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Joan Claybrook, President

April 10, 2006

Andrew Von Eschenbach, M.D., Acting Commissioner
U.S. Food and Drug Administration
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Von Eschenbach:

Public Citizen, representing more than 100,000 consumers nationwide, hereby petitions the Food and Drug Administration (FDA) pursuant to the Federal Food, Drug and Cosmetic Act 21 U.S.C. Section 355(e)(3), and 21 C.F.R. 10.30, to immediately remove from the market, the prescription version of Xenical (orlistat, Roche Pharmaceuticals). This drug, which treats obesity, causes a significant increase in the incidence of aberrant crypt foci, which are widely believed to be a precursor of colon cancer.[1,2] This finding makes it even clearer how ill-advised switching orlistat to OTC status would be, something FDA is currently considering. (An "approvable" letter, meaning FDA will approve the drug if certain conditions are met, is said to have been sent by the FDA to Glaxo—the manufacturer of the OTC version---in the past several days.) We are joined in this petition by Dr. Theresa Pretlow, Professor of Pathology and by Dr. Thomas Pretlow, Professor in the Departments of Pathology, Urology, Oncology, and Environmental Health Sciences at Case Western Reserve School of Medicine. Their research, consisting of some 42 papers on colorectal cancer including 15 specifically on aberrant crypt foci, has helped to establish the relationship between aberrant crypt foci and colon cancer.

As Director of the National Cancer Institute, which has funded a substantial portion of the work by Drs. Pretlow establishing the link between ACF and colon cancer, you have repeatedly talked about preventing death and suffering from cancer. The failure to ban the prescription version of this drug or, worse, to make it much more widely available by allowing OTC sales, is a decision that is likely to increase cancer incidence.

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[1] "Section 28: Gastrointestinal Tract. Genetic pathways in colorectal cancer" in *Cancer Medicine* 6th ed. Donald W. Kufe,. Raphael E.Pollock,; Ralph R. Weichselbaum, et al.,editors. Hamilton (Canada): BC Decker Inc; 2003. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Search&db=books&doptcmdl=GenBookHL&term=K-Ras+AND+cmed6%5Bbook%5D+AND+355023%5Buid%5D&rid=cmed6.section.26663. Accessed April 3, 2006.

[2] Radtke F, Clevers H. Self-renewal and cancer of the gut: two sides of a coin. *Science* 2005;307:1904-1909.

2006P-0154 CP1

Public Citizen's petition is based on 1) findings from the pharmacology review of Roche's own data that orlistat causes aberrant crypt foci in the colon of rats,[3] 2) a recent independent confirmation of the above finding that orlistat causes an increase in aberrant crypt foci in rats,[4] and 3) a large scientific literature that acknowledges the importance of aberrant crypt foci as the earliest identifiable neoplastic colonic lesion and putative precursor of colon cancer.[5,6,7]

Normal Intestinal Crypts

Crypts are invaginations of the internal lining of the intestine into the underlying connective tissue of the gastrointestinal tract, occurring along its entire length. In the small intestine, the epithelial lining of the crypts continues upward to form villi (upward finger-like protrusions of the mucosa), while in the colon, villi are absent. There is continued renewal of the single layer of the intestinal tract epithelium as stem cells, located at the base of the crypts, divide and migrate upward. Crypts' functions include absorption of liquid and secretion of mucus.

Aberrant Crypt Foci (ACF) (background and characteristics)

ACF were first described in 1987 in mice[6] and in 1991 in humans.[7] They have also been found in rats, hamsters, and dogs.[8] ACF are distinguished from normal crypts based on their appearance after staining: they are larger, have an increased pericryptal space (the space between them and normal crypts), a thicker layer of darker-staining epithelial cells, and an oval, instead of a round, opening into the intestine.[9]

To view ACF, the intact colon is isolated, slit open, fixed in formalin or ethanol, and dyed with methylene blue. The colon is spread out, mucosal side up, and examined under a microscope (see Figure)[10]. In humans, there is now a technique that allows for staining and visualization of ACF during a colonoscopy.[11]

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[3] David Hertig. FDA Pharmacology Review of Orlistat. April 28, 1997:53. Available at http://www.fda.gov/cder/foi/nda/99/020766a_xenical_phrmr_P5.pdf. Accessed March 2, 2006.

