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Washington, DC 20009

Re: Docket No. FDA-2011-P-0604

February 8, 2024

Dear Dr. Carome:

This letter responds to your citizen petition received August 17, 2011 (Petition). In your Petition, you request that the Food and Drug Administration (FDA or Agency):

1. Require that prednisone and all glucocorticosteroids currently on the market in the U.S. include central serous chorioretinopathy (CSC) as an adverse reaction in their drug labeling (Petition at 1, 3-4).
2. Require that the labeling for all synthetic glucocorticosteroids include "a warning about activation of latent infections due to special pathogens" (Petition at 4).
3. Require that the labeling for all synthetic glucocorticosteroids include "a precaution about the possible development of Kaposi's sarcoma" (Petition at 4).
4. Review the labeling of all glucocorticosteroids and "as appropriate, require additional label changes to ensure that other important information regarding the use and safety of these medications is presented in a consistent manner across all labels" (Petition at 1, 4).

We have carefully considered the issues raised in your Petition. For the reasons described below, your Petition is granted in part and denied in part.

In particular, we are partially granting requests two and three. We are requiring safety labeling changes with respect to glucocorticosteroids administered orally and by injection. To the extent the petition asks for labeling changes for other routes of administration, we are denying the request. We are denying request one, that FDA require safety labeling changes concerning the risk of CSC, and request four (universal labeling harmonization).

I. BACKGROUND

Glucocorticosteroids (also known as *glucocorticoids* or *corticosteroids*) are a specific type of steroid hormone that binds to the glucocorticoid receptor. Endogenous corticosteroids are produced by the adrenal gland, and synthetic corticosteroids have been marketed as drugs in the

United States for decades.¹ For clarity and accuracy, what your Petition refers to as “glucocorticosteroids” or “synthetic glucocorticoids” will be referred to in this response as “corticosteroids,” as this is the term FDA uses for the pharmacologic class.²

A. Corticosteroids

Corticosteroids are available in numerous formulations for various routes of administration (e.g., oral, injection, topical, ophthalmic, intranasal, etc.) and for various indications. For example, Solu-Medrol (methylprednisolone sodium succinate for injection, USP) (new drug application (NDA) 011856), with labeling updated on October 27, 2021, is indicated for 12 categories of diseases (e.g., allergic states, dermatologic diseases, endocrine disorders, neoplastic diseases, ophthalmic diseases) for multiple conditions within each category.³ In addition, there are intranasal formulations of corticosteroids indicated for allergic rhinitis, oral inhaled formulations indicated for maintenance treatment of asthma, and topical formulations indicated for multiple dermatologic conditions. Recently, Alkindi Sprinkle (hydrocortisone), an oral granules formulation was approved for replacement therapy in pediatric patients with adrenocortical insufficiency. Tarpeyo (budesonide) was also recently approved to reduce proteinuria in adults with primary immunoglobulin A nephropathy at risk of rapid disease progression. Given the long marketing history of corticosteroids and variety of formulations, over 150 corticosteroid drug products have been approved by FDA under an NDA or abbreviated new drug application (ANDA).

B. Labeling

Subpart B of part 201 of title 21, Code of Federal Regulations, sets forth labeling requirements for prescription drugs including those related to content and format.⁴

a. Adverse Reactions

Under 21 CFR 201.57(c)(7), the ADVERSE REACTIONS section of drug product labeling:

. . . must describe the overall adverse reaction profile of the drug based on the entire safety database. For purposes of prescription drug labeling, an adverse reaction is an undesirable effect, reasonably associated with use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events

¹ For example, in 1950, Drs. Philip Hench, Edward Kendall, and Tadeus Reichstein won the Nobel Prize in Medicine for the discovery of cortisone and its effect on rheumatic and non-rheumatic conditions, and a hydrocortisone drug product was approved by the FDA shortly thereafter (NDA 9864, approved in 1952).

² See <http://www.fda.gov/media/144963/download>, accessed September 18, 2023.

³ Solu-medrol Prescribing Information, updated October 27, 2021 available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/011856s139lbl.pdf, accessed September 20, 2023.

