



TRANSMITTED BY FACSIMILE

Susan H. Caballa
Vice President
Regulatory and Medical Affairs
Novartis Ophthalmics
11694 Johns Creek Parkway
Duluth, Georgia 30097

RE: NDA# 21-066
Zaditor (ketotifen fumarate ophthalmic solution), 0.025%
MACMIS ID# 11415

Dear Ms. Caballa:

This letter notifies Novartis Ophthalmics, Inc. (Novartis Ophthalmics) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the Food and Drug Administration (FDA) has identified a direct-to-consumer (DTC) television (TV) broadcast advertisement (ad) and websites (identified as www.z-drops.com/ae, www.Z-drops.com and www.Zaditor.com) that are in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Specifically, the 60-second DTC TV ad "Golf Balls" and Zaditor websites are misleading because they make unsubstantiated superiority claims and other claims that overstate the efficacy of the drug, and minimize or omit important risk information associated with the use of the drug.

Unsubstantiated Superiority Claims

Your website and TV ad are misleading because they contain a drug comparison that represents or suggests that Zaditor is more effective than other prescription drug products when such has not been demonstrated by substantial evidence or substantial clinical experience. (See 21 CFR 202.1(e)(6)(ii))

The www.Zaditor.com website contains textual claims that suggest or imply that Zaditor is superior to oral antihistamine "allergy pills." For example, a section of the website, entitled the "ZADITOR DIFFERENCE," promotes the following claim:

- "Taking an oral antihistamine for an eye allergy? You should know that Eye drops are more effective in relieving itching and swelling of the eyes."
"Ask your eye care practitioner if Zaditor would be a better choice for you."

A "patient brochure" on the website promotes:

- "You've got questions, we've got answers. If allergy pills aren't enough for your eyes - a solution."

In addition to promoting superiority over "allergy pills," the website promotes Zaditor as superior to other prescription eye drops. Specifically, the website uses patient testimonials and the results of a "patient satisfaction" survey questionnaire to suggest that Zaditor works better than other eye drops:

- "Since I started using Zaditor, my eye allergies no longer bother me. I've used other prescription drops but these work the best." (Patient testimonial)
- "85% (of patients) preferred Zaditor over their previous eye drop"

Similarly, the TV ad promotes Zaditor as being superior to oral prescription allergy medicines. The ad depicts a man who still has itchy eyes despite his oral prescription allergy medicine. He resorts to washing his eyeballs in a golf ball washer for relief. The voiceover in the ad offers Zaditor as a better option:

- "If allergy pills aren't enough for your itchy eyes...try Zaditor -- also called Z-drops."

The wording, context, and totality of these claims and presentations in your promotional campaign suggest Zaditor offers a superior way of treating eye allergy symptoms over other treatments. FDA is not aware of substantial evidence or substantial clinical experience demonstrating that Zaditor is superior to oral allergy medicines or other prescription eye drops for eye allergies. Therefore, these claims and presentations are misleading.

Overstatement of Efficacy

The www.Zaditor.com website contains claims that are misleading because they represent or suggest that Zaditor is more effective than has been demonstrated by substantial evidence or substantial clinical experience. (See 21 CFR 202.1(e)(6)(i))

The website presents misleading claims regarding the impact that Zaditor treatment can have on the lives of children with eye allergies. Specifically, the "PARENTS' CORNER" section of the website states:

- "They [i.e., Zaditor eye drops] provide immediate relief from itchy allergy eyes, so your child feels soothed and calmer in just minutes."

This claim of Zaditor's efficacy is included in a discussion of how children's allergies can cause missed school days, interrupted sleep, anxiety, difficulty concentrating and negative impact on school performance and social interactions. We are not aware of any data supporting that treatment with Zaditor can soothe or calm children, or alleviate or prevent these problems associated with children's allergies, as suggested by the context of your claim. Therefore, your promotion of the benefits of Zaditor in children is misleading.

The website also presents other misleading claims such as “...Zaditor is so effective at working fast and **keeping the itch away** (emphasis added)” and “You’ve got questions, we’ve got answers. If allergy pills aren’t enough for your eyes – **a solution** (emphasis added).” These claims suggest that Zaditor can provide long-term relief. However, the approved product labeling (PI) for Zaditor states that “Zaditor is indicated for the **temporary** prevention of itching of the eye due to allergic conjunctivitis (emphasis added).” In addition, FDA is not aware of substantial evidence or substantial clinical experience to support a claim for long-term relief for eye allergy symptoms. Therefore, your claims are misleading because they overstate the proven efficacy of Zaditor.

