DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED VIA FACSIMILE

Brian A. Markison
Chairman, President, and Chief Executive Officer
King Pharmaceuticals, Inc.
501 Fifth St.
Bristol, TN 37620

Re: NDA 21-260
Avinza® (morphine sulfate extended-release capsules) CII
MACMIS # 14970

WARNING LETTER

Dear Mr. Markison:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a twenty-two page File Card (File Card) (AVIN512-RCW) for Avinza (morphine sulfate extended-release capsules) (Avinza), submitted by Ligand Pharmaceuticals, Inc. (Ligand) under cover of Form FDA 2253[1]. The File Card for Avinza is false or misleading in that it presents efficacy claims for Avinza but fails to communicate and minimizes risks associated with its use, fails to present the limitations to its approved indication, and presents unsubstantiated efficacy claims. Therefore, the File Card misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §§ 352(a) and 321(n).

We are especially concerned from a public health perspective because the File Card fails to present any information from the extensive Boxed Warning and Warnings sections of the approved product labeling (PI) for Avinza or any information about the abuse potential of Avinza, a controlled substance under Schedule II of the Controlled Substances Act. These omissions are exacerbated by the fact that the File Card minimizes the little risk information that is presented. In addition, the File Card fails to disclose the limitations to the indicated use of Avinza, thereby implying that Avinza may be used for a much broader range of patients and conditions than are appropriate for the drug. The File Card also makes several unsubstantiated efficacy claims about the outcomes of treatment with Avinza. The combination of such broad and unsubstantiated efficacy claims about the benefits of Avinza and the omission of the serious, potentially fatal risks associated with its use, as well as its potential for abuse, is especially egregious and alarming in its potential impact on the public health.

[1] As of February 27, 2007, NDA 21-260 has been transferred to King Pharmaceuticals, Inc.

Background

The Indications and Usage section of the FDA-approved product labeling (PI) states:

> AVINZA capsules are a modified-release formulation of morphine sulfate intended for once daily administration indicated for the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time.
>
> AVINZA is **NOT** intended for use as a prn analgesic.
>
> The safety and efficacy of using AVINZA in the postoperative setting has not been evaluated. AVINZA is not indicated for postoperative use. If the patient has been receiving the drug prior to surgery, resumption of the pre-surgical dose may be appropriate once the patient is able to take the drug by mouth. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (see American Pain Society guidelines)

Avinza is associated with a number of serious risks, many of which are potentially fatal. The PI includes a Boxed Warning concerning potentially fatal overdosing if Avinza capsules are chewed, crushed, or dissolved, or combined with alcoholic beverages or medications containing alcohol:

WARNING:

AVINZA capsules are a modified-release formulation of morphine sulfate indicated for once daily administration for the relief of moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time. AVINZA CAPSULES ARE TO BE SWALLOWED WHOLE OR THE CONTENTS OF THE CAPSULES SPRINKLED ON APPLESAUCE. THE CAPSULE BEADS ARE NOT TO BE CHEWED, CRUSHED, OR DISSOLVED DUE TO THE RISK OF RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE. PATIENTS MUST NOT CONSUME ALCOHOLIC BEVERAGES WHILE ON AVINZA THERAPY. ADDITIONALLY, PATIENTS MUST NOT USE PRESCRIPTION OR NON-PRESCRIPTION MEDICATIONS CONTAINING ALCOHOL WHILE ON AVINZA THERAPY. CONSUMPTION OF ALCOHOL WHILE TAKING AVINZA MAY RESULT IN THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF MORPHINE.

The PI states that Avinza is contraindicated in patients with respiratory depression in the absence of resuscitative equipment and in patients with acute or severe bronchial asthma. The PI includes warnings related to the maximum daily dose of Avinza; the potentially fatal abuse potential of opioids; interactions with alcohol and drugs of abuse; impaired respiration; head injury and increased intracranial pressure; hypotensive effect; and gastrointestinal obstruction. There are a number of precautions associated with Avinza, including the general precaution that it is not appropriate as a prn (as needed) treatment for pain and that it is critical to adjust the dose of Avinza for each patient, taking into account the patient's prior experience with analgesics, as well as specific precautions relating to

use in patients with biliary tract disease, use in special risk groups (e.g., patients with severe renal or hepatic insufficiency, elderly or debilitated patients), risks associated with driving or operating machinery, and tolerance and physical dependence. The PI outlines several serious drug interactions for Avinza, including central nervous system (CNS) depressants, muscle relaxants, mixed agonists/antagonist opioid analgesics, monoamine oxidase inhibitors, and cimetidine.

Additionally, the Adverse Reactions section of the PI states that the most common adverse events occurring in patients receiving Avinza were constipation, nausea, somnolence, vomiting, headache, peripheral edema, diarrhea, abdominal pain, infection, urinary tract infection, accidental injury, flu syndrome, back pain, rash, sweating, fever, insomnia, depression, paresthesia, anorexia, dry mouth, asthenia and dyspnea.