⁴ For products described in § 201.56(b)(1), FDA regulations at § 201.57 apply, and, for purposes of this response, the term “PLR labeling” refers to labeling that meets these content and format requirements. For older drugs not described in § 201.56(b)(1), FDA regulations for specific requirements on content and format of labeling for human prescription drug and biological products are at § 201.80, and for purposes of the response, the term “non-PLR labeling” refers to labeling that meets these content and format requirements.

observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

FDA has noted that in general, the ADVERSE REACTIONS section includes only information that would be useful to health care practitioners making treatment decisions and monitoring and advising patients. Exhaustive lists of every reported adverse event, including those that are infrequent and minor, commonly observed in the absence of drug therapy, or not plausibly related to drug therapy should be avoided. Such lists are not informative and tend to obscure the more clinically meaningful information.⁵

FDA's Adverse Reactions Guidance states the following about causality:

Decisions on whether there is some basis to believe there is a causal relationship are a matter of judgment and are based on factors such as: (1) the frequency of reporting, (2) whether the adverse event rate for the drug exceeds the placebo rate, (3) the extent of dose-response, (4) the extent to which the adverse event is consistent with the pharmacology of the drug, (5) the timing of the event relative to the time of drug exposure, (6) existence of challenge and dechallenge experience, and (7) whether the adverse event is known to be caused by related drugs.

Pursuant to § 201.57(c)(7)(ii)(B), the ADVERSE REACTIONS section must list adverse reactions identified from domestic and foreign spontaneous reports. Regarding spontaneous reports, the Adverse Reactions Guidance states, "Decisions about whether to include an adverse event from spontaneous reports in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) number of reports, or (3) strength of causal relationship to the drug."

b. Warnings and Precautions

Under 21 CFR 201.57(c)(6)(i), the WARNINGS AND PRECAUTIONS section of drug product labeling must contain a description of:

clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification).

The WARNINGS AND PRECAUTIONS section is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are serious or are otherwise

⁵ See Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products—Content and Format (Adverse Reactions Guidance) (January 2006). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

clinically significant because they have implications for prescribing decisions or for patient management.⁶

As described in the Warnings and Precautions Guidance, to include an adverse event in the section, there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been definitively established. Some factors to consider in assessing whether there is reasonable evidence of a causal relationship include: (1) the frequency of reporting; (2) whether the adverse event rate in the drug treatment group exceeds the rate in the placebo and active-control group in controlled trials; (3) evidence of a dose-response relationship; (4) the extent to which the adverse event is consistent with the pharmacology of the drug; (5) the temporal association between drug administration and the event; (6) existence of dechallenge and rechallenge experience; and (7) whether the adverse event is known to be caused by related drugs.

C. Safety Labeling Change Authority

FDA is authorized to require holders of approved drug and biological product applications to make safety labeling changes for certain approved drugs based on new safety information that becomes available after the approval of the drug and that FDA believes should be included in the labeling (section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(o)(4)). As defined in section 505-1(b)(3) of the FD&C Act, *new safety information* includes information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3)), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k) of the FD&C Act; or other scientific data deemed appropriate by the Agency about, among other things, a serious or an unexpected serious risk associated with use of the drug that the Agency has become aware of since the drug was approved (and may be based on a new analysis of existing information).

II. DISCUSSION

You request that FDA require labeling changes for all corticosteroids to include CSC as an adverse reaction (Petition at 1 and 4). You also ask FDA to include a warning about activation of latent infections due to special pathogens and a precaution about the possible development of Kaposi's sarcoma in all corticosteroid labeling (Petition at 4). Finally, you request that FDA review the labeling of all corticosteroids and, as appropriate, require additional changes to ensure that other important information regarding the use and safety of these medications is presented in a consistent manner (Petition at 1 and 4). For the reasons discussed below, your requests are granted in part and denied in part.

In particular, we partially grant the request that FDA require specific warnings and precautions regarding latent infections due to special pathogens and Kaposi's sarcoma in the labeling of corticosteroid products, by requiring them in oral and injectable (hereafter referred to as

⁶ See Guidance for Industry Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format (Warnings and Precautions Guidance) (October 2011). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

systemic) corticosteroid products. To the extent your Petition requests these labeling changes with respect to other routes of administration (e.g., topical, ophthalmic, and inhaled (oral and nasal)), that request is denied. We deny the requests that FDA require including CSC as an adverse reaction in the labeling and that FDA review the labeling of all corticosteroids and, as appropriate, require additional labeling changes to harmonize other labeling information.

A. Requested Actions Regarding Labeling of Specific Adverse Reactions That May Be Associated With Use of Corticosteroid Drug Products

1. Scope of corticosteroids and formulations considered

Before discussing the individual safety issues raised by your Petition, it is important to address the scope of the products FDA considered. The Petition did not specifically limit the corticosteroids and formulations to be considered.

The Petition references several particular prescription products and describes the scope of corticosteroid prescribing. FDA does not read the Petition as implicating nonprescription drugs. Therefore, for purposes of responding to this Petition, FDA did not review, and the response does not address, nonprescription corticosteroids.