[4] Garcia SB, da Costa Barros LT, Turatti A. The anti-obesity agent orlistat is associated to increase in colonic preneoplastic markers in rats treated with a chemical carcinogen [dimethyl-hydrazine]. Cancer Letters 2005;December 22: ; [Epub ahead of print] PubMedID: 16377080

[5] Pretlow TP, Pretlow TG. Mutant KRAS in aberrant crypt foci (ACF): initiation of colorectal cancer? *Biochimica et Biophysica Acta* 2005;1756:83-96.

[6] Bird RP. Observation and quantification of aberrant crypts in the murine colon treated with a colon carcinogen: preliminary findings. *Cancer Lett.* 1987 Oct 30;37(2):147-51.

[7] Pretlow TP, Barrow BJ, Ashton WS et al. Aberrant crypts: putative preneoplastic foci in human colonic mucosa. *Cancer Res.* 1991;51:1564-1567.

[8] Pretlow TP, Pretlow TG. Mutant KRAS in aberrant crypt foci (ACF): initiation of colorectal cancer? *Biochimica et Biophysica Acta* 2005;1756:83-96.

[9] Pretlow TP, Pretlow TG. Mutant KRAS in aberrant crypt foci (ACF): initiation of colorectal cancer? *Biochimica et Biophysica Acta* 2005;1756:83-96

[10] Aberrant crypt focus. Available at: http://www.inra.fr/reseau-nacre/sci-memb/corpet/acf.html. Accessed April 3, 2006.

[11] Hurlstone DP, Karajeh M, Sanders DS et al. Rectal aberrant crypt foci identified using high-magnification-chromoscopic colonoscopy: biomarkers for flat and depressed neoplasia. *Am J Gastroenterol* 2005;100:1283-1289.

Fig. Stained ACF

Table 1. Additional Characteristics of aberrant crypt foci[12]

- Induced by colon-specific carcinogens in a dose dependent manner
- Each evolves from one altered cell
- Are neoplastic, sharing characteristics in common with colon cancers[13] (mutations of specific genes, dysplasia, and abnormal proliferation)
- Size and number of crypts per focus increase with time
- Features predict tumor outcome and risk
- More likely to be present in individuals at high risk for colon cancer

An aberrant crypt can exist as a single crypt or can multiply[14] to become a multi-crypt "focus" containing up to 100 or more crypts in humans.[15] In examining colons, researchers note the total number of ACF as well as the number of crypts per focus (multiplicity).

ACF are commonly seen in large numbers in people with either familial adenomatous polyposis (an inherited form of colon cancer, most of which have mutations in the APC gene) or in people with sporadic colorectal cancer (where mutations are not inherited). Of the genes that stand out as frequently mutated in colorectal cancer, K-Ras, APC, or beta-catenin, have been found in both rat and human ACF..[16,17]

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[12] Bird RP, Good CK. The significance of aberrant crypt foci in understanding the pathogenesis of colon cancer. *Toxicology Letters* 2000;112-113:395-402.

[13] Siu IM, Robinson DR, Schwartz S et al. The identification of monoclonality in human aberrant crypt foci. Cancer Res. 1999:59:63-66.

[14] Bird RP, Good CK. The significance of aberrant crypt foci in understanding the pathogenesis of colon cancer. *Toxicology Letters* 2000;112-113:395-402.

[15] Pretlow TP, Pretlow TG. Mutant KRAS in aberrant crypt foci (ACF): initiation of colorectal cancer? *Biochimica et Biophysica Acta* 2005;1756:83-96.

[16] Pretlow TP, Pretlow TG. Mutant KRAS in aberrant crypt foci (ACF): initiation of colorectal cancer? *Biochimica et Biophysica Acta* 2005;1756:83-96.

