DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Karen Horgan-Peltier, BSN, ET
Director, Promotional Compliance
Bristol-Myers Squibb
777 Scudders Mill Road
Mailbox P-1125
Plainsboro, NJ 08536

RE: NDA #[ ]
UFT (uracil and tegafur) capsules
MACMIS # 10137

Dear Ms. Horgan-Peltier:

This letter notifies Bristol-Myers Squibb (BMS) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified promotional activities that are in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Specifically, BMS was promoting its investigational new drug, UFT (uracil and tegafur) capsules as safe or effective at their commercial exhibit booth at the 37th American Society of Clinical Oncology (ASCO) Annual Meeting held in San Francisco, California in May 2001. Our specific objections follow:

Promotion of an Investigational Drug

In the commercial exhibit booth, BMS disseminated a promotional brochure[1] describing the safety or effectiveness of their investigational drug UFT capsules. The claims "Preference," "Tolerability," and "Efficacy" were prominently displayed on the cover of this promotional brochure that contained conclusionary statements such as:

> "4 out of 5 patients preferred oral UFT/LV over IV 5-FU/LV having experienced both treatment forms"
>
> "The combination of oral UFT/LV offers an acceptable alternative to bolus IV 5-FU, with improved tolerability and patient/prescriber convenience"
>
> "The results of these two pivotal studies show that UFT/LV is equal to 5-FU/LV (Mayo regimen) in terms of overall survival and other study endpoints"
>
> "With comparable efficacy, the improved safety profile of oral UFT/LV indicates that this treatment regimen has a better therapeutic index"

[1] A forty-four page promotional brochure titled "Product Overview UFT tegafur-uracil capsules"

Section 21 CFR 312.7 states, among other things, that an investigational new drug may not be promoted as being safe or effective for uses under investigation. Therefore, the above claims are in violation of the Act.

In addition, it is particularly concerning that BMS promoted this investigational drug as safe or effective in light of the fact that they received a "not approvable" letter from the U.S. Food and Drug Administration (FDA) in March of this year.

Requested Action

BMS should immediately cease the distribution of these and other similar promotional materials for the above drugs that contain the same or similar claims or presentations. BMS should submit a written response to DDMAC on or before August 3, 2001, describing its intent and plans to comply with the above. In its letter to DDMAC, BMS should include the date on which this and other similarly violative materials were discontinued.

BMS should direct its response to me by facsimile at (301) 594-6771 or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. In all future correspondence regarding this matter, please refer to MACMIS ID # 10137 in addition to the NDA number. DDMAC reminds BMS that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Joseph A. Grillo, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

