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Inspections, Compliance, Enforcement, and Criminal Investigations

Gsk



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

04/19/2010

Andrew Witty, Chief Executive Officer
GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

RE: NDA 22-055

Altabax® (retapamulin ointment), 1%
MACMIS# 18333

WARNING LETTER

Dear Mr. Witty:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional slim jim with pull out tab (ABX307R0) (slim jim) for Altabax® (retapamulin ointment), 1% (Altabax) submitted by GlaxoSmithKline (GSK) under cover of Form FDA-2253. The slim jim is false or misleading because it broadens the indication of Altabax, makes unsubstantiated superiority claims, and omits and minimizes important risk information associated with Altabax. Thus, the slim jim misbrands the drug 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)(3)(i), (ii); (e)(5); (e)(6)(i), (ii), (vii), & (xviii); (e)(7)(viii). These violations are concerning from a public health perspective because they suggest that Altabax is safer or more effective than has been demonstrated by substantial evidence or substantial clinical experience.

Background

According to the FDA-approved product labeling (PI) (in pertinent part, emphasis original): ALTABAX is indicated for use in adults and pediatric patients aged 9 months and older for the topical treatment of impetigo (up to 100 cm² in total area in adults or 2% total body surface area in pediatric patients aged 9 months or older) due to *Staphylococcus aureus* (methicillin-susceptible isolates only) or *Streptococcus pyogenes*. To reduce the development of drug-resistant bacteria and maintain the effectiveness of ALTABAX and other antibacterial drugs, ALTABAX should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

WARNINGS AND PRECAUTIONS

Local Irritation

In the event of sensitization or severe local irritation from ALTABAX, usage should be discontinued, the ointment wiped off, and appropriate alternative therapy for the infection instituted.

Not for Systemic or Mucosal Use

ALTABAX is not intended for ingestion or for oral, intranasal, ophthalmic, or intravaginal use. ALTABAX has not been evaluated for use on mucosal surfaces.

Potential for Microbial Overgrowth

The use of antibiotics may promote the selection of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

Prescribing ALTABAX in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Broadening of Indication

The slim jim is misleading because it suggests that Altabax is effective in a broader range of conditions than has been demonstrated by substantial evidence or substantial clinical experience.

The slim jim includes the following claims and presentations (footnotes omitted)¹:

- Bar graph entitled, "ALTABAX is more potent *in vitro* than mupirocin . . . All *S. aureus* isolates studied (n=1975)," which compares the MIC90 (µg/mL) of Altabax to mupirocin (page 2)
- "32x more potent *in vitro*. . . and ALTABAX was just as active *in vitro* against *S. aureus* resistant to mupirocin (ALTABAX MIC90 remained at 0.12 µg/mL)" (page 2)
- Bar graph entitled, "ALTABAX has a low propensity to develop resistance in an *in vitro* multipassage study . . . All *S. aureus* isolates studied (n=12)," which compares the percentage of *S. aureus* isolate with a MIC of ≤ 2 µg/mL after ≤ 20 days between Altabax and mupirocin (page 2)
- "TARGET PATHOGENS
 - ALTABAX is 32x more potent *in vitro* than mupirocin against *S. aureus*...
 - ALTABAX is the only prescription topical antibacterial for impetigo with simple 5-day b.i.d. dosing" (pages 3 and 5)
- "ALTABAX has superior efficacy vs. vehicle in the treatment of impetigo due to *Staphylococcus aureus* and *Streptococcus pyogenes*" (page 4)

These claims are misleading because they create the overall impression that Altabax is approved to treat all strains of *Staphylococcus aureus*, when this is not the case. For example, the graphs on page 2 suggest, among other things, that Altabax is active against all *S. aureus* isolates studied. This implication of broad efficacy against *S. aureus* is exacerbated by the footnote associated with the potency graph on page 2, which states:

A multicenter, global surveillance program tested clinical isolates including pathogens resistant to other commonly used antibiotics. Isolates were collected between March 2004 and March 2005 in countries including the US. Isolates were collected from adults and children who had hospital- or community-associated uncomplicated SSSIs, including impetigo, with only one isolate taken from each subject².