[17] Chapter 23. "Cancer". *Molecular Biology of the Cell*. by Bruce Alberts, Alexander Johnson, Julian Lewis, et al. Garland Publishing, 2002. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Search&db=books&doptcmdl=GenBookHL&term=K-Ras+AND+mboc4%5Bbook%5D+AND+374931%5Buid%5D&rid=mboc4.section.4323#4342. Accessed April 3, 2006.

The connection of ACF with carcinogenesis is so well recognized that the appearance of ACF in rats is used by many groups to test the potential carcinogenicity of chemicals. For example, the Environmental Protection Agency (EPA) uses an ACF assay in its tests of possible carcinogens.[18,19] The ACF assay is also used to examine compounds that may prevent cancer, i.e., prevent ACF formation.[20,21,22]

In the book, *Cancer Medicine*, written by leading U.S. cancer researchers, the authors state that, in the orderly progression from normal colonic mucosa to adenoma to carcinoma, "The earliest histologically recognizable lesion is the aberrant crypt focus (ACF)."[23] Similarly, the authors of a recent review on gastrointestinal cancer state that, "In the adenoma-carcinoma sequence,the earliest identifiable lesion is an aberrant crypt focus . . .",[24] A diagram of the ACF to adenoma to carcinoma progression is available on the web.[25]

Aberrant Crypt Foci: rat data from the orlistat pharmacology review:
Clearly, Roche was worried about orlistat causing the development of cell proliferation and ACF as they studied this in at least seven studies in the pharmacology submission for the New Drug Application (earlier studies were not available for our review).

Table 2. Roche studies submitted to FDA: Colonic cell proliferation and ACF formation

Study	Doses (mg/kg/day)	Findings
Mouse carcinogenicity	0, 375, 750, 1500	↑ cell proliferation with dose and duration ↑in crypt height
Rat carcinogenicity	0, 150, 500, 1000	↑ dose-related cell proliferation at ≥500 mkd
9-day rat	8.5, 117	↑ dose-related mucosal cell turnover
10-day rat	0, 8.5, 25, 127	↑ dose-related thymidine

[18] Geter DR, George MH, Moore TM, et al. Vehicle and mode of administration effects on the induction of aberrant crypt foci in the colons of male F344/N rats exposed to bromodichloromethane. *J Toxicol Environ Health A.* 2004;67:23-29.
[19] DeAngelo AB, Geter DR, Rosenberg DW, et al. The induction of aberrant crypt foci (ACF) in the colons of rats by trihalomethanes administered in the drinking water. *Cancer Letters* 2002;187:25-31.
[20] Corpet DE, Tache S. Most effective colon cancer chemopreventive agents in rats: a systematic review of aberrant crypt foci and tumor data, ranked by potency. *Nutr Cancer* 2002;43:1-21.
[21] Wargovich MJ, Chen CD, Steele JA et al. Aberrant crypts as a biomarker for colon cancer: evaluation of potential chemopreventive agents in the rat. *Cancer Epidemiol Biomarkers Prev.* 1996;5:355-360.
[22] Wargovich MJ, Jimenez A, McKee K, et al. Efficacy of potential chemopreventive agents on rat colon aberrant crypt formation and progression. *Carcinogenesis* 2000;21:114901155.
[23] "Section 28: Gastrointestinal Tract. Genetic pathways in colorectal cancer" in *Cancer Medicine* 6th ed. Donald W. Kufe,. Raphael E.Pollock,; Ralph R. Weichselbaum, et al.,editors. Hamilton (Canada): BC Decker Inc; 2003. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Search&db=books&doptcmdl=GenBookHL&term=K-Ras+AND+cmed6%5Bbook%5D+AND+355023%5Buid%5D&rid=cmed6.section.26663. Accessed April 3, 2006.
[24] Radtke F, Clevers H. Self-renewal and cancer of the gut: two sides of a coin. *Science* 2005;307:1904-1909.
[25] http://www.inra.fr/reseau-nacre/sci-memb/corpet/acfprogd.gif.