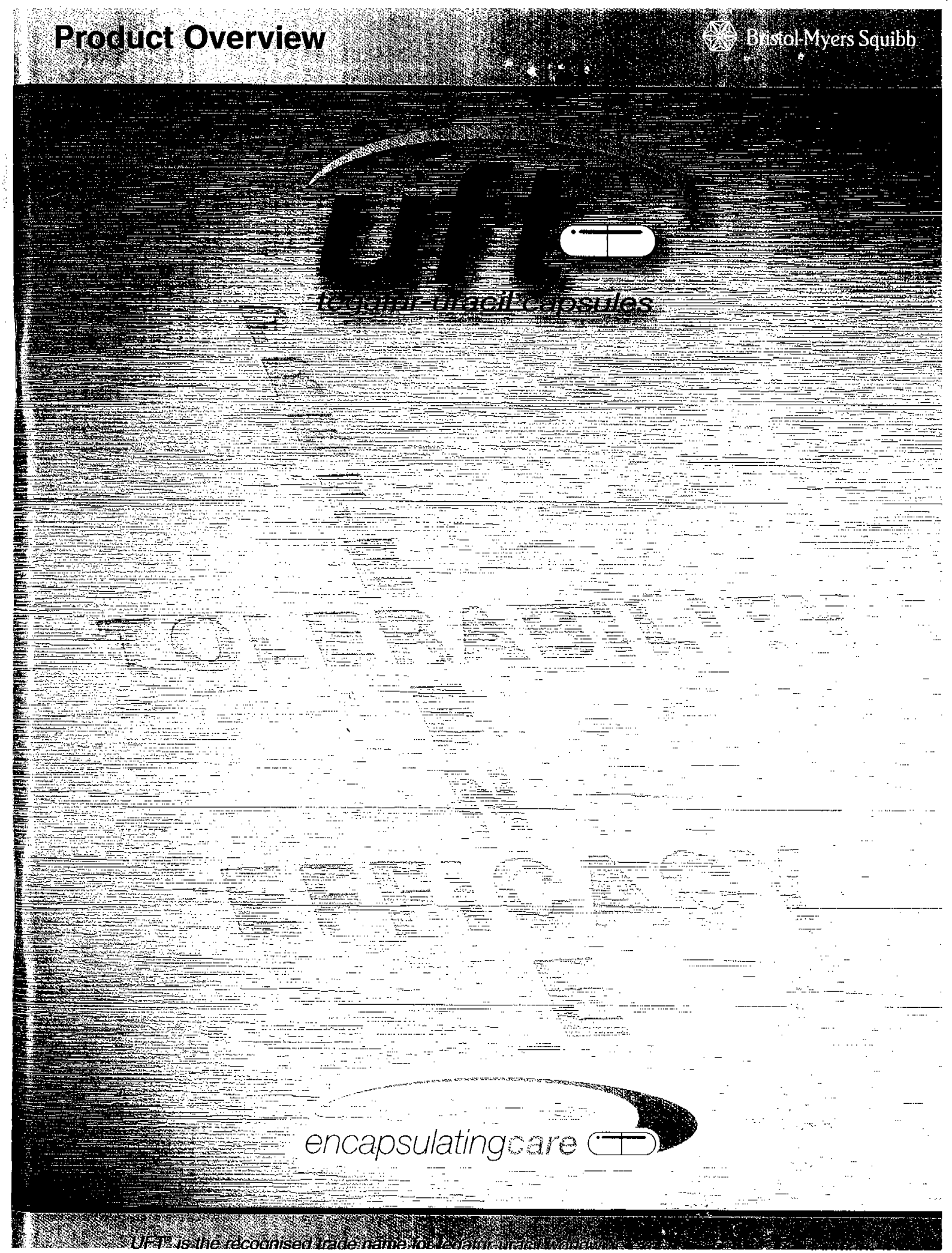
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joseph Grillo
7/20/01 02:08:47 PM

Product Overview

Bristol-Myers Squibb



UFT® is the recognised trade name for tegafur-uracil capsules

Oral UFT – the patient's preference

To investigate patient preference (and pharmacokinetic parameters, reviewed elsewhere) specifically in CRC, Borner and colleagues undertook a randomised, open-label, crossover trial. The trial compared oral UFT (tegafur-uracil; 300 mg/m²/day in three divided doses) plus leucovorin (LV; 90 mg/day), for 28 days followed by 7 days of rest, with IV 5-FU (425 mg/m²) plus LV (20 mg/m² IV bolus), for 5 consecutive days every 28 days in 37 patients as a first-line chemotherapy for metastatic CRC [35]. Before the first therapy cycle and at the end of the second, patients completed a therapy preference questionnaire.

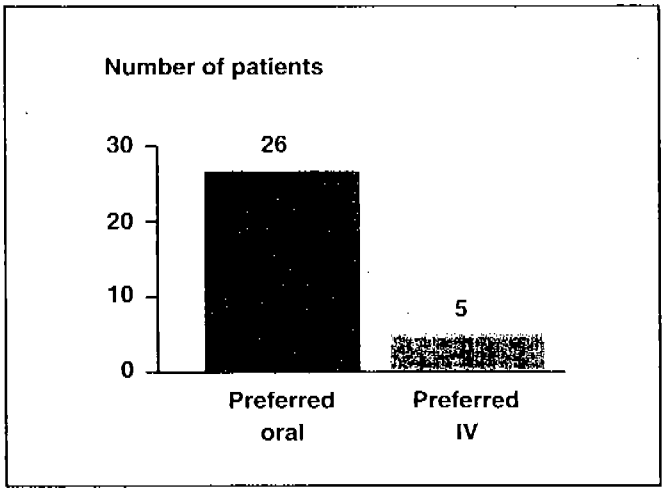


Figure 3.2. Patient preference for oral UFT therapy (adapted from Borner et al, 1999)[35]

Overall, 26 out of 31 patients (84%) preferred the oral UFT therapy, while five patients preferred the IV therapy (Figure 3.2). The main reasons most patients preferred the oral UFT were that it was a pill (73%), and that it could be taken at home (69%) (Table 3.2).