In addition to implying that Altabax is effective against all *S. aureus* strains, this description implies that Altabax is effective at treating uncomplicated SSSIs other than impetigo. This presentation is particularly concerning considering that Altabax is not approved for any other uncomplicated SSSIs and received a non-approval for the uncomplicated SSSIs indications of secondarily infected traumatic lesions (SITL) and secondarily infected dermatoses (SID). Furthermore, in clinical trials for SITL, Altabax *in vitro* susceptibility did not correlate with clinical success rates in patients with methicillin-resistant *S. aureus* (MRSA).

Similarly, the other presentations cited above in the slim jim contain prominent claims about the drug's efficacy in targeting *S. aureus* and suggest the drug is effective at treating all strains of *S. aureus*. However, Altabax is only approved to treat impetigo due to **methicillin susceptible isolates of *Staphylococcus aureus***. (emphasis added) Any implication that Altabax could be effective against other organisms, such as MRSA, is extremely concerning from a public health perspective as it could lead to irreparable harm in patients denied effective therapy.

We note that the approved indication for Altabax and the footnote, "Methicillin-susceptible isolates only," are presented at the bottom of pages one and four of the slim jim in small font in single-spaced block paragraph format. However, these disclosures are not sufficient to overcome the misleading impression created by the totality of the prominent claims and presentations in the piece that suggest that Altabax is effective against any strain of *S. aureus*.

Furthermore, especially when viewed in the context of the numerous other claims in the slim jim that otherwise broaden Altabax's indication, the claim cited above that Altabax "was just as active *in vitro* against *S. aureus* resistant to mupirocin" misleadingly suggests that Altabax is effective in treating infections caused by strains of *S. aureus* that are resistant to mupirocin, when this has not been demonstrated by substantial evidence or substantial clinical experience. The reference² cited in support of this claim only presents comparisons of *in vitro* data. As the slim jim itself notes at the bottom of page two, *in vitro* data do not necessarily predict or correlate with clinical efficacy. Accordingly, *in vitro* data, which have limited, if any, utility for healthcare practitioners with respect to their clinical experience with a drug, is insufficient to support such a claim. However, the presentation of this *in vitro* data to practicing clinicians (the ad's intended audience), particularly in the context of the overall impression created by the ad, misleadingly implies that the cited *in vitro* data are clinically relevant. That is, the presentation c

this *in vitro* data in the slim jim to practicing clinicians misleadingly implies that Altabax is clinically effective in treating infections caused by mupirocin-resistant *S. aureus*. We are not aware of substantial evidence or substantial clinical experience to support the implication that Altabax is effective against strains of *S. aureus* that are resistant to mupirocin. We note the inclusion of the statement, “*In vitro* results do not necessarily correlate with clinical efficacy,” at the bottom of page two. However, this inclusion does not mitigate the misleading suggestion conveyed by the above claim, by itself and in the context of the other claims in the slim jim, that Altabax will be clinically effective against infections caused by *S. aureus* strains that are resistant to mupirocin.

The slim jim also includes the following claims and presentations, which compare Altabax to mupirocin (footnotes omitted):

- Table comparing the mechanism of action of Altabax against that of Bactroban Ointment (mupirocin) (page 2)
- “...and ALTABAX has a longer postantibiotic effect than mupirocin *in vitro*” (page 2)
- Table comparing the number of applications per course of therapy for Altabax against that of Bactroban Ointment (pages 3 and 5)

These claims and presentations are misleading because they imply that Altabax is a safe and effective alternative to Bactroban Ointment (mupirocin) for the conditions and causative pathogens that mupirocin is indicated to treat, when this is not the case. Mupirocin ointment is indicated for the topical treatment of impetigo due to: *S. aureus* and *S. pyogenes*. However, unlike Altabax’s impetigo indication, the indication for mupirocin does not include limitations on specific microorganisms. Altabax is only indicated to treat “impetigo due to *Staphylococcus aureus* (**methicillin-susceptible isolates only**) or *Streptococcus pyogenes*.” (emphasis added) Therefore, these claims misleadingly broaden the indication of Altabax.

