MECHANISM OF ACTION





Roche

tablets
Xeloda®
capecitabine

CAPECITABINE:
ENZYMATIC BIOACTIVATION AND MECHANISM OF ACTION

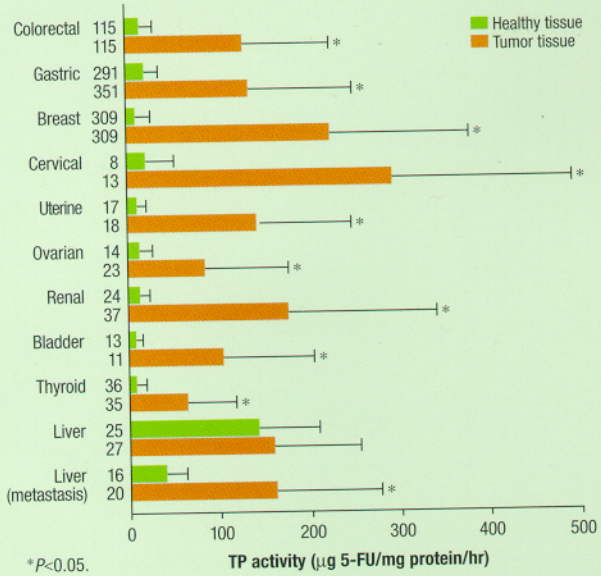
The First Phase of Capecitabine Conversion

- Capecitabine is readily absorbed from the gastrointestinal tract
- Once absorbed, capecitabine is hydrolyzed by a carboxylesterase (CE) to form 5'-deoxy-5-fluorocytidine (5'-DFCR)
- 5'-DFCR is then converted by cytidine deaminase (CyD) to 5'-deoxy-5-fluorouridine (5'-DFUR)

The Role of Thymidine Phosphorylase (TP)

- TP is a pivotal enzyme in the activation of capecitabine, converting 5'-DFUR to 5-FU
- TP activity is upregulated by:
  —Taxanes (eg, docetaxel, paclitaxel)[1]
  —Mitomycin C[1]
  —Radiation[2]
  —Others[2]
- Because TP activity is higher in most tumor tissue than in normal tissue, final conversion of capecitabine to 5-FU occurs preferentially in the tumor[3]

Tissue distribution of TP in human normal and tumor tissues[3]



*$P<0.05$.

