DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Bhavana Desai
Senior Director, Advertising and Promotional Compliance
Allergan, Inc.
2525 Dupont Drive AND-1M
P.O. Box 19534
Irvine, CA 92623-9534

RE: NDA #22-369
Latisse™ (bimatoprost ophthalmic solution) 0.03%
MACMIS #17844

Dear Ms. Desai,

As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the "FAQs"[1] and "About Safety"[2] pages of a consumer website and a "Launch display timeline" (timeline) (APC36ON09) for Latisse™ (bimatoprost ophthalmic solution) 0.03% (Latisse) submitted by Allergan, Inc. (Allergan) under cover of Form FDA-2253. These promotional materials are misleading because they omit and minimize risks associated with Latisse. Thus, the website and timeline misbrand Latisse in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) & (n); 321(n), and FDA implementing regulations. *See* 21 CFR 202.1(e)(3)(i); (e)(5) & (e)(7)(viii).

Background

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

> **LATISSE™** (bimatoprost ophthalmic solution) 0.03% is indicated to treat hypotrichosis of the eyelashes by increasing their growth including length, thickness and darkness.

Latisse is associated with several risks. The WARNINGS AND PRECAUTIONS section of the PI states (in pertinent part; emphasis in original):

> **Iris Pigmentation**
> Increased iris pigmentation has occurred when the same formulation of bimatoprost ophthalmic solution (**LUMIGAN®**) was instilled directly onto the eye. . . . [P]atients should be advised about the potential for increased brown iris pigmentation which is likely to be permanent.

[1] Latisse FAQs webpage, at http://www.latisse.com/FAQs.aspx?state=14 (last accessed June 19, 2009).
[2] Latisse About Safety webpage, at http://www.latisse.com/AboutSafety.aspx?state=20 (last accessed June 19, 2009).

. . . .

Lid Pigmentation
Bimatoprost has been reported to cause pigment changes (darkening) to periorbital pigmented tissues and eyelashes. . . .

Hair Growth Outside the Treatment Area
There is the potential for hair growth to occur in areas where **LATISSE™** solution comes in repeated contact with the skin surface. It is important to apply **LATISSE™** only to the skin of the upper eyelid margin at the base of the eyelashes using the accompanying sterile applicators, and to carefully blot any excess **LATISSE™** from the eyelid margin to avoid it running onto the cheek or other skin areas. . . .

Intraocular Inflammation
LATISSE™ solution should be used with caution in patients with active intraocular inflammation . . . because the inflammation may be exacerbated.
. . . .

Contamination of LATISSE™ or Applicators
The **LATISSE™** bottle must be kept intact during use. It is important to use **LATISSE™** solution as instructed, by placing one drop on the single-use-per eye applicator. The bottle tip should not be allowed to contact any other surface since it could become contaminated. The accompanying sterile applicators should only be used on one eye and then discarded since reuse of applicators increases the potential for contamination and infections. There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. . . .

Use with Contact Lenses
LATISSE™ contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to application of solution and may be reinserted 15 minutes following its administration. . . .

The PATIENT COUNSELING INFORMATION section of the PI states (in pertinent part; emphasis in original):

Potential for Unexpected Hair Growth or Eyelash Changes
Patients should be informed of the possibility of hair growth occurring outside of the target treatment area if **LATISSE™** repeatedly touches the same area of skin outside the treatment area. They should also be informed of the possibility of disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. . . .

The DOSAGE AND ADMINISTRATION section of the PI states (in pertinent part; emphasis in original):

. . . Do not apply to the lower eyelash line (see **WARNINGS AND PRECAUTIONS, 5.3** [**Lid Pigmentation**]. . . .)

Furthermore, the Latisse Patient Package Insert (PPI) states (in pertinent part; emphasis in original):

> **Are there any special warnings associated with LATISSE™ use?**
>
> **LATISSE™** solution is intended for **use on the skin of the upper eyelid margins at the base of the eyelashes**. . . . **DO NOT APPLY** to the lower eyelid. . . .