Although your Petition refers to all labeling for prednisone and other synthetic glucocorticoids currently on the market, it only provides examples of corticosteroids that are administered via the oral or injectable route of administration (Petition at 2-3) when discussing CSC, latent infections due to special pathogens and Kaposi's sarcoma. Your Petition did not provide any data or justification to support including these risks in the product labeling for other routes of administration (e.g., topical or inhalation).

Per a risk-based assessment, FDA is limiting the scope of the review and response regarding risks of Kaposi's sarcoma and reactivation of latent infections to systemic corticosteroids. Systemic corticosteroids would be expected to have the highest systemic exposure and greatest risk for systemic adverse events (i.e., Kaposi's sarcoma and reactivation of latent infection). While corticosteroids administered via other routes (e.g., topical or inhalation) can have systemic effects, the risks with these products are primarily local adverse events.

For CSC, while the Petition only gives examples of corticosteroids that are administered orally or by injection, FDA's review and response include all routes of administration of corticosteroids. Because the cause of CSC is poorly understood the Agency explored whether this adverse event was associated with systemic and/or localized exposure to corticosteroids.

2. Request To Include CSC as an Adverse Reaction in All Corticosteroid Labeling

The Petition requests that FDA require that the labeling of prednisone and other corticosteroids currently on the market in the United States include CSC as an adverse reaction, if not already included (Petition at 1). As noted above, under 21 CFR 201.57(c)(7), the definition of adverse reaction, "does not include all adverse events observed during use of a drug, only those adverse

events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.”

CSC is a condition in which fluid accumulates under the retina, causing blurred central vision and in some cases detachment of the retina. CSC can result in transient or permanent vision loss. The cause is unknown, but men are affected more than women, and stress appears to be a risk factor (Ross et al. 2011; Bouzas et al. 2002). It has been associated with a number of conditions in which patients are likely to be administered corticosteroids, including lupus erythematosus, ulcerative colitis, sarcoidosis, and organ transplantation (Carvalho-Recchia et al. 2002; Haimovici et al. 2004; Tarabishy et al. 2011; Bouzas et al. 2002).

FDA reviewed the information and references provided in your Petition⁷, as well as additional information regarding the association between corticosteroid use and CSC, including, but not limited to, individual case safety reports in the FDA Adverse Event Reporting System (FAERS) and the results of studies identified from FDA’s independent review of the biomedical literature⁸. Because CSC is associated with a number of conditions for which patients are likely to be administered corticosteroids, it is expected that CSC is reported in association with the use of corticosteroids. Elements of our analysis of individual case safety reports identified in FAERS suggest a possible association between corticosteroids and CSC. However, there is insufficient information (lack of reporting of other possible risk factors) and limitations to the cases (demographics mirror the general epidemiologic trends of the overall disease state, treated for disease states possibly associated with CSC or other ophthalmic manifestations that may mimic CSC) to draw conclusions of an overall class effect. Furthermore, reported cases of CSC following use of corticosteroids in the eye (e.g., topical, sub-tenons and intravitreal use), in which concentrations of corticosteroids in the eye are much higher than those following use of corticosteroids administered via other routes (e.g., topical skin, oral, intravenous, intramuscular, inhaled, intranasal, epidural, and intraarticular administration), are extremely rare. This raises doubt about the causal association of CSC with corticosteroid use. Additionally, many CSC cases were described as single, unilateral retinal pigment epithelial detachments, which are not consistent with drug-induced cases. If corticosteroids were associated with CSC, we would have expected to commonly find the development of bilateral, multifocal serous detachments of the retinal pigment epithelium; however, this was not found. Finally, our review of epidemiological studies identified in our literature search did not find a clear and consistent association between CSC and corticosteroids.

Therefore, we found insufficient information to support a causal effect of corticosteroids on development of CSC. FDA disagrees that CSC should be added to the adverse reaction section of all corticosteroids’ labeling.

However, we agree with your Petition that CSC is listed as an adverse reaction in some corticosteroid labeling. As noted above, FDA has received spontaneous reports of cases of CSC

⁷ See References Carvalho-Recchia et al. 2002; Haimovici et al. 2004; Karadimas et al. 2004; Levy et al. 2005; Gemenetzi et al. 2010; Sang, et al. 2010

⁸ In June 2020, the Office of Surveillance and Epidemiology/Division of Epidemiology conducted a search of PubMed using the terms “corticosteroids” and “chorioretinopathy” with restrictions to English publications of observational studies, not reviews.

reported with corticosteroid use submitted to the FAERS database and FDA is aware of some reports in published medical literature. As described in the Adverse Reactions Guidance, “Decisions about whether to include an adverse event from spontaneous reports in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) number of reports, or (3) strength of causal relationship to the drug.” Because the Agency evaluates spontaneous reporting on a case-by-case basis, there are sometimes differences in the adverse reaction section of labeling for different products in the same drug class. If an applicant proposes to include CSC as a reported adverse event for a drug product in which CSC has been reported, the Agency will evaluate the proposal and determine if the adverse event should be included on a case-by-case basis.

As with all drug products, we will continue to monitor the safety of corticosteroids and take further action if we determine it is appropriate to do so.

3. Request To Include a Precaution About Kaposi’s Sarcoma in All Corticosteroids’ Labeling

The Petition requests that FDA require labeling for all corticosteroids to include a precaution about the possible development of Kaposi’s sarcoma (Petition at 4). Under 21 CFR 201.57(c)(6)(i), the WARNINGS AND PRECAUTIONS section of the labeling must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug) and other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions). FDA’s Warnings and Precautions Guidance describes what adverse reactions should be identified in the WARNINGS AND PRECAUTIONS section:

The WARNINGS AND PRECAUTIONS section is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are *serious* or are *otherwise clinically significant* because they have implications for prescribing decisions or for patient management. To include an adverse event in the section, there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been definitively established.

Kaposi’s sarcoma is a cancer of the connective tissue caused by the Kaposi’s sarcoma herpesvirus (also known as Human Herpesvirus-8). Kaposi’s sarcoma is a life-threatening adverse event that can involve the skin, lungs, and gastrointestinal (GI) tract, and typically affects individuals with immune systems weakened by drugs or disease.

While your Petition did not provide references to support the association between Kaposi’s sarcoma and the use of corticosteroids, the occurrence of this disease in patients with immunosuppression, including patients with AIDS (Epidemic Kaposi’s sarcoma) and post-organ transplantation (Immunosuppressive Treatment-related Kaposi’s sarcoma), is widely recognized (PDQ® Adult Treatment Editorial Board 2018). In a Pubmed search for Kaposi’s sarcoma and corticosteroids, multiple articles report Kaposi’s sarcoma following exposure to corticosteroids in the absence of other immunosuppression (Vincent et al. 2000; Trattner et al. 1993; Casoli and Turniati 1992; Gonzalez-Sixto et al. 2007; Choi et al. 2009). Development of Kaposi’s sarcoma after corticosteroid therapy has been observed in patients after solid organ transplant (Shepherd

et al. 1997), most commonly kidney (Einollahi et al. 2009), autoimmune disorders and chronic inflammatory diseases which include ulcerative colitis (Herculano et al. 2014), asthma (Guttman-Yassky et al. 2006), rheumatoid arthritis (Taniguchi et al. 2011), and systemic lupus erythematosus (Greenfield et al. 1986). Immunosuppressive therapy, including corticosteroid use, is the leading cause of Kaposi's sarcoma among patients who have received solid organ transplant with an incidence in kidney transplant that ranges from 0.5% up to 5.3% (Shepherd et al. 1997). It has been shown that glucocorticoid receptors are present in high levels on Kaposi's sarcoma lesions and that receptors can be upregulated by exogenous glucocorticoids that can induce the growth of Kaposi's sarcoma cell lines in a dose-dependent manner (Cai J et al. 1997 and Guo et al. 1995). Clinical evidence of immune recovery is demonstrated by regression of Kaposi's sarcoma lesions and the return of normal CD4⁺ T cells. In many cases of Kaposi's sarcoma developing in the posttransplantation period, spontaneous regression of Kaposi's sarcoma occurred after discontinuation of the immunosuppressive therapy, and this has been the mainstay of treatment (Shepherd et al. 1997 and Penn 1993). Kaposi's sarcoma associated with corticosteroids is a serious adverse reaction, and there is evidence that withdrawal of immunosuppression, including corticosteroids, is often associated with spontaneous regression, and therefore the need for more aggressive therapies may be unnecessary. Based on this evidence, there is reasonable evidence of a causal association between corticosteroid use and Kaposi's sarcoma. Currently, some of the systemic corticosteroids' labeling notes that Kaposi's sarcoma has been reported with corticosteroid use, but this is not consistent. Labeling that contains information about Kaposi's sarcoma also states, "discontinuation of corticosteroids may result in clinical improvement," thereby providing information useful for patient management.