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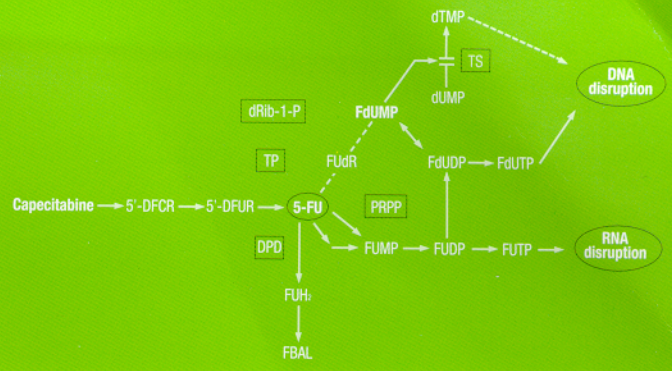
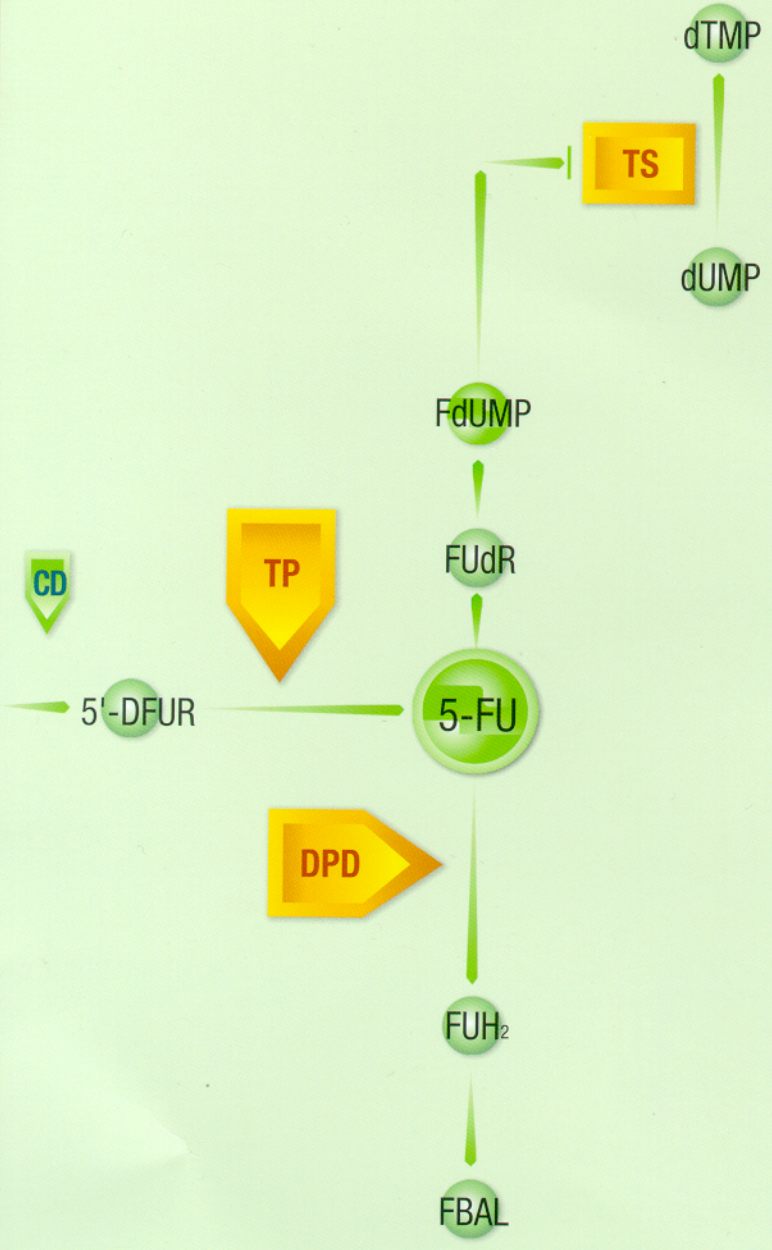




The Inhibition of Thymidylate Synthase (TS) by 5-FU

- 5-FU is metabolized to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP)
- FdUMP binds to methylenetetrahydrofolate and TS to form a ternary complex, thereby inhibiting the function of TS and DNA synthesis

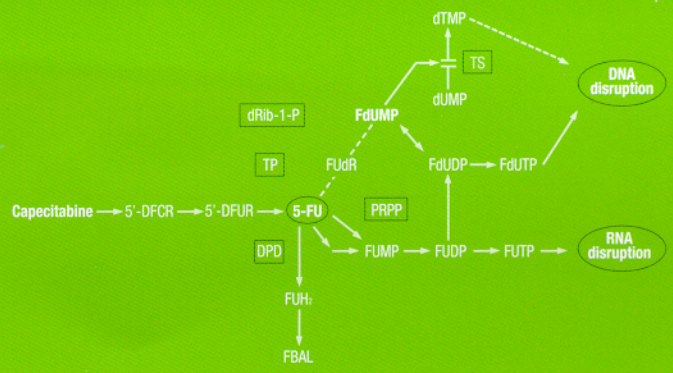
The Degradation of 5-FU by Dihydropyrimidine Dehydrogenase (DPD)

- DPD is the initial and rate-limiting catabolic enzyme of 5-FU
- DPD degrades 5-FU into an inactive metabolite, thereby reducing the level of 5-FU in cells

tablets
Xeloda®
capecitabine

CAPECITABINE+

ENZYMATIC BIOACTIVATION AND MECHANISM OF ACTION



CAPECITABINE: Key Enzyme Roles

- TP converts capecitabine into 5-FU preferentially in tumor tissue
- FdUMP inhibits TS which disrupts DNA and RNA synthesis
- DPD degrades 5-FU into inactive metabolite, thereby reducing the level of 5-FU in cells