Unsubstantiated Superiority Claims

The slim jim contains multiple claims regarding the superior potency of Altabax over mupirocin. These claims include the following (footnotes omitted):

- Bar graph entitled, “ALTABAX is more potent *in vitro* than mupirocin. . . ,” which compares the MIC90 ($\mu\text{g/mL}$) of Altabax to mupirocin (page 2)
- “32x more potent *in vitro*. . . and ALTABAX was just as active *in vitro* against *S. aureus* resistant to mupirocin (ALTABAX MIC90 remained at 0.12 $\mu\text{g/mL}$)” (page 2)
- “ALTABAX is 32x more potent *in vitro* than mupirocin against *S. aureus*” (pages 3 and 5)

Taken together, the totality of these presentations implies that Altabax is a more effective agent for treating impetigo than mupirocin. However, the reference² cited in support of these presentations does not present a head-to-head clinical comparison of Altabax to mupirocin. The reference presents comparisons of *in vitro* data only. As noted above, *in vitro* data do not necessarily predict clinical efficacy. Additionally, the cited study² tested isolates obtained from multiple countries. These data are not sufficient to predict and compare *in vitro* activity of topical antibacterials against isolates solely encountered in U.S. environments. Furthermore, the cited study² tested isolates obtained between March 2004 and March 2005. Because there is a correlation between increases in exposure to antibiotics and resistance patterns, these data may not reflect the current *in vitro* resistance profile of Altabax. We are not aware of substantial evidence or substantial clinical experience to support the implication created by this slim jim that Altabax is superior to mupirocin for the treatment of impetigo.

In addition, the slim jim includes the following claims and presentations, which suggest that Altabax is clinically superior to mupirocin in terms of resistance (footnotes omitted):

- “ALTABAX has a low propensity to develop resistance in an *in vitro* multipassage study” (pages 2, 3 and 5)
 - o Bar graph which compares the percentage of *S. aureus* isolates with a MIC of $\leq 2 \mu\text{g/mL}$ after ≤ 20 days between Altabax and mupirocin. The graph shows that Altabax has 100% of isolates with a MIC of $\leq 2 \mu\text{g/mL}$ after ≤ 20 days and mupirocin has 0% of isolates with a MIC of $\leq 2 \mu\text{g/mL}$ after ≤ 20 days (page 2)
- “ALTABAX demonstrated a lower potential to develop resistance” (page 2)
- “Mupirocin demonstrated a higher potential to develop resistance” (page 2)
- “Resistance to mupirocin occurred as early as Day 4” (page 2)

The above claims create an overall impression that Altabax is associated with less resistance than mupirocin in clinical practice. The FDA is not aware of substantial evidence or substantial clinical experience to support claims that Altabax has (or will have) a lower propensity to develop resistance than mupirocin. These claims rely on *in vitro* data³ for support. However, *in vitro* data are not substantial evidence to support a claim of less resistance for Altabax. Furthermore, the PI for Altabax includes a Warning and Precaution regarding the potential development of drug resistance. The PI states

"Prescribing ALTABAX in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of development of drug-resistant bacteria." The implication that Altabax has less resistance is especially concerning in light of the slim jim's suggestion that Altabax is safe and effective for the treatment of all strains of *S. aureus*, when this is not the case.

Finally, the slim jim includes the following claims and presentations, which suggest that Altabax has a superior mechanism of action to other antibacterials, including Bactroban (footnotes omitted):

- "Not all topical antibiotics agents are the same. . ." (page 2)
- "ALTABAX is the first in a new and different class of prescription antibacterials – *the pleuromutilins*" (page 2)
- Table comparing the mechanism of action of Altabax to Bactroban Ointment (mupirocin) (page 2)

These claims misleadingly imply that Altabax is clinically superior to mupirocin because Altabax affects three aspects of protein synthesis while Bactroban Ointment (mupirocin) affects only one aspect of protein synthesis. However, there is no evidence that interference with more than one aspect of protein synthesis results in greater clinical efficacy. Furthermore, the FDA is not aware of adequate and well-controlled head-to-head clinical trials that compare the clinical efficacy of Altabax and Bactroban Ointment and/or any other mupirocin products. Altabax was only shown to be superior to placebo (vehicle) in a clinical efficacy study in patients with impetigo due to *Staphylococcus aureus* (methicillin-susceptible isolates only) or *Streptococcus pyogenes* in patients aged 9 months or older.

