DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Chris Santos, MS
Associate Director, Regulatory and Quality Affairs
Victory Pharma, Inc.
11682 El Camino Real, Suite 250
San Diego, CA 92130

RE: ANDA #40-556 and 40-658
Xodol 5/300, 7.5/300, 10/300 (5, 7.5, 10 mg hydrocodone bitartrate and 300 mg acetaminophen tablets)
MACMIS ID #17030

Dear Mr. Santos:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional sales aid (XOD017A0507) for Xodol® 5/300, 7.5/300, 10/300 (5, 7.5, 10 mg hydrocodone bitartrate and 300 mg acetaminophen tablets) (Xodol) submitted by Victory Pharma, Inc. (Victory Pharma) under cover of Form FDA 2253. This promotional material is false or misleading because it minimizes the risks, presents misleading safety information, omits and minimizes important risk information associated with the use of Xodol, and broadens the indication for Xodol. The sales aid, therefore, misbrands Xodol in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) & 321(n). *Cf*. 21 CFR 202.1(e)(5); (e)(6)(i); (e)(6)(ii) & (e)(6)(xviii). This promotional piece is concerning from a public health perspective because it suggests that Xodol is safer and effective for use under broader conditions than has been demonstrated by substantial evidence or substantial clinical experience.

Background

According to its FDA-approved product labeling (PI), "Xodol® is indicated for the relief of moderate to moderately severe pain." Xodol is contraindicated in patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen and in patients known to be hypersensitive to other opioids as they may exhibit cross sensitivity to hydrocodone. The PI also includes warnings regarding respiratory depression, head injury and increased intracranial pressure, and acute abdominal conditions. The PI also contains precautions regarding: use in patients with severe impairment of hepatic function; the avoidance of Xodol with alcohol and other CNS depressants, which may produce additive CNS depression; habit-forming characteristic of hydrocodone; the need for monitoring serial liver function tests in patients with severe hepatic disease; and drug interactions with other narcotics, antihistamines, antipsychotics, antianxiety agents or CNS depressants (including alcohol), stating that "when combined therapy is contemplated, the dose of one or both agents should be reduced."

The PI contains the following information regarding the Drug Abuse and Dependence of Xodol (in pertinent part):

> **Controlled Substance:** Xodol® is classified as a Schedule III controlled substance.
>
> **Abuse and Dependence:** Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, this product should be prescribed and administered with caution.

In addition, the Overdosage section of the PI states that dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect associated with acetaminophen overdosage.

The PI also contains the following information regarding the Dosage and Administration of Xodol:

Xodol 5/300: The usual adult dosage is one or two tablets every four to six hours as needed for pain.

Xodol 7.5/300 and Xodol 10/300: The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.

Minimization of Risk

The sales aid is false or misleading because it suggests that Xodol is safer than has been demonstrated by substantial evidence or substantial clinical experience. Specifically, the sales aid minimizes the risks associated with Xodol when this drug is taken with alcohol and over-the-counter (OTC) medications. For example, the second page and back cover of the sales aid present a large picture of a power strip labeled "Xodol®" into which plugs that are labeled "STATIN," "OTCs," and "ALCOHOL," respectively, are inserted. On page two of the sales aid, to the right of the power strip, the sales aid states, "**Reduce the risk for patients who may take other prescription or OTC products, or consume alcohol**," and the back cover of the sales aid states "**Xodol® relieves the pain while reducing the risk**." Another, similar graphic appears on the front cover of the sales aid. Furthermore, the sales aid also presents the tagline, "**Relieves the pain. Reduces the risk**." These prominent graphics and claims misleadingly suggest that patients may safely consume alcohol and use OTC medications while taking Xodol. The PI, however, includes precautions against patients using alcohol and other CNS depressants or other narcotics, antihistamines, antipsychotics, or antianxiety agents concomitantly with Xodol and states that the use of Xodol with alcohol and other CNS depressants should be avoided because such patients may develop an additive CNS depression. We note the fourth bullet under the Safety Profile on page three of the sales aid states, "Alcohol and other CNS depressants may produce an additive CNS depression when taken with this combination product and should be avoided." The inclusion of this information, however, does not mitigate the misleading impression created by the prominent presentations in the sales aid suggesting that patients may safely use alcohol and OTC medications while on Xodol therapy.

In addition, the sales aid misleadingly suggests that Xodol is safer than has been demonstrated with respect to hepatotoxicity. For example, the first and second pages of the sales aid imply that use of Xodol reduces the potential for hepatotoxicity and overload of the liver. We recognize that, depending on the total dose administered, the 300 mg of acetaminophen per tablet in Xodol may be less hepatotoxic than larger doses of acetaminophen. However, the PI still includes potentially fatal hepatic necrosis as the most serious adverse effect of acetaminophen overdosage (as well as a precaution regarding use in patients with severe impairment of hepatic function), and dosing recommendations for the Xodol 5 mg/300 mg tablet (1-2 tablets up to 6 times/day) still gives a dose of up to 3600 mg/day of acetaminophen. Moreover, in users of alcohol, lower doses can be hepatotoxic. While we note the statements on the last page of the piece that dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect associated with acetaminophen overdosage and that Xodol should be used with caution in patients with severe impairment of hepatic function, the inclusion of these statements does not mitigate the misleading presentation created by the piece as a whole that Xodol is safer than has been demonstrated.

