U.S. FOOD & DRUG ADMINISTRATION

Robert J. Moccia
President and CEO
Encore Dermatology, Inc.
5 Grand Valley Parkway, Suite 200
Malvern, PA 19355

October 16, 2020

RE: Docket No. FDA-2020-P-1421

Dear Mr. Moccia:

This letter responds to your citizen petition received on May 22, 2020 (Petition), submitted on behalf of Encore Dermatology, Inc. (Encore or Petitioner). In the Petition, you request that the Food and Drug Administration (FDA, the Agency, or we) refuse to approve the Glenmark Pharmaceuticals Limited (Glenmark) abbreviated new drug application (ANDA), and other similarly formulated proposed products submitted under 21 U.S.C. 355(j) seeking approval to market a generic version of Encore's Impoyz (clobetasol propionate) topical cream, 0.025%.

Specifically, your Petition requests that FDA take the following actions:

(1) Refuse to approve the Glenmark generic topical clobetasol propionate product submitted under ANDA 214191, and any similarly formulated generic products.[1]

(2) Require Glenmark and similarly situated generic applicants to submit their new formulations under a new drug application with adequate data demonstrating safety and effectiveness.[2]

(3) If FDA does allow Glenmark, and similarly situated generic applicants, to proceed with an ANDA, require Glenmark and others to: (a) establish bioequivalence with a comparative clinical endpoint study; and (b) support their ANDAs with (i) systemic exposure data, (ii) HPA axis suppression data, and (iii) local safety data to ensure that the proposed formulations have the same safety profile as Impoyz.[3]

FDA has carefully considered the information submitted in the Petition. For the reasons set forth below, your Petition is denied without comment on whether we will take the actions you request.

[1] Petition at 2.
[2] Id.
[3] Id.

U.S. Food & Drug Administration
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I. BACKGROUND

A. Impoyz (clobetasol propionate)

Encore holds new drug application (NDA) 209483 for Impoyz (clobetasol propionate) topical cream, 0.025%. FDA approved the NDA for Impoyz (clobetasol propionate) topical cream, 0.025%, for topical administration, on November 28, 2017. Impoyz is a corticosteroid drug product indicated for the treatment of moderate to severe plaque psoriasis in patients 18 years of age and older. The product labeling indicates that it is not known if Impoyz is safe and effective in children under 18 years of age. The labeling further states that because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of systemic toxicity, including hypothalamic pituitary-adrenal (HPA) axis suppression, when treated with topical drugs. Rare systemic toxicities such as Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients, especially those with prolonged exposure to large doses of high potency topical corticosteroids.[4]

The active ingredient (or drug substance) in Impoyz is clobetasol propionate.[5] Impoyz is an oil-in-water emulsion product. Impoyz contains the following inactive ingredients: butylated hydroxytoluene, cetostearyl alcohol, cyclomethicone, diethylene glycol monoethyl ether (Transcutol or DEGEE), glyceryl stearate and PEG 100 stearate, isopropyl myristate, methyl paraben, propyl paraben, purified water and white wax.[6] Topical administration to the affected skin areas is limited to twice daily for up to 2 consecutive weeks of treatment. Treatment beyond 2 consecutive weeks is not recommended.[7]

B. Section 505(q) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

Section 505(q) of the FD&C Act (21 U.S.C. 355(q)) was added by section 914 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85, 121 Stat. 823) and was amended by the Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112-144, 126 Stat. 993), which was signed into law on July 9, 2012. Section 505(q) of the FD&C Act, as originally added by the FDAAA, applies to certain citizen petitions and petitions for stay of Agency action that request that FDA take any form of action relating to a pending application submitted under section 505(b)(2) or (j) of the FD&C Act (21 U.S.C. 355(b)(2) or (j)) and governs the manner in which these petitions are treated. Among other things, section 505(q)(1)(F) of the FD&C Act governs the time frame for final Agency action on a petition subject to section 505(q). Under this provision, FDA must take final Agency action on a petition no later than 150 days after the date on which the petition is submitted. The 150-day period is not to be extended for any reason.