		incorporation: 1.9, 2.4, and 5.0-fold
4-week rat	0, 3, 9, 20, 45	↑ dose-related cell proliferation
9-month rat (high fat/low calcium	0, 3, 6, 14 (male) 0, 4, 9, 22 (female)	Mean crypt grade significantly greater for high dose females
9-month rat (high fat/normal calcium)	0, 3, 7, 15 (male) 0, 4, 10, 22 (female)	Treatment-related increase in ACF

The FDA pharmacology review of Roche's high fat/low calcium study noted that, in rats, "There was a treatment-related increase in the number of colonic aberrant crypt foci noted in mid- and high-dose females. This number was still increased for females after the recovery period [a period of time that rats are kept without drug following treatment]."[26] This increase in ACF occurred even though the highest doses used in this study were only 40% (males) and 60% (females) of the human exposure, based on body surface area. Normally, one would test at many times the human level to increase the sensitivity of the assay.,

Unfortunately, we can not know the full story as to what occurred in rats because, in addition to the lack of adequately high doses, the FDA reviewer accepted the sponsor's conclusions without doing his own independent analyses. There are often important details hidden in reports that are missing from sponsor's summaries. Sponsors tend to put the best possible face on their data in writing reports, sometimes omitting important points. It is only by a careful analysis of the raw data and the methods used to obtain them that one can know what the effects of a drug really are. When one reads this FDA pharmacology review and continually finds statements such as "according to the sponsor" or "findings were considered by the sponsor to be", one is left with the feeling that the true picture lies hidden.

Furthermore, we cannot know the answer as to whether orlistat causes colon cancer in rodents because of these same problems (low doses and lack of critical independent analyses). In the carcinogenicity studies, the FDA statistical reviewer found the highest doses used in the studies were set high enough only for male rats (but not for female rats or male and female mice).[27] The statistical reviewer cautioned that, as a result, "The reviewing pharmacologist is advised to take such an inadequacy of the design into account in the determination of the carcinogenic potential of this drug," a gentle way of saying that the studies were not valid.

Aberrant Crypt Foci: animal data from the literature:
There are many studies looking at the induction of ACF in rodents, usually initiated[28] with known colon carcinogens such as azoxymethane or 1,2-dimethylhydrazine.[29,30]

[26] David Hertig. FDA Pharmacology Review of Orlistat. April 28, 1997:54. Available at http://www.fda.gov/cder/foi/nda/99/020766a_xenical_phrmr_P5.pdf. Accessed March 2, 2006.
[27] Ted (Jiyang) Guo, Ph.D. FDA Mathematical Statistical Review. March 24, 1997:23. Available at http://www.fda.gov/cder/foi/nda/99/020766a_xenical_phrmr_P6.pdf. Accessed March 2, 2006.
[28] An initiator is an agent that induces a change in a chromosome or gene that leads to the induction of tumours after a second agent, called a promoter, is administered to the tissue. http://www.sis.nlm.nih.gov/enviro/glossaryi.html.
[29] Nambiar PR, Masako N, Gupta R, et al. Genetic signatures of high- and low-risk aberrant crypt foci in a mouse model of sporadic colon cancer. *Cancer Research* 2004;64:6394-6401.

A recent study specifically examined orlistat. All rats were treated with the carcinogen,1,2-dimethylhydrazine and fed either a normal diet or a high-fat diet for 30 days either with or without orlistat at a level 5 times the human exposure.[31] The investigators found that the number of ACF per cm^2 was increased 60% in rats fed orlistat (on a low fat diet) as well as in rats fed a high fat diet (without orlistat). This number was further increased, however, to 2.4-fold in the group receiving both high fat and orlistat (the baseline being rats fed a low fat diet and no orlistat). Thus, both a high-fat diet and orlistat (which by itself increases the excretion of fat) increased ACF formation.