Furthermore, page two of the slim jim contains the claim, ". . . and ALTABAX has a longer postantibiotic effect than mupirocin *in vitro*." This claim is misleading because it implies that Altabax is clinically superior to mupirocin because of a longer post-antibiotic effect, when this has not been demonstrated by substantial evidence or substantial clinical experience. As discussed above, *in vitro* data do not necessarily correlate to clinical efficacy, and it is misleading to use such data to imply any clinical effect. Post-antibiotic effect (PAE) is typically defined as the continued suppression of bacterial growth after administration of a systemic antibiotic has ceased and the serum concentration of the drug has fallen below the MIC. It is a characteristic of the metabolism of systemic antibiotics. The clinical significance of PAE for topical antibiotics, such as Altabax, is unclear.

The misleading nature of these claims is amplified by the overall impression created by the slim jim that Altabax is superior to mupirocin. We note that the footnotes, "*In vitro* results do not necessarily correlate with clinical efficacy," and "The effectiveness of ALTABAX versus mupirocin has not been studied in a clinical trial," are presented at the bottom of pages two, three, and five of the slim jim. However, these footnotes are not sufficient to mitigate the misleading impression created by the totality of the prominent claims and presentations in the piece, which convey that Altabax has a superior resistance profile, greater potency, and superior mechanism of action to mupirocin, and suggest it is therefore clinically superior to mupirocin.

In summary, the FDA is unaware of any data demonstrating the superior efficacy of Altabax to mupirocin for the treatment of impetigo, such as data showing Altabax to (1) be more potent; (2) have less resistance; (3) have a superior mechanism of action; or (4) have a longer post-antibiotic effect than mupirocin. In the absence of adequate and well-controlled head-to-head clinical studies of Altabax versus mupirocin demonstrating the superiority of Altabax, these claims and presentations are misleading.

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. The only risk disclosure presented for Altabax in the slim jim is the most common drug-related adverse reaction, which is found at the bottom of page three written in small font size in single-spaced block paragraph format and on page four. However, the slim jim misleadingly fails to communicate any of the Warnings and Precautions for Altabax. The omission of the Warning and Precaution information regarding the potential development of drug resistance is particularly concerning given the numerous misleading claims in the piece implying Altabax is effective against strains of *S. aureus* it is not indicated to treat and implying Altabax is associated with very low resistance.

Conclusion and Requested Action

For the reasons discussed above, the slim jim misbrands Altabax in violation of the Act, 21 U.S.C. 352(a) & 321(n). Cf. 21 CFR 202.1(e)(3)(i), (ii); (e)(5); (e)(6)(i), (ii), (vii), & (xviii); (e)(7)(viii).

DDMAC requests that GSK immediately cease the dissemination of violative promotional materials for Altabax such as those described above. Please submit a written response to this letter on or before May 3, 2010, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Altabax that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Because the violations described

above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional 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 facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS ID #18333, in addition to the NDA number. We remind you that only written communications are considered official. If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Altabax comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely

/S/

Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

1 Please note that for the purpose of this letter, page one represents the front cover of the slim jim, page two represents the inside spread of the slim jim, page three represents the back cover of the slim jim, and pages four and five represent a tabbed pull-out card that is inserted in a pocket inside the slim jim.

2 Data on file ABX107-01, GlaxoSmithKline.

3 Kosowska-Shick K, Clark C, Credito K, et al. Single- and multistep resistance selection studies on the activity of retapamulin compared to other agents against *Staphylococcus aureus* and *Streptococcus pyogenes*. *Antimicrob Agents Chemother*. 2006;50:765-769.

Links on this page: