DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

APR - 6 2000

TRANSMITTED VIA FACSIMILE

Jerome M. Prahl
Associate Director
Regulatory Affairs
G.D. Searle & Co.
4901 Searle Parkway
Skokie, Illinois 60077

RE: NDA 20-998 Celebrex (celecoxib) capsules
NDA 19-908 Ambien (zolpidem tartrate) tablets
MACMIS ID #8518

Dear Mr. Prahl:

As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC), has become aware of promotional materials for Celebrex (celecoxib) capsules and Ambien (zolpidem tartrate) tablets disseminated by G.D. Searle & Co. (Searle) in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Reference is made to a "homemade" professional sales aid, disseminated by two Searle representatives in Virginia that was used to promote both Celebrex and Ambien. Our specific objections concerning the promotion of Celebrex and Ambien follow:

Celebrex (celecoxib) capsules

Misrepresentation of Safety Information

Promotional materials are false or misleading if they contain representations or suggestions that a drug is more effective, safer, or useful in a broader range of conditions and patients than has been demonstrated by substantial evidence. Your "homemade" professional sales aid presents claims that misrepresent the safety profile for Celebrex, including but not limited to:

- You present the claim, "Celebrex can be used in Coumadin patients." This claim suggests that Coumadin, the brand name product for warfarin, may be used in combination without risk. However, this claim lacks important information regarding the risks that are known about the use of Celebrex in combination with warfarin. Specifically, the concurrent use of Celebrex and warfarin has caused bleeding events in some patients, especially the elderly. In addition, this sales aid fails to disclose the fact that anticoagulant activity should be monitored, particularly in the first few days, after initiating or changing CELEBREX therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of

bleeding complications. Your failure to disclose this important information misrepresents the safety profile for Celebrex. Consequently, the sales aid is misleading.

- You present the claim, "Celebrex – Can be used in Aspirin Patients." This claim suggests that Celebrex is safe to use in patients taking any dose of aspirin. However, this suggestion is misleading because there is a risk when using these drugs in combination. Specifically the Precaution sections of the approved product labeling (PI) states, "...concomitant administration of aspirin with CELEBREX may result in an increased rate of GI ulceration or other complications, compared to use of CELEBREX alone." Therefore, failure to disclose this important risk information misrepresents the safety profile for Celebrex, and is thus, misleading. Furthermore, the suggestion that Celebrex may used in combination with any dose of aspirin is misleading because the PI states, "Celebrex can be used with **low dose** aspirin" (emphasis added).

Unsubstantiated Comparative Claims

Promotional materials are false or misleading if they contain a drug comparison that represents or suggests that a drug is safer or more effective than another drug when such has not been demonstrated by substantial evidence or substantial clinical experience. Some examples of misleading comparative claims in your "homemade" professional sales aid include:

- You present several unsubstantiated comparative claims, comparing Celebrex to Relafen (nabumetone) that suggest that Celebrex is more effective than Relafen, safer than Relafen, and has fewer side effects than Relafen when such has not been demonstrated by substantial evidence. Specifically, you present a side-by-side comparison of selected information from the PIs of both of these products in your sales aid. For example, your presentation that Relafen contains "Standard NSAID labeling," presented adjacent to the headline "Safety," misleadingly suggests that Celebrex is safer than Relafen because the PI for Celebrex does not contain standard NSAID class labeling where the PI for Relafen does. However, Celebrex's PI does contain traditional NSAID class labeling. For instance, the gastrointestinal (GI) warning common to all NSAIDs that states, "Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteriodal anti-inflammatory drugs (NSAIDs)," is included in the PI for Celebrex. Consequently, your suggestion that Celebrex does not contain "Standard NSAID labeling" is misleading.

- You also present several unsubstantiated comparative claims comparing Celebrex to Vioxx, including but not limited to, the claim that "Celebrex – can be used in Coumadin patients," presented adjacent to the claim that Vioxx is "Contraindicated in Coumadin Patients." These claims suggest that Celebrex may be used in a broader patient population, i.e., Coumadin patients, than Vioxx. However, this suggestion is false. In fact, the PIs for Celebrex and Vioxx both state that anticoagulant activity should be monitored when therapy with either Celebrex or Vioxx is initiated or changed, particularly in the first few days of therapy, in patients receiving warfarin or similar agents.

Fair Balance

Promotional materials must present information relating to the contraindications, warnings, precautions, and side effects with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of the product. The "homemade" professional sales aid is lacking in fair balance with respect to the content and presentation of risk information related to the use of Celebrex.

For example, although this piece contains numerous claims for the efficacy and safety of Celebrex, **you have not presented any risk information** concerning the contraindications, warnings, precautions, or side effects associated with Celebrex's use (emphasis added).

Ambien (zolpidem tartrate) tablets

Misrepresentation of Efficacy information

- You selectively present only part of Ambien's approved indication throughout the "homemade" professional sales aid. For example you present claims that Ambien is, "The ONLY proven Reliable Choice for Insomnia," and "Over 4 billion nights of insomnia treatment worldwide." These claims are misleading, because this selective presentation of Ambien's indication does not convey the restrictions of Ambien's use in the treatment of insomnia. Specifically, you fail to disclose that Ambien is indicated for the short-term treatment of insomnia. The indication section of the PI states, "Hypnotics should generally be limited to 7 to 10 days of use, and reevaluation of the patient is recommended if they are to be taken for more than 2 to 3 weeks."

- Additionally, you present claims that guarantee Ambien does not affect next-day mental performance. For instance, you state, "no next day residual effects, and "next-day functioning not compromised." However, the PI states, "**In most instances** memory problems can be avoided if you take Ambien only when you are able to get a full night's sleep (7-8 hours) before you need to be active again" (emphasis added). Therefore, your guarantee that next-day mental performance will not be affected is misleading. In addition, these claims lack important qualifying information that is contained in the PI for Ambien. Specifically, only when the patients are able to get between seven to eight hours of nighttime sleep are memory problems likely to be avoided. Consequently, these claims are also misleading, because this important qualifying information is not disclosed.

Unsubstantiated Comparative Claims

- You present several unsubstantiated comparative claims for Ambien. For example, you present the subheader that Ambien is "the ONLY proven reliable choice for insomnia," along with comparative claims, including but not limited to, "fewer nighttime awakenings" and "more total sleep time." These statements make broad superiority claims to all other sedative and hypnotic agents that are used for the treatment of insomnia. However, these global

superiority claims have not been demonstrated by substantial evidence, and are therefore, misleading.

- Other unsubstantiated claims of Ambien superiority include a cost comparison chart for Ambien and Sonata (zaleplon) capsules headed by the question, "What is the COST for a night of 'QUALITY' sleep or a 'NAP'?" This presentation implies that only Ambien, when compared to Sonata, can provide "quality sleep," where as, Sonata can only provide a "nap." However, this implication of Ambien's superiority to Sonata has not been demonstrated by substantial evidence. Therefore, these unsubstantiated comparative claims of Ambien superiority are false or misleading.

- You present several cost comparisons to not only Ambien and Sonata, but also between Celebrex and Relafen, and Celebrex and Vioxx. However, these comparisons are misleading because they imply that the drugs compared are equally safe, effective, and interchangeable. Furthermore, this cost information lacks substantiation and does not provide a reference as to the source of the cost information presented.

Fair Balance

The "homemade" professional sales aid is also lacking in fair balance with respect to the content and presentation of risk information related to the use of Ambien. Although this piece contains numerous claims for the efficacy and safety of Ambien, **you have not presented any risk information** concerning the contraindications, warnings, precautions, or adverse events associated with Ambien's use (emphasis added).

Failure to Submit

Promotional materials must be submitted to the FDA under Form FDA 2253 at the time of initial dissemination. However, our records indicate the "homemade" professional sales aid was not submitted at the time of initial use.