In addition, the Latisse PPI states (in pertinent part; emphasis in original):

> **What are the possible side effects of LATISSE™?**
>
> . . . If you develop a new ocular condition (e.g., trauma or infection), experience a sudden decrease in visual acuity, have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, you should immediately seek your physician's advice concerning the continued use of **LATISSE™** solution.

The most frequently reported adverse events associated with Latisse are eye pruritis, conjunctival hyperemia, skin hyperpigmentation, ocular irritation, dry eye symptoms, and erythema of the eyelid.

Omission and Minimization of Risk Information

Promotional materials are misleading it they fail to reveal material facts 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. Promotional materials are also misleading if they fail to present risk information associated with a drug with a prominence and readability reasonably comparable with the claims of effectiveness related to the drug.

Launch Display Timeline

The Launch Display Timeline presents an exhibit of the "Evolution of Lash Enhancers" starting in 4000 B.C., where "darkening powders [were] used to embellish the eye," and leading up to the present day with the "arrival" of Latisse. Specifically, at the end of the timeline describing the various "eyelash enhancers" through time, a large, colorful logo for Latisse is presented in conjunction with the large bolded headline, "2009, LATISSE™ Arrives," and other efficacy claims for Latisse such as, "LATISSE™ introduces an historic innovation in eyelash enhancement. LATISSE™ is the first and only prescription treatment approved by the FDA for hypotrichosis of the eyelashes (inadequate or not enough lashes) that is used to grow eyelashes, making them longer, fuller and darker. . . ." In stark contrast to this efficacy presentation, the only risk information that is presented for Latisse is included on a small placard to the lower right of the timeline exhibit. As such, this display fails to present risk information with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of the drug.

Furthermore, the risk information that is presented on the placard omits important risks associated with Latisse. In particular, the risk disclosure fails to convey the risk of hair growth outside of the treatment area if Latisse comes in repeated contact with the skin surface. In addition, although we note that the placard claims, "LATISSE™ solution is intended for use on the skin of the upper eyelid margins at the base of the eyelashes," this claim fails to state that Latisse should **not** be applied to the lower eyelash line, or lower eyelid, as stated in the Latisse PI and PPI, respectively. We note the statements, "Full prescribing information is available at www.latisse.com and www.allergan.com. Also available here." However, these statements do not mitigate this misleading omission and minimization of risk information.

The overall effect of this presentation minimizes the risks associated with Latisse and misleadingly suggests that Latisse is safer than has been demonstrated.

"FAQs" and "About Safety" Webpages

Similarly, the "FAQs" and "About Safety" webpages are misleading because they omit and minimize risks associated with Latisse treatment, thus implying that Latisse is safer than has been demonstrated by substantial evidence or substantial clinical experience.

For example, the webpages omit important risks associated with Latisse, including the risk of bacterial keratitis from contamination of Latisse or the applicators, and the risk of use with contact lenses. In addition, the webpages do not mention the potential for disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and the direction of eyelash growth. Moreover, the body of the "About Safety" webpage fails to communicate the potential for excess hair growth outside of the treatment area.

In addition, the risk presentations that are included on the webpages further minimize the risks associated with Latisse. For example, the webpages make the following claims (emphasis added):

- "Eye redness may occur immediately after use, but should usually last only for a short period of time. Eye redness alone is **not an allergic reaction** or inflammation, and doesn't mean that your eyes are being harmed . . . " ("FAQs" webpage);

- "Eye itching may occur immediately after use, but should usually last only for a short period of time (one to two weeks during initial use). Eye itching alone is **not an allergic reaction**, and doesn't mean that your eyes are being harmed. Consult your doctor if the itching persists or you notice other symptoms as well" ("FAQs" webpage); and

- "The most common side effects after using LATISSE® solution are an itching sensation in the eyes and/or eye redness, which were reported in approximately 4% of patients. These may occur immediately after use, but should usually last only for a short period of time. Eye itching and eye redness are **not allergic reactions**, and do not mean that your eyes are being harmed . . . " ("About Safety" webpage).

