DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Karen L. Walles, M.S.
Assistant Director, Regulatory Affairs
Astellas Pharma US, Inc.
3 Parkway North
Deerfield, IL 60015

RE: NDA #21-518
VESIcare® (solifenacin succinate) Tablets
MACMIS #18451

Dear Ms. Walles:

This letter notifies Astellas Pharma US, Inc. (Astellas), and by copy, GlaxoSmithKline, which promotes VESIcare® (solifenacin succinate) tablets (VESIcare) for Astellas, that as part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a webpage[1] for VESIcare. The webpage is false or misleading because it presents unsubstantiated superiority claims and overstates the efficacy of VESIcare. Thus, the webpage misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a) & (n), and FDA implementing regulations. *See* 21 CFR 202.1(e)(5)(i); (e)(6)(i), (ii) & (e)(7)(i).

Background

According to the INDICATIONS AND USAGE section of its FDA-approved product labeling (PI):

> VESIcare is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

VESIcare is associated with numerous risks. The PI for VESIcare contains Contraindications concerning patients with urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, and in patients who have demonstrated hypersensitivity to the drug substance or other components of the product. The PI also contains Precautions regarding bladder outflow obstruction, gastrointestinal obstructive disorders and decreased gastrointestinal motility, controlled narrow-angle glaucoma, reduced renal and hepatic function, use with ketoconazole or other potent CYP3A4 inhibitors, and use in patients with congenital or acquired QT prolongation. The most common adverse events reported in clinical trials in patients treated with VESIcare were dry mouth, constipation, blurred vision and dyspepsia and the incidence of these side effects was higher in the 10 mg dose group compared to the 5 mg dose group.

[1] VESIcare webpage, at http://vesicare.com/hcp/about_vesicare/efficacy.html (last accessed April 12, 2010).

Unsubstantiated Superiority Claims

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 this has not been demonstrated by substantial evidence or substantial clinical experience. The webpage includes the following claims (emphasis in original; footnote omitted):

> Drier than tolterodine
> 59% of patients receiving VESIcare 5 mg or 10 mg reported no incontinence episodes at 12 weeks, versus 49% of [patients] receiving tolterodine 4 mg extended release in a head to head study (P=0.006). . . .

These claims are presented in conjunction with a graph depicting the percentage of patients reporting relief of incontinence at 12 weeks following VESIcare 5 mg or 10 mg (59%) or tolterodine 4 mg extended release (49%) administration. This presentation misleadingly implies that VESIcare is superior to tolterodine. Generally, claims of superiority must be supported by two adequate and well-controlled head-to-head clinical trials comparing appropriate doses and dose regimens of your drug and the comparator drug. The webpage cites to the STAR Trial from the Chapple, et al. reference[2] to support these claims. The STAR Trial was designed as a 12-week non-inferiority study comparing VESIcare with tolterodine extended release. Moreover, the results from the STAR Trial were based on an exploratory secondary analysis of a secondary endpoint with no pre-specified analysis plan. Thus, the STAR Trial does not constitute substantial evidence or substantial clinical experience to support a claim of superiority for VESIcare versus tolterodine. We note that the webpage discloses that these results are "from a secondary endpoint" below the graph; however, this does not mitigate the misleading implication conveyed by the overall presentation that VESIcare is superior to tolterodine.

Overstatement of Efficacy

Promotional materials are misleading if they represent or suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The webpage presents the following claims regarding VESIcare's effectiveness (emphasis in original; footnote omitted):

> Drier at 12 weeks
> 51% of subjects who took VESIcare once-daily 5 mg reported no incontinence episodes in their consecutive three-day diary prior to the end of the study, compared to 38% of subjects who were administered placebo.

These claims are presented in conjunction with a graph depicting the percentage of patients reporting no incontinence episodes at 12 weeks following VESIcare 5 mg (51%) or placebo (38%). This presentation misleadingly overstates the efficacy of VESIcare by suggesting that compared with placebo, a greater percentage of patients treated with VESIcare had no

[2] Chapple et al., *A Comparison of the Efficacy and Tolerability of Solifenacin Succinate and Extended Release Tolterodine at Treating Overactive Bladder Syndrome: Results of the STAR Trial*, 47 EUR. UROL. 464, 464-470 (2005).

incontinence episodes or were "drier at 12 weeks." The webpage cites to the Brunton, et al. article[3] to support these claims. This reference consists of a post-hoc subgroup secondary responder analysis of data pooled from secondary study endpoints. This study did not have a prospectively defined endpoint with a pre-specified statistical analysis plan. Furthermore, incontinence was not a requirement for study eligibility, and the number of patients with baseline incontinence was not provided. Thus, this study does not constitute substantial evidence or substantial clinical experience to support such a presentation. We note the webpage includes a statement below the graph disclosing the results are "from a post hoc responder analysis;" however, this does not mitigate the misleading implication conveyed by the overall presentation that patients on VESIcare are "drier at 12 weeks."

The webpage also includes the following claims (emphasis in original; footnote omitted):

> Drier at 1 year
> 60% of patients treated with VESIcare reported no incontinence episodes at the end of a 40-week, open-label extension safety study in a post hoc responder analysis.

These claims are presented in conjunction with a graph depicting the percentage of patients reporting no incontinence episodes following VESIcare 5 mg or 10 mg administration through 52 weeks (60%) or placebo administration through 12 weeks (about 40%). The webpage cites to the Haab, et al. reference[4] to support these claims. This reference consists of a 40-week, open-label, uncontrolled extension of a double-blind, placebo-controlled, 12-week efficacy study. In general, data derived from open-label studies are **not** sufficient to support such efficacy claims because the studies do not include sufficient measures to minimize bias. Additionally, the absence of a control group after 12 weeks makes it impossible to determine whether any improvement beyond 12 weeks in the study was due to drug treatment alone or due to other factors. Thus, this study does not constitute substantial evidence or substantial clinical experience to support the presentation on the webpage. We note that webpage discloses that the study was "open-label . . . in a post hoc responder analysis;" however, this does not mitigate the misleading implication conveyed by the overall presentation that VESIcare patients are "drier at 1 year."

Finally, the webpage includes the following claims (emphasis in original; footnote omitted):

> Warning Time
> Warning Time is defined in one study as the duration from the first sensation of urgency to voiding. Because the difference between making it to the restroom and having an incontinence episode may be a matter of seconds, an increase in Warning Time may help to improve some of your patients' chances of staying drier.
>
> VESIcare is the first once-daily OAB treatment that has demonstrated the ability to significantly increase Warning Time compared to placebo at the approved dose. . . .

---

[3] *See* Brunton S. & Kuritzky L., *Recent developments in the management of overactive bladder: focus on the efficacy and tolerability of once daily solifenacin succinate 5 mg*, 21 CURR. MED. RES. OPIN. 71, 71-80 (2005).
[4] Haab F, et al. *Long-Term Open-Label Solifenacin Treatment Associated with Persistence with Therapy in Patients with Overactive Bladder Syndrome*, 47 EUR. UROL. 376-384 (2005).

These claims are presented in conjunction with a graph titled, "**A Significant Improvement in Warning Time vs. Placebo**" (emphasis in original), depicting the median change in "warning time" from baseline following VESIcare (31.5 seconds) or placebo (12.0 seconds) administration. This presentation misleadingly overstates the efficacy of VESIcare by suggesting that patients experienced "a significant improvement" in the "duration from first sensation of urgency to voiding." The VENUS Trial, included in the reference cited[5] to support these claims, was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study that assessed the efficacy and safety of daily oral administration of VESIcare 5 mg and 10 mg. According to this trial, "WT [warning time] was measured using a stopwatch for the voids on the day preceding the baseline and the 12 week 3-day diary assessment." The VENUS Trial does **not** constitute substantial evidence or substantial clinical experience to support claims for "warning time." First of all, FDA is not aware of any data that support stopwatch measurements of "warning time" as a valid tool. Second, there is no accepted standard clinical definition of "warning time." Furthermore, the use of the term "urgency" in the definition of "warning time" is not well understood and may be interpreted differently among individuals. Lastly, FDA is not aware of valid and reliable data regarding patient responses to questions about "urgency."

Conclusion and Requested Action

For the reasons discussed above, the webpage misbrands VESIcare in violation of the Act, 21 U.S.C. 352(a) & (n), and FDA implementing regulations. *See* 21 CFR 202.1(e)(5)(i); (e)(6)(i), (ii) & (e)(7)(i).

DDMAC requests that Astellas immediately cease the dissemination of violative promotional materials for VESIcare such as those described above. Please submit a written response to this letter on or before April 26, 2010, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for VESIcare that 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, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS #18451 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 VESIcare comply with each applicable requirement of the Act and FDA implementing regulations.

[5] Data on file. Astellas Pharma US, Inc. (reporting data extracted from Study 905-UC-005 entitled, *A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Assess the Efficacy And Safety of Daily Oral Administration of 5 and 10 mg VESIcare (solifenacin succinate) for the Treatment of Urgency Associated with Overactive Bladder (VENUS)*).

Sincerely,

{See appended electronic signature page}

Janice Maniwang, Pharm.D., M.B.A.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

CC: Michele Hardy, Senior Director, US Regulatory Affairs
GlaxoSmithKline
5 Moore Drive
Research Triangle Park, NC 27709-3398

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21518	ORIG-1	ASTELLAS PHARMA US INC	VESICARE(SOLIFENACIN SUCCINATE) 5/10MG

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANICE L MANIWANG
04/12/2010