Omission and Minimization of Risk

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The File Card is misleading because it presents numerous efficacy claims for Avinza but omits and minimizes the serious risks associated with Avinza. For example, the File Card includes the following claims:

- "Continuous 24-Hour Pain Relief To Get Back to Active Living"
- "Avinza—Get Patients Back to Active Living"
- "Back to Active"
- "The Benefits of Continuous 24-Hour Pain Control and Long-Lasting Relief"
- "Avinza—Improved Overall Function"
- "Long-Lasting Improvements in Physical Function"
- "Improvement in Daily Activities…"
- "Avinza—Improved Sleep Quality"
- "Significant improvement in physical and social function"

The File Card, however, fails to present <u>any</u> risk information from the Boxed Warning, Contraindications, Warnings, or Drug Interactions sections of the Avinza PI. The only risk information that the File Card presents are some of the most common adverse events associated with the use of opioids and minimal information about the drug's physical dependence.

Inclusion of the statement, "Please see full Prescribing Information enclosed," in fine print on the bottom of the last page of the twenty-two page File Card, does not mitigate this misleading omission of risk information.

The File Card not only omits these important risks, but also minimizes the few risks that are disclosed, thus completely misrepresenting the risk profile of the drug. The following statements are the only references in the File Card to the risks associated with the use of Avinza:

"Avinza has been proven to be safe and well tolerated" (Page 8)

"**Managing Side Effects**

> Common adverse events seen on initiation of therapy with *AVINZA* are dose dependent, and are typical opioid-related side effects, including constipation, nausea, and somnolence.
>
> In general, *AVINZA* has been proven to be safe and well tolerated.
>
> Physicians should start patients on a bowel regimen from the onset of therapy to manage opioid-induced constipation.
>
> **Discontinuation of *AVINZA* Therapy**
>
> In general, opioids should not be abruptly discontinued. Instead, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient."
>
> (Page 12) (emphasis original)
>
> "Proven safety and tolerability" (back cover)

These claims minimize the seriousness and severity of the risks associated with Avinza in several ways. First, the title of the presentation on page 12 ("Managing Side Effects") creates the misleading impression that the risk information contained in that section is a comprehensive presentation of the risks associated with Avinza therapy and the steps needed to address those risks. The fact that the File Card contains no other disclosure of drug risks reinforces this misleading impression. Furthermore, the File Card—in direct contradiction of the PI for Avinza—implies that no serious or life-threatening risks (e.g., risk of respiratory depression, overdose, or death) can be caused by Avinza, both by disclosing only "common adverse events" (e.g., constipation, nausea, and somnolence) and by emphasizing the drug's "proven safety and tolerability" throughout the piece. Finally, by framing its discussion of common adverse reactions as one of "managing" them, and by providing no disclosure to the contrary, the File Card misleadingly implies that common adverse reactions associated with the use of Avinza may ordinarily be alleviated or mitigated, and therefore do not pose a risk to patients. The disclosures on pages 13 and 16 that the dose of Avinza may be reduced if unnamed "excessive" or "unacceptable" side effects occur does not mitigate this misleading impression. Your minimization of the serious risk profile associated with your drug raises significant public health concerns.

Broadening of Indication/Failure to State Full Indication

The File Card fails to set forth the complete indication for Avinza because it fails to disclose the limitations to the drug's indication. This omission is especially problematic from a public health perspective given the serious risks associated with the drug and the serious deficiencies in the presentation of risk information. Specifically, the File Card presents broad claims that Avinza is indicated "For Chronic Moderate-to-Severe Pain" (front cover) and "Continuous 24-Hour Pain Relief" (front cover) without revealing that Avinza is only for the relief of moderate-to-severe pain *requiring* continuous, around-the-clock therapy for an extended period of time, is not intended for use as a prn analgesic (i.e., is not intended for use as an analgesic that may be taken "as needed"), and is not indicated for post-operative use. By failing to disclose these limitations, the File Card misleadingly implies that Avinza is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. The fact that the File Card contains the

statement "Please see full Prescribing Information enclosed" on the back cover does not mitigate this misleading omission.

Unsubstantiated Effectiveness Claims

As noted above, the File Card includes the claims:

- "To Get Back to Active Living" (front cover; pages 2, 4 & 6)
- "Back to Active" (tag line presented throughout the piece)
- "AVINZA – Get Patients Back to Active Living" (back cover)

These claims are misleading because they imply that an outcome of treatment with Avinza is the ability to resume an active lifestyle. FDA is not aware of any evidence to support these claims. In fact, no references were cited to support them. Furthermore, the accuracy of this implication is called into question by the modest reduction in pain intensity Avinza has been shown to provide. Avinza reduced pain intensity by an average of 18.5% (Avinza 30 mg QAM: 17% and Avinza 30 mg QPM: 20%) versus 4% pain reduction in patients taking placebo (see Page 1 of File Card).[2] We are not aware of any studies demonstrating that this 14.5% reduction in pain above placebo corresponds with the ability to resume an active lifestyle. If you have data to support these claims, please submit the data to FDA for review.