II. DISCUSSION

[4] Impoyz labeling (NDA 209483), Full Prescribing Information, USE IN SPECIFIC POPULATIONS, *Pediatric Use* subsection.
[5] The full chemical name of clobetasol propionate is [17-(2-chloroacetyl)-9-fluoro-11-hydroxy-10,13,16-trimethyl-3-oxo-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-17-yl] propanoate.
[6] Impoyz labeling (NDA 209483), Full Prescribing Information, DESCRIPTION section.
[7] Impoyz labeling (NDA 209483), Full Prescribing Information, DOSAGE AND ADMINISTRATION section.

In your Petition, you contend that Glenmark submitted ANDA 214191 for generic clobetasol propionate topical cream that relies on Impoyz as the reference listed drug (RLD). Furthermore, you assert that, according to a Paragraph IV notice letter you received from Glenmark, Glenmark's proposed product is formulated using propylene glycol, and thus, you assert, the Glenmark product is unlikely to be formulated with DEGEE. Therefore, you request that FDA refuse to approve the Glenmark ANDA, and other similarly formulated proposed products submitted under 21 U.S.C. 355(j). In support of your three requests, the Petition raises the following arguments:

(1) The mechanistic differences between propylene glycol and DEGEE are such that significantly more active ingredient, which is potentially toxic, is absorbed into the blood stream when propylene glycol is used as an inactive ingredient.

(2) The potential absorption of active ingredient into the system is not captured by a vasoconstrictor assay study, and therefore clinical trials are needed to establish the safety and efficacy of a product with a formulation containing propylene glycol; HPA axis suppression testing is needed to assess the safety of a product with propylene glycol in the formulation; and local safety data is needed to support the safety of a product with propylene glycol in the formulation.

In support of your first argument, you state that DEGEE is a penetration modifier because it can produce an intracutaneous depot, or reservoir effect.[8] Additionally, you argue that propylene glycol is a traditional penetration enhancer but does not depot in the stratum corneum and it increases the partitioning of the active ingredient into the skin.[9] You contend that the use of propylene glycol raises safety and efficacy concerns because it increases systemic absorption of clobetasol propionate.[10]

You assert that the use of DEGEE provides effectiveness of clobetasol propionate, at a lower strength, while limiting the potentially harmful systemic absorption of clobetasol propionate.[11] You contend that because of the depot effect of DEGEE in Impoyz, there is less active ingredient that is available for systemic absorption.[12] To support your contentions, you describe an ex vivo permeation and penetration study comparing Impoyz to Temovate, clobetasol propionate topical cream (0.05%).[13] The study results showed that Impoyz achieved statistically the same level of clobetasol propionate in the dermis as Temovate, but only 6% of the potential systemic exposure.[14] Furthermore, you argue that an in vivo relative bioavailability study between Impoyz and Temovate E topical cream (0.05%) showed that mean plasma concentrations of clobetasol propionate were about 2.6 times higher in the Temovate E group than for Impoyz.[15] Finally, the Petition states the difference in the absorption of clobetasol propionate is important

[8] Petition at 6.
[9] Petition at 7.
[10] Petition at 7, 10.
[11] Petition at 7.
[12] Id.
[13] Petition at 8.
[14] Id.
[15] Id.

because systemic absorption of corticosteroids raises serious safety concerns such as HPA axis suppression.[16] You conclude that FDA regulations preclude the submission of an ANDA where formulation differences (specifically, the use of propylene glycol rather than DEGEE in a proposed product such as Glenmark's) raise serious questions about the safety or efficacy of the drug product.[17]

In support of your second argument, you state that the vasoconstrictor assay (VCA) is not sufficiently sensitive to account for the formulation differences between the Glenmark product and Impoyz.[18] You posit that the VCA study is not sufficient when there are qualitative changes in the composition of the drug product.[19] You state that the dermatokinetic profile of Impoyz is qualitatively different from a product formulated with propylene glycol, and therefore, you contend that clinical studies are needed to show the bioequivalence of a generic drug product using propylene glycol in its formulation.[20]

Furthermore, you argue that the Impoyz formulation is specifically designed to limit systemic absorption and its safety profile was supported by systemic and HPA axis testing.[21] You assert that the VCA studies are not suitable because the potential drug absorption cannot be ascertained because it is not known whether drug product that is not involved in the blanching response is on the skin's surface or has been absorbed systematically.[22] Accordingly, you contend that an ANDA for a product formulated with propylene glycol should be supported by systemic and HPA axis suppression data.[23]

Finally, in support of your second argument, you contend that the differences in formulation between Impoyz and a generic formulation containing propylene glycol could lead to a less favorable safety profile because of the risk of allergic reaction, irritant contact dermatitis, or eczematous skin reactions.[24] You conclude that an ANDA applicant whose formulation contains propylene glycol should submit local safety data to show that the safety profile of its product is the same as Impoyz.[25]

As described in section I.B. of this response, section 505(q)(1)(F) of the FD&C Act requires FDA to take final Agency action on the Petition within 150 days of submission. Therefore, we must take action on the Petition at this time. For the reasons explained below, we deny without comment the specific requests in your Petition regarding the approvability of any specific 505(j) application.