Aberrant Crypt Foci: human data from the literature

Study 1 (see Table 3): This study was done on patients undergoing routine colonoscopy. Suspect ACF were flushed in situ with a dye (indigo carmine) allowing visualization of diagnostic features. These investigators found a correlation between higher multiplicity of the ACF (that is, more crypts per focus) with a more advanced cancer stage (in the path of ACF to adenoma to cancer).[32]

Table 3. Relation of stages leading to colon cancer and the number of crypts per focus

Stage of cancer	Median number of aberrant crypts per focus
None (normal)	1 (reference)
Adenoma	9
Cancer	38

Study 2: This study was designed to take a more detailed look at the changes in ACF as they progressed toward adenomas and cancer. The investigators used magnifying endoscopy to study the number and type of ACF in 171 normal patients, 131 patients with adenoma, and 48 patients with colorectal cancer. The ACF seen in these patients were placed into sub-categories depending on their characteristics after staining during endoscopy.

The investigators subdivided ACF into nondysplastic and dysplastic. ACF (vs. normal crypts) had darker methylene blue border staining, larger diameters (often with oval or slit-like openings), and thicker linings. Dysplastic ACF, a more advanced stage, had a compressed or an indistinct lumen and a much thicker lining. The investigators found a correlation between the stage (normal, adenoma, or colorectal cancer) and the prevalence of both nondysplastic and dysplastic ACF (see Tables 4 and 5).[33]

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[30] Bird RP, Good CK. The significance of aberrant crypt foci in understanding the pathogenesis of colon cancer. *Toxicology Letters* 2000;112-113:395-402.

[31] Garcia SB, da Costa Barros LT, Turatti A. The anti-obesity agent orlistat is associated to increase in colonic preneoplastic markers in rats treated with a chemical carcinogen. *Cancer Letters* 2005; [Epub ahead of print] PubMedID: 16377080.

[32] Hurlstone DP, Karajeh M, Sanders DS, et al. Rectal aberrant crypt foci identified using high-magnification-chromoscopic colonoscopy: biomarkers for flat and depressed neoplasia. *Am J Gastroenterol* 2005;100:1283-1289.

[33] Takayama T, Katsuki S, Takahashi Y, et al. Aberrant crypt foci of the colon as precursors of adenoma and cancer. *New Engl J Med* 1998;339:1277-1284.

Table 4. Patients at different stages of colon cancer and their relative risk of having nondysplastic foci

Patients at different stages of cancer	Relative risk
None (normal)	1.0 (reference)
Adenoma	1.1
Cancer	1.3

Table 5. Patients at different stages of colon cancer and their relative risk of having dysplastic foci

Patients at different stages of cancer	Relative risk
None (normal)	1.0 (reference)
Adenoma	4.0
Cancer	18

Conclusions

There is a general consensus that ACF represent an early stage in the multiple steps that lead toward development of colon cancer. Two independent research groups, using a rat model, have shown that ACF were produced by orlistat. In people, there was a correlation between the stage of colon cancer and the relative risk of having an advanced form of ACF, i.e., those with colon cancer had a 30% increased risk of having nondysplastic ACF and an 18-fold greater risk of having dysplastic aberrant foci (foci further along the path toward colon cancer) compared to those people without colon cancer.

Orlistat Efficacy:

In two recently published clinical trials, there was only a 2.8% absolute difference in weight loss between patients taking orlistat and those on placebo after four years. [The treated group went from a mean of 242 lbs to 229 lbs (loss of 13 lbs) while the placebo went from 242 lbs to 235 lbs (loss of 7 lbs)]. Both groups were on a reduced-calorie diet and had help from a dietician and encouragement to exercise throughout the study. Much of the initial weight loss was regained over the four years on drug.[34,35]

Adverse events:

1) Gastrointestinal adverse events

Orlistat, because it prevents the breakdown of fat, causes a cluster of gastrointestinal symptoms relating to bowel movements including oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation, and fecal incontinence. Oily spotting and flatus with discharge occurred in almost 25% of patients.

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[34] Torgerson JS, Boldrin MN, Hauptman J, Sjostrom L. Xenical in the prevention of diabetes in obese subjects (XENDOS) study. *Diabetes Care* 2004;27:155-161.

[35] Kelley DE, Bray GA, Pi-Sunyer FX, et al. Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes. *Diabetes Care* 2002;25:1033-1041.

