DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

December 22, 1998

TRANSMITTED VIA FACSIMILE

Allen Chao
Chairman, CEO, and President
Watson Pharmaceuticals, Inc.
311 Bonnie Circle
Corona, CA 91720

RE: NDA# 20-529
Condylox Gel 0.05% (podofilox gel)
MACMIS # 7343

WARNING LETTER

Dear Mr. Chao:

This Warning Letter concerns Oclassen Pharmaceuticals, Inc.'s (Oclassen), a subsidiary of Watson Pharmaceuticals, Inc., advertising and labeling materials for the promotion of Condylox Gel 0.5% (podofilox gel).[1] The Division of Drug Marketing, Advertising and Communications (DDMAC) has reviewed these promotional materials as part of its routine monitoring and surveillance program. From its review, DDMAC has concluded that Oclassen is disseminating promotional materials for Condylox that contain statements or suggestions that are false, lacking in fair balance, or otherwise misleading, in violation of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 331(a) and (b), 352(a), and 352(n) and applicable regulations.

Introduction

Condylox Gel (Condylox) is indicated for the topical treatment of external genital warts and perianal warts. Condylox may be applied directly by the patient and its use results in necrosis of visible wart tissue.

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[1] These materials include, but are not limited to: brochures W-036 (June 1998) and W-12021; file cards W-12003a (March 1998) and G1206/1(190); journal advertisement W-12002/R and Internet web pages (http://www.watsonpharm.com/site/branded/womanBranded.html and www.watsonpharm.com/site/press/031797.html (9/18/98)).

Risk Information: Lacking in Fair Balance and Inadequate Disclosure

Promotional materials are false or misleading, lacking in fair balance, or otherwise misleading if they fail to present the information relating to contraindications, warnings, precautions, and side effects associated with the use of a drug with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of the drug. These criteria refer to all techniques likely to achieve emphasis including, but not limited to, factors such as typography, layout, contrast, headlines, paragraphing, and white space. DDMAC concludes from its review of Oclassen's promotional materials that Oclassen failed to provide adequate disclosure of the risks associated with the use of Condylox.

First, brochure W-036 is an eight page brochure presenting claims of efficacy and benefits for Condylox.[2] The claims are presented in easy-to-read, bolded, and bulleted text on all pages. However, the adverse event information is only presented on the bottom of page five of the brochure in a non-bolded, non-bulleted, and significantly smaller-sized font.

Second, Oclassen's statement of adverse information regarding Condylox in this brochure fails to disclose the severe reactions associated with the use of Condylox. Oclassen's risk presentation in the brochure states:

> While using Condylox Gel, patients may experience some pain, burning, erosion, inflammation, itching, and bleeding of the treated warts. These effects are generally manageable and predominantly mild to moderate in nature.

However, the approved product labeling for Condylox states that while the severity of local adverse reactions were predominantly mild or moderate and did not increase during the treatment period, **severe reactions were reported in the clinical trials** and included in the adverse events section of the final labeling. For example, burning and pain were reported as:

Adverse Reaction	Mild	Moderate	Severe
Burning	37.1%	25.9%	11.5%
Pain	23.7%	20.4%	11.5%

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[2] Additional examples include brochure W-12021 and journal advertisement W-12002/R.

Oclassen failed to disclose these significant incidence rates in its promotional materials for Condylox.

Third, some promotional materials for Condylox either do not include any risk information or lack adequate disclosure. For example, file cards W-12003a and G1206/1(190) contain benefit claims but do not present any risk information. In addition, the World Wide Web site lists prescription drug products (including Condylox) with their respective indications but does not provide the approved product labeling for any of the products. The presentation of a claim, representation, or statement of intended use in promotional materials triggers the need for the approved product labeling and balancing information.

Finally, many of Oclassen's pieces present claims that there is "no need to wash off" Condylox after application. This claim lacks appropriate context and minimizes the risk information contained in the warning and precaution sections of the approved product labeling. The cautionary information states Condylox is not indicated for use on mucous membranes and that patients using Condylox should wash their hands thoroughly before and after each application and should avoid contact with the eyes.

False and Misleading Efficacy Presentations

Promotional materials are misleading if they contain a representation or suggestion, not approved in the labeling, that a drug is better or more effective than has been demonstrated by substantial evidence. In brochure W-036, Oclassen presents efficacy data for Condylox as the percent of all warts cleared (41-71%) and the rates "as reported in the literature" for wart clearance (45-88%). In addition, Oclassen claims that patients will have positive results in just 1 week. These claims are inconsistent with labeling and attempt to show Condylox as far more effective than has been shown by substantial evidence. The efficacy data from Condylox's approved product labeling states that in the two clinical trials, only 38.4% and 25.6% of patients, respectively, had complete clearing of the wart tissue at the end of 4 weeks of treatment. Thus, Oclassen claims that Condylox is more effective in its promotional pieces than was demonstrated by substantial evidence.