FDA has made no final determination on whether to approve or not approve any ANDA for a generic topical clobetasol propionate product of the type described in your Petition. FDA's

[16] Petition at 9.
[17] Petition at 10.
[18] Petition at 12.
[19] Id.
[20] Petition at 12-14.
[21] Petition at 14.
[22] Petition at 15.
[23] Petition at 14, 17.
[24] Petition at 18.
[25] Petition at 18-19.

decision to approve or not approve a specific application for a product formulated with propylene glycol will be based on the particular facts that are applicable to that application at the time of the decision, including whether the data and information submitted in the application are sufficient to support approval. Therefore, we must determine whether it would be appropriate for us to take final Agency action on the approvability of a specific aspect of an application before taking final action on the approvability of the application as a whole. To make this determination, we believe it is appropriate to evaluate the statutory and regulatory provisions governing the content and review of 505(j) applications in connection with the statutory provision of section 505(q) of the FD&C Act governing the time frame for action on the Petition.

The FD&C Act and FDA regulations establish procedural protections for applicants in the context of application review. Section 505 of the FD&C Act and FDA's regulations at 21 CFR part 314 describe certain procedures by which the Agency reviews an NDA or ANDA and notifies an applicant if it determines that an application is approved or may not be approved, or identifies the deficiencies in the application and the steps an applicant may take to respond to the deficiencies.[26] In addition, the statute and regulations describe a specific process through which an applicant whose application the Agency has found does not meet the requirements for approval may challenge the Agency's determination.[27] Under this process, the Agency will give the applicant notice of an opportunity for a hearing on whether the application is approvable, with a specific time frame and process, should the applicant request such a hearing.[28] These procedures ensure that applicants have an adequate opportunity to challenge a finding by the Agency that a product does not meet the requirements for approval.

There is no evidence that in enacting section 505(q) of the FD&C Act, Congress intended to bypass the application review process or to lessen an applicant's procedural rights by requiring that the Agency make decisions that constitute final Agency action regarding the approvability of certain aspects of pending applications on a piecemeal basis outside of the process established under the FD&C Act and FDA regulations.[29] Therefore, we do not interpret section 505(q) of the FD&C Act to require that the Agency render a final Agency decision within the statutory deadline on the approvability of a specific aspect of an application when a final decision on the approvability of any such application has not yet been made.[30] Accordingly, we are denying

[26] See 21 CFR 314.105(a) and (d) (FDA will approve an NDA or ANDA and send the applicant an approval letter if none of the reasons in 314.125 or 314.127 for refusing to approve the NDA or ANDA applies). See also section 505(c) and (j) of the FD&C Act, 21 CFR 314.125 and 314.127 (listing reasons that FDA may refuse to approve an NDA or ANDA); 21 CFR 314.110 (setting forth the requirements for a complete response letter).
[27] See section 505(c)(1)(B) and (d) of the FD&C Act; 21 CFR 314.200.
[28] Id.
[29] In other citizen petition responses, we have responded to requests related to general standards for approval (e.g., bioequivalence criteria for generic drug products) that may pertain to one or more pending drug applications without commenting on the approvability of any particular aspect of a specific pending application. We believe that this approach of describing our general policies or standards for approval of a drug application (beyond that described in this response) would not be appropriate in this case because, as stated, our review of a given ANDA would inform our decisions regarding the sufficiency of the specific data and information needed for approval. We will continue to evaluate each citizen petition on a case-by-case basis on the appropriateness of responding to requests regarding any pending application.
[30] Under 21 CFR 314.430, we are generally prohibited from disclosing any determinations regarding the receipt or approvability of any pending 505(j) application before we have reached a final decision on whether to approve or not approve the application.

without comment your requests on the specific requirements for approval of any application of the type described in your Petition.

III. CONCLUSION

For the reasons described above, the Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

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