Conclusions and Requested Actions

Issues concerning "homemade" promotional pieces are not new issues relating to your promotion of Celebrex. On September 10, 1999, we sent you a written inquiry concerning the extent of your involvement in the dissemination of two promotional pieces that were allegedly disseminated by Searle representatives. Both promotional pieces were entitled "Top 10 Reasons To Choose Celebrex Over the Other Branded COX 2 product," and were lacking in fair balance, contained unsubstantiated comparative claims, and misrepresented Celebrex's safety profile.

In your response, dated September 24, 1999, you confirmed that your representatives disseminated these "homemade" promotional materials, and characterized the activity as an isolated occurrence. Furthermore, you assured us that your company considers any distribution of "homemade" promotional materials to be a serious matter and that your "Guidelines for Employee Conduct" state that a representative will only use promotional materials that have

been approved by the Searle Regulatory Approval Committee. Additionally, you stated that, "As a means of reinforcing this policy, our Vice President of Sales has sent a communication to each representative in the company describing the receipt of the DDMAC complaint letter, reminding them of our company policy, and cautioning them on the consequences of violating this policy."

Notwithstanding these assurances, your representatives continue to engage in violative promotional practices. On December 1, 1999, we sent you a written inquiry about the alleged dissemination of the "homemade" professional sales aid that is the subject of this letter. On December 15, 1999, you responded that your representatives did indeed create and disseminate this professional sales aid and use it in the promotion of these two drug products.

We are concerned that the activities described above demonstrate a continuing pattern and practice of violative behaviors that evince widespread corporate involvement and acquiescence with your employees' activities. Although we do not believe that we should interfere with, or comment on, a drug sponsor's internal policies and procedures that are being instituted in response to serious violations of the law, it appears that your actions have not been successful in bringing your promotional practices into compliance with the law.

Consequently, we request that you provide a detailed response to this issue. In addition, you should immediately cease distribution of promotional materials for Celebrex and Ambien that contain the same or similar claims or presentations. You should submit a written response, on or before, April 20, 2000, describing your intent and plans to comply with the above. Your letter should also include a list of materials discontinued and the date on which these materials were discontinued.

If you have any questions or comments, please contact me by facsimile at (301) 594-6771, or by writing at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding this matter, please refer to the MACMIS # 8518 and the NDA numbers.

Sincerely,

/S/

Spencer Salis, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

	Celebrex	Relafen
Efficacy:	-Equal to 1000 mg Naproxen	-Equal to ONLY 500mg Naproxen
Safety:	-1st Cox-1 sparing agent -0.04% bleed rate 2 out of 5,285 patients had bleed in clinical trials -10 MILLION Rxs -Refill rate 5x better -200 Million days of patient use	-Inhibits both Cox-1 and Cox-2 -Standard NSAID labeling -FDA states in WARNING letter same ulcer risk as traditional NSIADs- 2 to 4%
Side Effects:	-Diarrhea 5.6% -Dyspepsia 8.8% -Abdominal Pain 4.1%	14% 13% 12%
Cost:	-200mg QD #30 $62.00	-500 mg BID #60-$74.99 -750 mg BID #60-$86.99

Powerful relief, Safely delivered

Millions of patients...

- OVER 10 Million Rxs to date
- On average, Over 50,000 written daily

Millions of refills...

- Higher rate than any other NSAID at 6 months post-launch

Celebrex:

Most successful product EVER in pharmaceutical history!!