Omission or Minimization of Risk Information

Your websites and TV ad omit or minimize risk information about Zaditor. Most notably, the www.z-drops.com/ae website contains claims promoting the effectiveness of Zaditor in alleviating eye allergies, but presents no risk information about the drug.

The TV ad is misleading because it fails to clearly communicate, and thereby minimizes, the risks associated with the use of Zaditor. The risk information is stated in a fast-paced voiceover that impedes the ability of the consumer to understand, much less comprehend, this important information. Moreover, the competing audio and graphic presentations during the risk information interfere with communication of the risk information. During the audio presentation of the adverse event risk information that “clinical studies show 10-25% experienced eye redness, headache, and hay fever similar to symptoms with eye allergies,” the TV ad displays graphics of the Zaditor bottle sitting on the grass, accompanied by a SUPER relaying the efficacy information “Relieves and prevents itchy eyes due to allergies.” Presenting these competing and directly contradictory risk and textual efficacy messages together interferes with and undermines the consumer’s ability to hear and comprehend the risk information. In fact, in this context, the voiceover information could be mistaken for a description of the patients who were successfully treated with Zaditor, rather than a description of the patients experiencing adverse events with Zaditor. The juxtaposition of these cognitively dissonant messages therefore further undermines the communication of risk information and minimizes the risk profile of the drug. The totality of competing audio and visual elements during the fast-paced risk presentation misleadingly suggests that Zaditor is safer than has been demonstrated by substantial evidence or substantial clinical experience (See 21 CFR 202.1(e)(6)(i)).

The www.Zaditor.com website also minimizes the risks associated with Zaditor. The website claims “Zaditor is so safe it’s been approved for treating children age three and older.” The fact that a drug is approved in children does not mean that it is “safe” in an absolute sense, but rather that the potential benefits of the drug justify the potential risks in that patient population. To suggest that approval in children means that Zaditor is especially “safe” is misleading.

Your www.Zaditor.com website also is misleading because it minimizes the risks associated with the use of Zaditor by failing to present them with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of the drug. (See 21 C.F.R. 202.1 (e) (7)(viii)) The website presents the large, colorful headline “ZADITOR DIFFERENCE” followed by bulleted efficacy claims such as “Quick relief from itchy irritation” and “Continued relief for up to 12

hours.” In contrast, the risk information on this page is presented without a headline or any additional emphasis, on the bottom of the page, in a small print single-spaced paragraph.

Failure to Make Adequate Provision for Dissemination of the PI

FDA’s prescription drug advertising regulations require sponsors of broadcast ads to present a "brief summary" of risk information or alternatively, make “adequate provision...for dissemination of the approved or permitted package labeling in connection with the broadcast presentation” (21 CFR 202.1(e)(1)). The Zaditor TV ad does not contain a brief summary. Consequently, the regulations require that adequate provision be made for dissemination of the approved package labeling (or “PI”) in connection with the ad. The TV ad offers the website address www.z-drops.com/ae as one of the mechanisms by which consumers can receive “more information” about Zaditor. However, this website fails to provide the Zaditor PI or indicate where it can be accessed. (We further note that this website includes a link to another website, www.z-drops.com, that also does not display a link to the Zaditor PI or otherwise direct consumers to the location of the Zaditor PI on the website.) Therefore, the www.z-drops.com/ae website referenced in the TV ad fails to “make adequate provision for dissemination” of the approved package labeling (including full risk information) for Zaditor.

Failure to Submit Post-Marketing Reports

The www.Zaditor.com website was not submitted on Form FDA 2253 at the time of initial dissemination, as required by the post-marketing reporting requirements (21 CFR 314.81(b)(3)(i)).

Conclusions and Requested Actions

Novartis Ophthalmics should immediately discontinue the TV ad, websites, and all other promotional materials and activities for Zaditor that contain the same or similar violative presentations. Novartis Ophthalmics should submit a written response to DDMAC on or before July 2, 2003, describing its intent and plans to comply with the above. In its letter to DDMAC, Novartis Ophthalmics should include the date on which these and other similarly violative materials were discontinued.

Novartis Ophthalmics should direct its response to the undersigned by facsimile at (301) 594-6771, or in writing at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857. In all future correspondence on this matter, please refer to MACMIS ID# 11415 as well as the NDA number. DDMAC reminds you that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Joan Hankin, JD
Consumer Promotion Analyst
Division of Drug Marketing,
Advertising, and Communications

{See appended electronic signature page}

Sonny Saini, 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
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/s/

Sonny Saini
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Joan Hankin
6/18/03 04:30:59 PM

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Quick Facts

pollen counts are highest between 5 and 10 a.m.

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ABOUT EYE ALLERGIES



About Eye Allergies

What exactly causes itchy eyes due to allergies? An allergy is an exaggerated immune response to a relatively harmless foreign substance such as pollen or dust mites (allergens). When an allergen comes in contact with a sensitized eye, a cascade of chemical and cellular reactions starts:

- Mast cells on the surface of the eye rupture, releasing histamine and other chemical Mediators that start to cause redness, itching and swelling.
- In response, other cells called eosinophils are attracted into the area.
- These cells also rupture, releasing more agents that keep the allergic response going.

An estimated 40 million Americans suffer from eye allergies, the most common of which are seasonal and perennial allergic conjunctivitis.

Seasonal conjunctivitis (hay fever conjunctivitis) is more prevalent:

- Triggered by tree, grass and weed pollens during spring and fall
 - Causes red, itchy, watery eyes, and sometimes involves the nose and throat
- Perennial conjunctivitis is a year-round allergic condition:
- Triggered by animal dander, dust, molds and other nonseasonal allergens
 - Causes similar symptoms to seasonal conjunctivitis, although usually milder

Living with eye allergies is easier when you know the cause and can limit your exposure. Your eye care physician can help you find the culprit and recommend the right medication for you.

In mild cases, lubricating eye drops like GenTeal® can be used to wash out allergens and sooth eye irritation. For most allergy sufferers, though, a prescription multiple action eye drop is needed to provide fast, long-lasting relief.

Multiple action ZADITOR eye drops are especially effective because they prevent recurrence of symptoms for up to twelve hours. Because they are applied directly to the affected area, eye drops bring relief in minutes compared to antihistamine tablets which may take an hour or more to work. ZADITOR is so safe it's been



approved for treating children age three and older.

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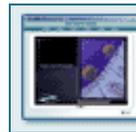
Quick Facts

Wood or tile flooring harbors fewer allergens than carpeting.

ZADITOR DIFFERENCE



ZADITOR Works Three Ways To Relieve Itchy Allergy Eyes



HOW
 ZADITOR WORKS

Fast relief that lasts 12 hours. That's what ZADITOR eye drops can do for your itchy allergy eyes. Just minutes after application, your eyes are already feeling better.

In clinical trials, ZADITOR has been proven to provide relief with a high level of patient satisfaction. That's because ZADITOR has a multiple mechanism that works on different parts of the complex immune response in your eyes. Targeting more than one stage of the process is why Zaditor is so effective at working fast and keeping the itch away.

ZADITOR gives you:

- Quick relief from itchy irritation
- Continued relief for up to 12 hours
- Prevention of symptom recurrence (with twice-a-day use)

It's a difference you can feel right away. In a recent survey* of 2,700 patients with eye allergies:

- 85% preferred ZADITOR over their previous eye drop
- Nearly 90% said they would ask their doctor to prescribe it again

* commissioned by Novartis Ophthalmics in 2000

ZADITOR is easy to use-just one drop in the affected eye twice a day and you're done. If you wear soft contact lenses, wait at least 10 minutes before inserting them. And never wear contact lenses if your eyes are red. Do not use ZADITOR to treat irritation from contacts.

Taking an oral antihistamine for an eye allergy? You should know that:

- Eye drops are more effective in relieving itching and swelling of the eyes

Ask your eye care practitioner if ZADITOR would be a better choice for you.



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Quick Facts

An allergy is an exaggerated immune response to a relatively harmless foreign substance.

Helping Your Child Cope With Ocular Allergies

Missed school days, interrupted sleep, anxiety, difficulty concentrating. The disruptive impact of your child's allergy goes far beyond its physical symptoms. It can even affect school performance and social interactions.