Additionally, in conjunction with a graph entitled, Improvement in Physical Function Score From baseline (mm), the File Card presents the following claims (Page 3):

- "Avinza—Improved Overall Function"
- "Long Lasting Improvements in Physical Function" (footnote omitted)
- "Improvement seen as early as Week 1"
- "Sustained improvement over 6 months"

Moreover, on the same two-page spread as the physical function claims referenced above, the File Card makes the following claims (page 4):

- "Improvement in Daily Activities Includes
  Walking on a flat surface ✓
  Standing or sitting ✓
  Climbing stairs ✓
  Getting in and out of bed or bath ✓
  Ability to perform domestic duties ✓"
  (footnote omitted)

- "Significant improvement in physical and social function" (back cover) (footnote omitted)

[2] Caldwell JR, Rappaport RJ, Davis JC, et al. Efficacy and safety of a once-daily morphine formulation in chronic moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and open-label extension trial. *J Pain Symptom Manage.* 2002:23: 278-291

These claims are misleading because they overstate the efficacy of Avinza by suggesting that patients who are treated with the drug experience an improvement in their overall function, social function, and ability to perform daily activities when this has not been demonstrated by substantial evidence or substantial clinical experience. In support of these claims, the file card references study TRG004-04.[2] This study included a 4-week placebo controlled, double-blind trial to determine the analgesic efficacy of Avinza compared to placebo and the safety of Avinza compared to twice-daily MS Contin® (morphine sulfate controlled-release) and a 26-week open-label, uncontrolled extension trial which was primarily designed to evaluate Avinza's safety. Secondary endpoints in the 4-week placebo controlled trial included an evaluation of the effects of treatment on physical functioning, but statistically significant differences in physical function were not achieved among Avinza-treated patients for these secondary endpoints (i.e., physical function and stiffness subscales of the Western Ontario and McMaster Universities [WOMAC] functional assessment). In addition, even if the secondary endpoints had shown a statistically significant result, this presentation is misleading because it implies, through listing out individual domains and check-marking each one, that Avinza can improve patients' function for the *individual* items of the WOMAC (i.e., walking on a flat surface, standing or sitting, climbing stairs, getting in and out of bed or bath, ability to perform domestic duties). To our knowledge, the individual items of the WOMAC scale have not been validated. Consequently, we are not aware of evidence to suggest that the responses are valid.

Furthermore, in conjunction with a graph entitled, Improvement in Sleep Scores From Baseline (0-100 mm), the File Card makes the following claims (Page 5):

- "Avinza—Improved Sleep Quality"
- "Improvement in Quality of Sleep" (footnote omitted)

In addition, the File Card makes the following claims (Page 6):

"Improved Quality of Sleep Includes
- Sustained sleep improvement over 6 months
- Reduced need for sleep medication
- Increased ability to fall asleep
- Increased duration of sleep each night
- Less awakening at night" (footnote omitted)

These presentations, which claim that Avinza improves sleep quality, are misleading. In support of these claims, the file card again references study TRG004-04.[2] In addition to measuring effects on physical functioning, secondary endpoints in this study evaluated the effects of treatment on sleep measures using a self-reporting sleep questionnaire. However, the study was not adequately designed to assess these secondary endpoints, and consequently claims cannot be based on these endpoints. In order to make claims regarding improvement in sleep measures, appropriate baseline assessment of sleep parameters must be obtained to establish abnormal sleep patterns in the subjects. These parameters must be reassessed during an adequate and well-controlled trial designed appropriately to assess this endpoint. In addition to suggesting the Avinza improves overall sleep quality, these claims also misleadingly suggest that Avinza will improve the *individual* sleep measures in the questionnaire (i.e., sustained sleep improvement over 6 months, reduced need for sleep medication, increased ability to fall asleep, increased duration of sleep each night, less awakenings at night). To our knowledge, the

individual items of the questionnaire have not been validated; consequently, we are not aware of evidence that the responses are valid.

Furthermore, the above presentations (Pages 3 through 6) are misleading because they claim that patients who are treated with Avinza experience a sustained improvement in physical functioning and sleep quality, when this has not been demonstrated by substantial evidence or substantial clinical experience. As stated above, Study TRG004-04 included a 26-week open-label, uncontrolled extension trial that evaluated physical functioning and sleep measures. But such a trial, lacking a control group, cannot evaluate the effect of a drug on variable and subjective endpoints such as physical functioning and sleep measures. If you have data to support these claims, please submit them to FDA for review.

Conclusions and Requested Actions

The File Card minimizes and fails to communicate important risk information for Avinza, fails to disclose the limitations to its indication, and makes numerous unsubstantiated efficacy claims for the drug. Thus, these materials misbrand your drug in violation of the Act, 21 U.S.C. §§ 352(a) and 321(n).

DDMAC requests that King Pharmaceuticals immediately cease the dissemination of violative promotional materials for Avinza such as those described above. Please submit a written response to this letter on or before April 7, 2008, stating whether you intend to comply with this request, listing all violative promotional materials for Avinza such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705, facsimile at 301-847-8444. In all future correspondence regarding this particular matter please refer to the MACMIS ID # 14970 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Avinza comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above 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/

Kristin Davis
3/24/2008 04:40:34 PM
Signing on behalf of Thomas W. Abrams