	Celebrex	Vioxx
Drug Interactions-	-Fluconazole -Lithium	-Cimetidine -Lithium -Lotensin -Methotrexate -Coumadin
Side Effects-	Comparable to PLACEBO at ALL Doses	Comparable to Placebo at 12.5 & 25mg dosage; ↑ Hypertension and Edema at 50mg dose
Cost-	200mg QD #30 $62.00 100mg BID #60 $74.98	12.5/25mg QD #30 $76.46 50mg dose 25mg BID #10 $30.90 (DO NOT USE >5 DAYS)

	Celebrex	Vioxx
Efficacy-	OA- Naproxen 1000mg Diclofenac 75mg BID Ibuprofen 800mg TID (States in DPI: Indicated to treat signs & symptoms of OA and RA including–PAIN and INFLAMMATION)	OA- Ibuprofen 800mg TID Diclofenac 50mg TID Pain- Ibuprofen 400mg (=2 Aleve) Not studied >5 days
Safety-	-Can be used in Aspirin Patients -Can be used in Coumadin Patients	-Not studied in Aspirin Patients -Contraindicated in Coumadin Patients
Renal Effects-	-CAN BE USED in patients with mild to moderate insufficiency	-USE W/CAUTION; ↑ Hypertension and Edema
Hepatic Effects-	-Elevation in enzymes COMPARABLE to PLACEBO Celebrex-6% Placebo-5%	-Increase in enzymes comparable to Ibuprofen and lower than diclofenac

Ambien

(zolpidem tartrate)

The ONLY Proven Reliable Choice for Insomnia–
More Sleep for your MONEY!!

- Flown on the Space Shuttle
- A Member of the U.S. Olympic Team
- Over **4 BILLION** Nights of Insomnia Treatment Worldwide
- Studied in OVER 75,000 Patients in MORE THAN 100 Clinical Trials
- Prescribed for OVER 6 Years in the US and 11 Years in Europe

Elderly Patients–	Familiar Dosing for ADULTS–
5 mg	10 mg

Ambien

(zolpidem tartrate)

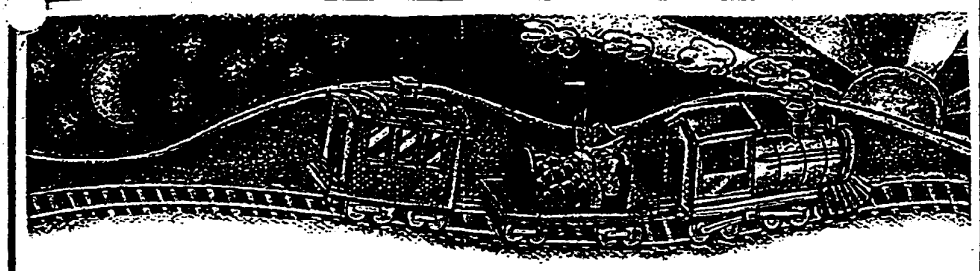
The ONLY Proven Reliable Choice for Insomnia--
More Sleep for your MONEY!!

- Quick Onset
- Fewer Nighttime Awakenings
- More Total Sleep Time (6-8 hrs.)
- No Next Day Residual Effects
- Preserves Sleep Stages

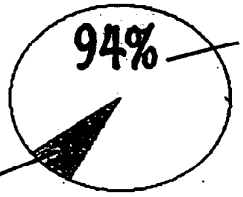
Elderly Patients-	Familiar Dosing for ADULTS-
5 mg	10 mg

What is the COST for a night of "QUALITY" sleep or a "NAP"?

	AMBIEN		Sonata	
Wal-Mart:	5 mg 10 mg	$56.72 $60.99	5 mg 10 mg	$55.89 $68.78
K-Mart:	5 mg 10 mg	$63.97 $75.97	5 mg 10 mg	$62.97 $75.97
CVS:	5 mg 10 mg	$62.59 $76.59	5 mg 10 mg	$67.59 $81.99
Rite-Aid:	5 mg 10 mg	$56.98 $69.98	5 mg 10 mg	$60.98 $74.98



Typical insomnia patients need a full night's sleep



94% Reported 2 or more symptoms of insomnia

- ►Trouble falling asleep
- ►Trouble staying asleep
- ►Trouble waking too early

6% Reported only one symptom

Treat ALL Three symptoms with AMBIEN--

→ 6 Years PROVEN clinical experience

→ OVER 4 BILLION nights of treated insomnia

Elderly patients–	Familiar Dosing for ADULTS–
5 mg	10 mg