2) Loss of fat-soluble vitamins

A second important problem is also related to how orlistat works: fat-soluble vitamins are excreted along with the fat (beta-carotene and vitamins A, D, E, and K). This loss resulted in lower plasma levels of D, E, K, and beta-carotene, which, according to the Medical Team Leader, "show a disturbing tendency to decrease [worsen] during treatment".[36] The medical reviewer suggested a post-marketing study "evaluating the efficacy and safety of vitamin supplementation".[37] In rats fed orlistat, and supplemented with vitamin E, liver stores of vitamin E nevertheless dropped up to 75%.[38] However, no phase 4 [post-marketing] study was ever requested of the sponsor.

3) Breast cancer risk

Orlistat was not approved initially because of an increase in breast cancer in the orlistat treated groups. In the seven randomized, controlled clinical trials, there were 10 cases of breast cancer in the treated groups with only one in the control groups. The relative risk of getting breast cancer while taking orlistat (compared to placebo) was calculated several times by both FDA and the sponsor and found to vary between 4- and 7-fold, depending on the analysis.[39] These results caused the FDA Medical Officer to rescind his original approval.

The mechanism is not known but the pharmacology reviewer noted that there were fatty changes and fatty infiltrations of rat tissues "probably attributed to inhibition of cellular lipases" due to absorption of drug. [40]

FDA's Dr. Karen Johnson recommended in her consult that product labeling should "address issues related to breast cancer risk" with language similar to that used for Premarin. She also recommended a post-marketing registry be established to collect tumor data.[41] Nevertheless, in the end, the FDA accepted the sponsor's assurances that breast cancer was not a drug-related adverse event, and nothing about it appears in the label.

Our own analysis of orlistat [post-marketing] adverse reaction reports in the FDA Adverse Events database showed that, from the time of marketing through June 2005, there were 28 reported cases of breast cancer. Eight lacked information on duration of therapy and 3 were of a month or less. The distribution of exposures for the remaining seventeen is shown in the table below:

Table 6. Number of patients diagnosed with breast cancer after increasing durations of treatment with orlistat

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[36] Gloria Troendle. FDA Team Leader Comments on [orlistat] NDA. May 1, 1997.
[37] Eric Colman, M.D. FDA Medical Officer's Review of Orlistat NDA. May 1, 1997:101. Available at http://www.fda.gov/cder/foi/nda/99/020766a_xenical_medr_P12.pdf. Accessed February 21, 2006.
[38] David Hertig, FDA Pharmacology Review of Orlistat. April 28, 1997:42. Available at http://www.fda.gov/cder/foi/nda/99/020766a_xenical_phrmr_P5.pdf Accessed March 2, 2006.
[39] Lee-Ping Pian, Ph.D. FDA Mathematical Statistician Memo. June 24, 1997. Available at http://www.fda.gov/cder/foi/nda/99/020766a_xenical_statr_P1.pdf. Accessed March 27, 2006.
[40] David Hertig. FDA Pharmacology Review of Orlistat. April 28, 1997:54 Available at http://www.fda.gov/cder/foi/nda/99/020766a_xenical_phrmr_P5.pdf. Accessed March 27, 2006
[41] Karen Johnson, M.D., Ph.D. FDA Medical Consult. January 14, 1998. Available at http://www.fda.gov/cder/foi/nda/99/020766a_xenical_medr_P5.pdf Accessed March 28, 2006.

2-3 months	4-6 months	12 months	14-16 months
2	4	8	3

In contrast, there were two cases of breast cancer with Meridia, another weight loss drug, between its approval in November 1997 through June 2005. This resulted in an approximately 10-fold difference in reported cases per million prescriptions, based on IMS data.

Table 7. Incidence of breast cancer in patients taking two antiobesity drugs

Drug	Cases of breast cancer reported to FDA (per 10^6 prescriptions)
Xenical (orlistat)	3.4
Meridia (sibutramine)	0.33

4) Colonic cell proliferation and colon cancer
Animal data: Seven rodent studies submitted to the FDA for orlistat showed a dose-related increase in colonic cell proliferation (see Table 2). In the mouse carcinogenicity study, where fecal fat was measured, there was an increase in unesterified fatty acids at all dose levels.[42] ..