Misleading Safety Presentation

Page three of the sales aid presents the claim, "Xodol® is appropriate for use >10 days even when taken at the highest recommended dosage." Below this claim is a graph representing that this extended therapy results in patients consuming less than 2600 mg of acetaminophen (APAP) a day. Underneath the chart, the sales aid claims "**Extend therapy >10 days without changing brand or dosage strength**." Furthermore, the back page contains the claim, "Xodol® provides effective pain relief and complies with APAP consumption guidelines when used for > 10 days." These presentations are misleading because they suggest that the use of Xodol, including Xodol 5 mg/300 mg, as recommended in the PI for over 10 days complies with the presented acetaminophen guideline recommendation of <2600 mg of acetaminophen per day, when this is not the case. The PI states that "The usual adult dosage is one or two tablets every four to six hours as needed for pain." Thus, when used as directed, a patient could consume up to 3600 mg of acetaminophen a day, which is well over the acetaminophen guideline recommendation of 2600 mg/day as presented in the sales aid. While we note that the last page of the sales aid suggests that the daily dosage of Xodol 5 mg/300 mg should not exceed eight tablets a day, which in turn would lead to a patient consuming no more than 2400 mg of acetaminophen per day, this disclosure does not mitigate the overall misleading implication created by these claims and presentations.[1]

Omission and Minimization of Risk

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made or with respect to the consequences that may result from the use of the drug as recommended or suggested in the materials. Although the sales aid contains information regarding the most frequently reported adverse reactions, precautions, and some warnings related to respiratory depression and acute abdominal conditions, it fails to communicate the full contraindication. Specifically, the sales aid fails to disclose that Xodol

[1] Should Victory Pharma wish to limit the dosing regimen for all strengths of Xodol to less than 2600 mg of acetaminophen a day, it should consider submitting a supplement to amend the Dosage and Administration section of the drug's PI.

should not be administered to patients who have previously exhibited hypersensitivity to acetaminophen or hydrocodone. Furthermore, it fails to adequately communicate that Xodol is contraindicated in patients known to be hypersensitive to other opioids as they may exhibit cross sensitivity to hydrocodone. While we note that the sales aid states, "As with all Schedule III hydrocodone products, patients known to be hypersensitive to opioids may exhibit cross sensitivity to hydrocodone," this statement fails to convey that in these patients, the use of Xodol is contraindicated. In addition, the sales aid fails to sufficiently disclose the risk of drug abuse and dependence associated with Xodol, a Schedule III controlled substance. While we note that the sales aid includes the statements "Warning: May be habit-forming" and "Hydrocodone may be habit-forming," these statements are either buried within the text or printed in small type underneath the drug's name. This information is not communicated with a prominence and readability reasonably comparable to claims about efficacy. We also note that the sales aid fails to display the symbol corresponding to a Schedule III controlled substance, as required by the Controlled Substances Act. 21 U.S.C. 825(b); 21 CFR 1302.03(b). By omitting this important risk information, the sales aid misleadingly suggests that Xodol is safer than has been demonstrated. The fact that the sales aid contains the statement, "Please consult accompanying complete Prescribing Information for XODOL® 5/300, 7.5/300, and 10/300" on the third page and back cover does not mitigate these misleading omissions.

Broadening of Indication

The sales aid suggests that Xodol is effective for use under broader conditions than has been demonstrated by substantial evidence or substantial clinical experience. For example, the tagline states, in relevant part, "**Relieves the pain**." On page two, the sales aid states:

- "**Xodol®-pain relief that reduces overload**"
- "**Only Xodol® combines the efficacy of hydrocodone with the lowest dose of APAP-for effective pain relief**..."

On the back cover, the sales aid states, "**Xodol® relieves the pain while reducing the risk.**"

These claims are misleading because they fail to convey the limitations to the indication for Xodol. As stated in the PI, "Xodol® is indicated for the relief of moderate to moderately severe pain." By failing to identify the limitations to the indication, these claims imply that Xodol is effective for the treatment of all pain when, to FDA's knowledge, this has not been demonstrated by substantial evidence or substantial clinical experience.

Conclusion and Requested Actions

For the reasons discussed above, the promotional piece misbrands Xodol in violation of the Act, 21 U.S.C. 352(a) & 321(n). *Cf*. 21 CFR 202.1(e)(5); (e)(6)(i); (e)(6)(ii) & (e)(6)(xviii).

DDMAC requests that Victory Pharma immediately cease the dissemination of violative promotional materials for Xodol that are the same as or similar to those described above. Please submit a written response to this letter on or before December 30, 2008, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for Xodol as of the date of this letter, identifying which of these

materials contain violations such as those described above, and explaining your plan for discontinuing use of such violative 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 20705-1266 or by facsimile at (301) 847-8444. In all future correspondence regarding this matter, please refer to the MACMIS ID #17030 in addition to the ANDA numbers. 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 Xodol comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

JuWon Lee, 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/

Juwon Lee

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