The claim that Condylox Gel is "the first patient-applied therapy for anogenital warts" is false because another product for genital warts that is applied by the patient was approved prior to the approval of Condylox.

Misleading Comparisons

Promotional materials are misleading if they contain a drug comparison that represents or suggests that a drug is safer or more effective than another drug when it has not been demonstrated to be safer or more effective by substantial evidence. In file card G1206/1(190), Oclassen presents a side-by-side comparison of Condylox Gel and Aldara Cream regarding median response time, duration of treatment, and total cost of therapy. This comparison is misleading. Specifically, Oclassen compares package inserts to suggest that Condylox is superior to Aldara based on information about each product's median response time, duration of treatment, and cost. However, this implied superiority presentation is not supported by substantial evidence. The data cited by Oclassen cannot support these claims because the data were not derived from head to head comparisons of the drugs in well-controlled studies. Furthermore, these data are inadequate because they do not take into account a variety of factors that influence valid comparisons including, but not limited to, variations in wart burden and complete wart clearance.

Furthermore, in brochure W-12021, Oclassen presents a claim that Condylox has a *faster clearance than Aldara with an asterisked reference that states* "based on a double-blind, placebo-controlled clinical trial conducted by 3M Pharmaceuticals." This trial, however, did not compare Aldara to Condylox. Instead, this study compared Aldara to its topical vehicle base. Thus, the comparison disclosed by Oclassen and its claim of "faster" are false or misleading.

Misleading Claims Related to Cost

In many of its pieces, Oclassen misleadingly presents claims related to the cost of the product and treatment options. Specifically, in brochure W-036, Oclassen presents a cost comparison of Condylox Gel, Aldara, and podophyllin under the headers "Cost-effective" and "least expensive treatment option available" with reference to a publication by Strauss MJ, et al.[3] However, Oclassen does not present any information to support a clinical comparison between Condylox and Aldara. The Strauss article does not contain cost information or clinical comparisons between Aldara and Condylox. Strauss is a review article that discussed 40 publications regarding treatments of genital warts with podophyllin, trichloroacetic acid (TCA), podofilox, cryotherapy, and laser therapy from 1977 to 1992. Moreover, Strauss does not support comparative claims. The authors concluded that because there was such a high

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[3] *Strauss MJ, Khanna V, Koenig JD, et al.* The cost of treating genital warts. Int J Dermatol. 1996;35:240-348.

variable success and recurrence rate among the treatment methods in the literature review, no therapy was consistently more effective than another.

In addition, the mere presentation of average wholesale price comparisons, as referenced in the brochure, is misleading and clearly not adequate to support such claims. In the absence of substantial evidence that demonstrates that the treatment effects are comparable, the product cost comparisons are misleading.

Conclusions and Requested Actions

Oclassen has disseminated promotional materials that lack fair balance and contain false or misleading claims and comparisons. Thus, in order to address these violations, Oclassen should:

1) Immediately cease the dissemination of the promotional materials and other promotional materials that contain the same or similar violations. Disseminate, a message to all sales representatives and marketing personnel involved in the sale and marketing of Condylox, instructing them to immediately cease dissemination of the promotional materials identified in this letter.

2) Provide a complete list of all promotional materials for Condylox that Oclassen will discontinue as a result of this Warning Letter and a complete list all materials that Oclassen intends to continue to disseminate subsequent to this letter.

3) Provide a plan of action, including the mailing and publication of a "Dear Healthcare Professional" letter, describing how Oclassen will correct the misleading impressions in the market place that Condylox has minimal side effects and is superior to Aldara.

Oclassen should respond in writing to DDMAC by January 11, 1999, of its intent to comply with DDMAC's requests. If Oclassen has any questions or comments, please contact Leah Palmer, Pharm.D. or Norman A. Drezin, R.Ph., J.D. by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-40, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds Oclassen that only written communications are considered official.

In all correspondence regarding this particular matter, please refer to MACMIS ID #7343 in addition to the NDA number.

Sincerely,

Minnie Baylor-Henry, R.Ph., J.D.
Director
Division of Drug Marketing,
Advertising and Communications