Table 3.2. Patient preferences before and after a crossover trial comparing oral UFT with IV 5-FU therapy (adapted from Borner et al, 1999)[35]

Characteristics of ideal treatment (%) (n=31)		Reasons why oral UFT preferred (%) (n=26)		Reasons why IV 5-FU preferred (%) (n=5)	
No vomiting	77	Pill	73	Injection	80
No diarrhoea	55	Can be taken at home	69	Less nausea	80
No mouth sores	52	Less mouth sores	46	Less diarrhoea	80
Can be taken at home	48	Interfered less with daily activity	46	Less vomiting	60
No risk of infection	39	Less diarrhoea	31	Less tired	20

'4 out of 5 patients preferred oral UFT/LV over IV 5-FU/LV having experienced both treatment forms'

Summary

UFT has been developed to improve the therapeutic index of 5-FU for the treatment of MCRC. It contains two components that are well absorbed following oral administration: a 5-FU prodrug (tegafur) to provide adequate and sustained intracellular exposure to the cytotoxic species and uracil to increase the amount of available 5-FU. The use of this combination has enabled tegafur to be given at lower doses, while retaining equivalent efficacy to the older IV regimen. Furthermore, this lower dose has also brought about a reduction in toxicity. When administered three times daily, oral UFT results in prolonged exposures to 5-FU concentrations without the need for an IV catheter. When co-administered with LV, the combination is highly effective. In terms of the patient's comfort and convenience, orally administered forms of chemotherapeutic medications show clear advantages over IV forms.

The combination of oral UFT/LV offers an acceptable alternative to bolus IV 5-FU, with improved tolerability and patient/prescriber convenience.

Table 5.3. Patients with severe (grade III–IV) toxicity (%)

Safety parameter	Study					
	CA 146-011			CA 146-012		
	UFT/LV (n=406)	5-FU/LV (n=396)	*p*	UFT/LV (n=188)	5-FU/LV (n=185)	*p*
Stomatitis/mucositis	1	19	≤0.001	2	16	≤0.001
Diarrhoea	21	16	NS	18	11	NS
Nausea/vomiting	13	10	NS	9	9	NS
Febrile neutropenia	0	13	≤0.001	1	8	≤0.001
Liver function						
Alkaline phosphatase	4	4	NS	5	8	NS
SGOT	2	1	NS	1	2	NS
SGPT	1	1	NS	1	2	NS
Total bilirubin	15	8	0.006	15	10	NS
Renal function						
BUN	3	3	NS	2	2	NS
Creatinine	<1	1	NS	0	0	NS
Haematology						
Leucopenia	<1	19	≤0.001	2	12	≤0.001
Neutropenia	1	56	≤0.001	3	31	≤0.001
Thrombocytopenia	0	2	0.003	1	2	NS
Anaemia	3	7	≤0.032	5	4	NS

NS = not significant; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; BUN = blood urea nitrogen

Summary

Intravenous 5-FU/LV, administered according to the 'Mayo Clinic regimen' (intermittent IV 5-FU and low dose LV for 5 days every 4–5 weeks) is the only regimen approved worldwide for the treatment of CRC because it prolongs survival and is the most frequently used comparator for Phase III trials[56]. Therefore this regimen was used as a control in studies CA 146-011 and CA 146-012. These studies indicate that oral UFT/LV represents a successful modulation of IV therapy by providing orally bioactive drugs that permit prolonged therapeutic exposure with added convenience for patients. Consequently, solely oral treatment of MCRC with UFT/LV has become possible, in keeping with patient preference for oral palliative chemotherapy compared with IV treatment[34].

'The results of these two pivotal studies show that UFT/LV is equal to 5-FU/LV (Mayo regimen) in terms of overall survival and other study endpoints'

The studies have also shown that UFT/LV is much better tolerated than IV 5-FU/LV therapy (Mayo regimen). There was a significantly reduced incidence of mucositis, stomatitis, neutropenia and febrile neutropenia in the UFT/LV-treated patients in both studies. Patients treated with IV 5-FU/LV required more supportive care in the form of antiemetics and parenteral antibiotics. Anti-tumour effects were comparable in the two treatment arms of both studies with equivalent median survival times.

'With comparable efficacy, the improved safety profile of oral UFT/LV indicates that this treatment regimen has a better therapeutic index'