Human data: Colonic cell proliferation was a concern of the FDA Medical Officer in his 1997 review of orlistat.[43] He cited observational studies that implicated high dietary fat levels on the occurrence of colon cancer, the mechanism being the proliferative effect of fat on colonic mucosa. The malignant process was studied by measuring biomarkers of cell proliferation in a small group of patients on either orlistat 120 mg per day or placebo for 7 weeks. The Medical Officer concluded that, "These data do suggest that there is a direct correlation between increased levels of fecal total fat and FFA [free fatty acids] with increased activity of the biomarkers for proliferation in the orlistat group, but not in the placebo group."

These results led to a request for a consultant review from the FDA's division evaluating gastrointestinal drugs. FDA's consultant worried about the hazards posed by long-term use "during which time there is ample opportunity for the occurrence of presently unforeseeable mucosal colonic changes". Dr. Gallo-Torres recommended postmarketing surveillance for people with risk factors for colon cancer, those with predisposing conditions, and those with premalignant lesions ("dysplasia, adenomatous polyps, bilious adenomas, familial polyposis, previous colon cancer and schistosomiasis").[44] However, there is nothing in the approval letter about this issue.[45]

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[42] David Hertig, FDA Pharmacology Review of Orlistat. April 28, 1997:14. Available at: http://www.fda.gov/cder/foi/nda/99/020766a_xenical_phrmr_P2.pdf Accessed April 6, 2006.
[43] Eric Colman, M.D. Medical Review of Orlistat. May 1, 1997:80. Available at: http://www.fda.gov/cder/foi/nda/99/020766a_xenical_medr_P11.pdf Accessed March 2, 2006.
[44] Hugo Gallo-Torres, M.D., Ph.D. FDA Consultant from Division of Gastrointestinal and Coagulation Drug Products. March 6, 1997. Available at: http://www.fda.gov/cder/foi/nda/99/020766a_xenical_medr_P14.pdf. Accessed March 2, 2006.
[45] Approval letter. Available at: http://www.fda.gov/cder/foi/appletter/1999/20766ltr.pdf Accessed March 2, 2006.

Other potential uses of orlistat

Fatty acid synthase is a key enzyme in the formation of palmitate, a fatty acid. There are reports that the enzyme's activity increases in some tumor cells and thus there is interest in finding specific inhibitors. Although there are some preliminary data in the literature that orlistat inhibits fatty acid synthase (FAS) and thus may inhibit tumor growth, those studies have mainly been done in tissue culture cells.[46,47] Removing orlistat from the market for the treatment of obesity would not affect the further investigation into other uses. At this point, the evidence of orlistat's ability to cause cancer is much stronger than any potential ability to prevent it.

Recommendation:

Orlistat is a drug that has shown minimal efficacy coupled with both known and potentially important serious adverse events. Orlistat has been shown by two independent groups of investigators to cause the formation of ACF, the earliest identifiable neoplastic colonic lesion and putative precursor of colon cancer. FDA is now considering increasing the number of people exposed to the drug by allowing OTC use. There is no scientific justification for this decision.

The FDA should not allow a drug, in this case orlistat, to remain on the market for the long-term treatment of a non-lethal condition when it combines so little efficacy coupled with a still unresolved potential to cause breast and colon cancer.

ENVIRONMENTAL IMPACT STATEMENT

Nothing requested in this petition will have an impact on the environment.

CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

We look forward to a prompt response to this petition.

Sincerely,

Elizabeth Barbehenn

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Research Analyst

Sidney Wolfe, M.D.
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[46] Menendez JA, Vellon L, Lupu R. Orlistat: from antiobesity drug to anticancer agent in Her-2/neu (erbB-2)-overexpressing gastrointestinal tumors? *Exp Biol Med (Maywood)* 2005;230:151-154.

[47] Kridel SJ, Axelrod F, Rozenkrantz N, Smith JW. Orlistat is a novel inhibitor of fatty acid synthase with antitumor activity. *Cancer Research* 2004;64:2070-2075.

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