Because it's often difficult to determine what's an allergy or just a cold, see your pediatrician early and get a referral to an allergy specialist if further diagnosis is needed.

Finding the right ocular medication can be crucial. Ask your doctor to prescribe ZADITOR eye drops. They're so safe, they're approved for children as young as three. They provide immediate relief from itchy allergy eyes, so your child feels soothed and calmer in just minutes. ZADITOR lasts 12 hours, so you only have to administer the drops twice a day.

To help you learn more about children's allergies and how to help your child adapt, see our list of [related links](#).



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ZADITOR DIFFERENCE



Testimonials

"I really love these drops. ZADITOR stops my eyes from itching and they feel soothing, too."

- Beverly Reibman, Delray Beach, FL

"Since I started using ZADITOR, my eye allergies no longer bother me. I've used other prescription drops but these work the best."

- Steve Armus, Racine, WI



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**THE PRESCRIPTION EYE DROP THAT BOTH
PREVENTS AND RELIEVES ITCHY EYES
DUE TO ALLERGIES FOR UP TO 12 HOURS.**



You've got questions, we've got answers. If allergy pills aren't enough for your eyes – a solution.

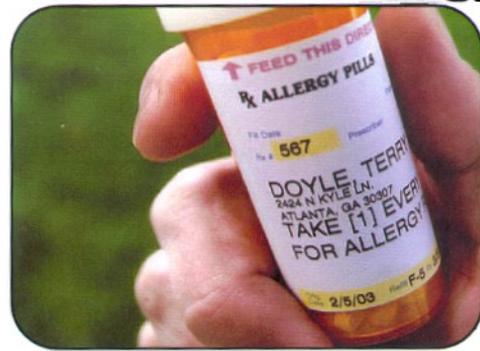




VISUAL: Open on a grounds keeper mowing grass, clippings flying. Two men carrying golf clubs walk past.



VISUAL: The main character rubs his eyes, which are all itchy and watery. The pollen hangs heavy in the afternoon haze.



VISUAL: He reaches into his pocket and pulls out his allergy pills taking a look at the directions.



VISUAL: He studies the pill bottle with a look of confusion.



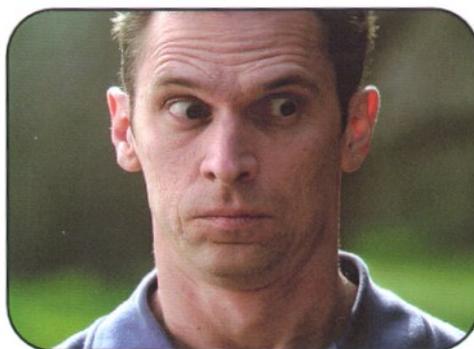
VISUAL: Man slaps himself on the back of the head, and his eyeball pops out onto his hand.



VO: If allergy pills aren't enough for your itchy eyes...
VISUAL: He washes the extracted "eyeball" in the ball washer.



VO: ...try Zaditor - also called Z-drops.
VISUAL: Man #2 looks on with a look of confusion.



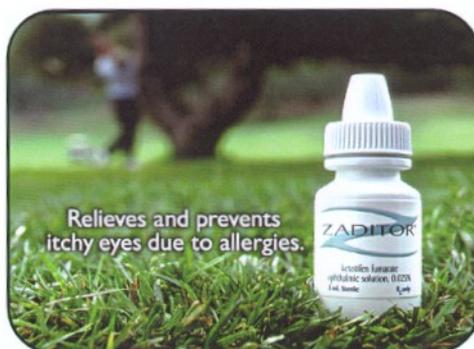
VO: The prescription eye drop that...
VISUAL: Man #1 pops back into screen with both eyes open.



VO: ...relieves and prevents itchy eyes due to allergies, for up to 12 hours.
VISUAL: Man #1 looks pleased and nods to man #2.



VO: Side effects are generally mild.
VISUAL: Man #2 gives man #1 an exaggerated look of approval.



VISUAL: Product on screen,
SUPER: Relieves and prevents itchy eyes due to allergies.



VO: Ask your doctor if Zaditor's right for you. And call today for more information, plus a ten-dollar rebate.
VISUAL: Z-drops, 800#, website and magazine information on screen.