For more information, please visit us at:

www.xeloda.com

References: 1. Sawada N, Ishikawa T, Fukase Y, et al. Induction of thymidine phosphorylase activity and enhancement of capecitabine efficacy by Taxol/Taxotere in human cancer xenografts. *Clin Cancer Res.* 1998;4:1013-1019. **2.** Sawada N, Ishikawa T, Sekiguchi F, et al. X-ray irradiation induces thymidine phosphorylase and enhances the efficacy of capecitabine (Xeloda) in human cancer xenografts. *Clin Cancer Res.* 1999;5:2948-2953. **3.** Miwa M, Ura M, Nishida M, et al. Design of a novel fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. *Eur J Cancer.* 1998;34:1274-1281.

Roche Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199
www.rocheusa.com

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You & Your Xeloda Therapy

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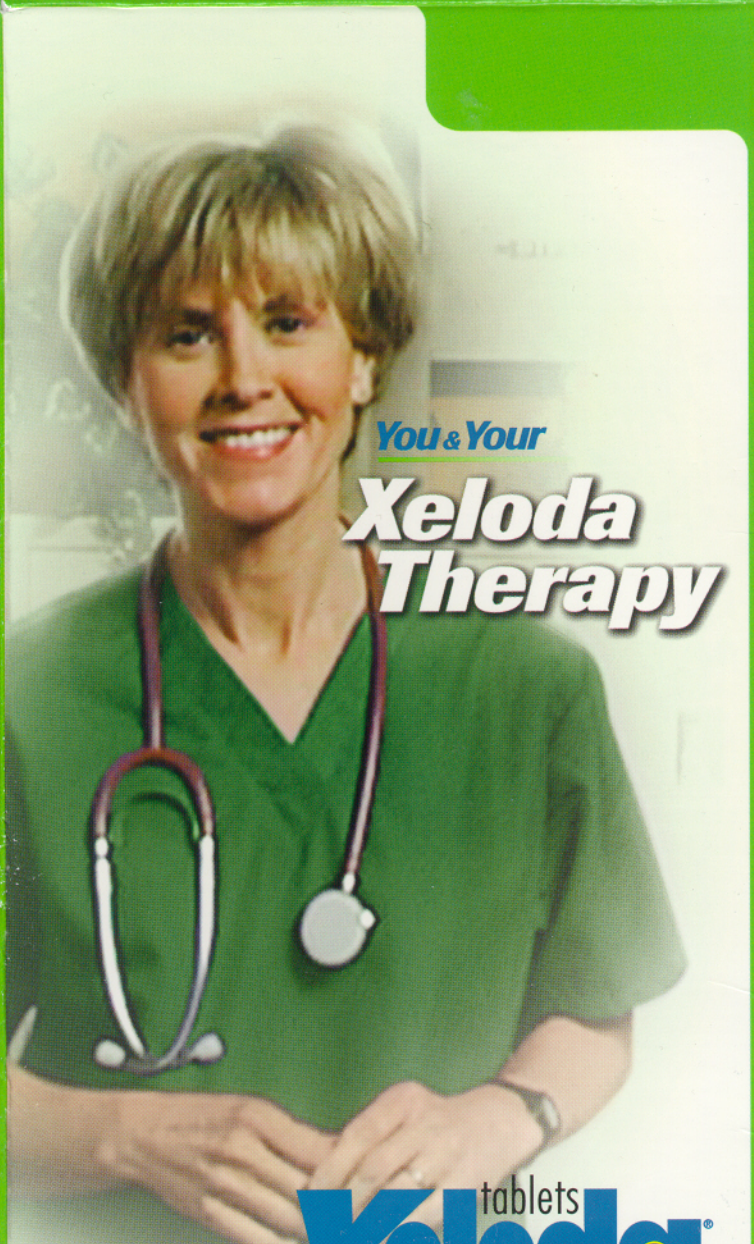

You & Your

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