These claims minimize the risks associated with Latisse because they misleadingly suggest that eye itching and redness are **not** associated with allergic reactions of the eyes related to Latisse treatment. However, according to Latisse's PI, allergic conjunctivitis is an adverse reaction reported with bimatoprost ophthalmic solution, which is the same active ingredient that is used in Latisse. Moreover, eye redness and itching, which are frequent symptoms of an allergic reaction, usually resolve only after discontinuation of the drug. These claims are also concerning because patients are highly unlikely to be able to differentiate between eye redness associated with conjunctival hyperemia, allergic reaction, or inflammation without the advice of a healthcare provider. We note the statement, "Consult your doctor if the itching persists or you notice other symptoms as well," in the second bulleted claims; however this does not mitigate the misleading impression that patients with eye itching or redness are not having an allergic reaction and should not be concerned.

Furthermore, the "FAQs" and "About Safety" webpages contain the following statement (emphasis added):

- "Increased brown iris pigmentation has occurred when **similar** medications were instilled directly into the eye to treat elevated intraocular pressure/glaucoma."

This statement misleadingly suggests that only "similar" medications have been associated with the risk of increased iris pigmentation. However, brown iris pigmentation has been reported with bimatoprost ophthalmic solution, which is the **same** active ingredient present in Latisse. By omitting this material information and suggesting this side effect has only occurred with "similar" medications, this claim minimizes the risk of increased iris pigmentation.

In addition, the "About Safety" webpage presents the following question and answer presentation (emphasis in original):

- "**Is LATISSE® safe?**
  LATISSE® is an FDA-approved prescription treatment for hypotrichosis used to grow eyelashes, making them longer, thicker and darker. Hypotrichosis is another name for having inadequate or not enough eyelashes. The FDA reviewed clinical study results to verify the identity, potency, purity and stability of the ingredients, and demonstrated that the product is safe and effective for its intended use if used as prescribed."

The answer to the question, "Is LATISSE® safe?" fails to include any mention of the fact that the use of Latisse is associated with side effects, or to mention **any** of these side effects. In addition, the answer implies that Latisse is **especially** safe because the FDA has verified the identity, potency, purity, and stability of the ingredients in Latisse. This presentation thus significantly minimizes the risks of the drug.

Furthermore, the "FAQs" webpage contains the following presentation:

- "Why do the directions say to only apply LATISSE® solution to the base of the upper eyelashes?

> A clinical trial of LATISSE® was conducted on patients who applied the product to the base of their upper lashes only. Applied nightly, the transfer of LATISSE® solution from the upper to lower eyelid may occur naturally because the eyelids are closed and the eyelashes touch each other. . . ."

This presentation is misleading because the answer provided above omits material contextual information regarding the risk of excess hair growth outside of the treatment area if Latisse comes in continued contact with the skin area; it is because of this risk that the directions say to only apply Latisse to the base of the upper eyelashes. The above presentation also fails to disclose that Latisse should **not** be applied to the lower eyelash line, or lower eyelid, as stated in the Latisse PI and PPI, respectively.

Conclusion and Requested Action

For the reasons discussed above, the timeline and webpages misbrand Latisse in violation of the Act, 21 U.S.C. 352(a) & 352(n); 321(n), and FDA implementing regulations. *See* 21 CFR 202.1(e)(3)(i); (e)(5) & (e)(7)(viii).

DDMAC requests that Allergan immediately cease the dissemination of violative promotional materials for Latisse such as those described above. Please submit a written response to this letter on or before September 24, 2009, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for Latisse 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, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS # 17844 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 Latisse comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Sharon M. Watson, PharmD
LCDR, USPHS
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22369	ORIG-1	ALLERGAN INC	BIMATOPROST SOLUTION 0.03%

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

/s/

SHARON M WATSON
09/10/2009