Because Kaposi's sarcoma associated with corticosteroids is a serious adverse reaction, there are implications for patient management, and there is reasonable evidence of a causal association between corticosteroid use and Kaposi's sarcoma, the FDA has determined that the following Kaposi's sarcoma language should be included in the WARNINGS AND PRECAUTIONS section of systemic corticosteroid labeling:

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

4. Request to Include a Warning About Activation of Latent Infection Due to Special Pathogens in All Corticosteroids' Labeling

The Petition requests FDA require labeling for all corticosteroids to include a warning about activation of latent infections due to special pathogens (Petition at 4). As noted above, 21 CFR 201.57(c)(6)(i) describes what adverse events must be included in the WARNINGS AND PRECAUTIONS section of the labeling and the Warnings and Precautions Guidance describes several factors that are considered when determining whether to include an adverse reaction in the WARNINGS AND PRECAUTIONS section of labeling.

The relationship between corticosteroids and susceptibility to infections, including latent infections, is well known, particularly because corticosteroids inhibit the immune system and inflammatory response. General pharmacology textbooks include information regarding this increased susceptibility to infection (Goodman & Gilman's The Pharmacological Basis of

Therapeutics – 12th Edition. 2010), as does the labeling of many systemic corticosteroids.⁹ However, the warning language and the extent of information provided are not consistent across labeling.

Reactivation of latent infections due to special pathogens can be serious and potentially fatal. In addition, labeling recommendations to rule out certain latent infections before initiating corticosteroid therapy and restricting corticosteroid therapy for tuberculosis to fulminating or disseminated tuberculosis have implications for prescribing decisions and for patient management.

Because the activation of latent infections due to special pathogens associated with corticosteroids is a serious adverse reaction, because it carries implications for prescribing decisions and for patient management, and because there is reasonable evidence of a causal association between corticosteroid use and activation of latent infections due to special pathogens, the Agency agrees information about the risk of activation of latent infections due to special pathogens should be included in the WARNINGS AND PRECAUTIONS section of systemic corticosteroid labeling.

B. Safety Labeling Change

We agree that systemic corticosteroids are associated with increased risk of Kaposi's sarcoma and activation of latent infections due to special pathogens. This information appears in some (but not all) labeling. Therefore, we have determined that there is new safety information about these risks that should be added to the labeling for corticosteroids administered orally or by injection, where it is missing.¹⁰

We have notified the applicants of all systemic corticosteroids, except, for reasons explained further below, Alkindi Sprinkle (hydrocortisone) and Tarpeyo (budesonide), that the labeling should include the following language under WARNINGS AND PRECAUTIONS or WARNINGS, as applicable¹¹:

Corticosteroids, including DRUG-X, suppress the immune system and increase the risk of infection with any pathogen, including viral, bacterial, fungal, protozoan, or helminthic pathogens. Corticosteroids can:

- Reduce resistance to new infections
- Exacerbate existing infections
- Increase the risk of disseminated infections
- Increase the risk of reactivation or exacerbation of latent infections

⁹ See, e.g., Celestone (betamethasone sodium phosphate and betamethasone acetate) injectable suspension, USP label available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/014602s062lbl.pdf (noting the risk of *Infections Special Pathogens* “Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba*, *Candida*, *Cryptococcus*, *Mycobacterium*, *Nocardia*, *Pneumocystis*, and *Toxoplasma*”).

¹⁰ Please note that as for all drug products, FDA will continue to monitor adverse event reports and other postmarketing safety surveillance data for all the various corticosteroid formulations.

¹¹This risk will be included under WARNINGS AND PRECAUTIONS or WARNINGS depending on whether the corticosteroid is subject to PLR or non-PLR labeling requirements, respectively.

- Mask some signs of infection

Corticosteroid-associated infections can be mild but can be severe and at times fatal. The rate of infectious complications increases with increasing corticosteroid dosages.

Monitor for the development of infection and consider DRUG-X withdrawal or dosage reduction as needed.

Do not administer DRUG-X by an intraarticular, intrabursal, intratendinous, or intralesional route in the presence of acute local infection. **(NOTE: This will only be included in injectable corticosteroid labeling)**

Tuberculosis

If DRUG-X is used to treat a condition in patients with latent tuberculosis or tuberculin reactivity, reactivation of tuberculosis may occur. Closely monitor such patients for reactivation. During prolonged DRUG-X therapy, patients with latent tuberculosis or tuberculin reactivity should receive chemoprophylaxis.

Varicella Zoster and Measles Viral Infections

Varicella and measles can have a serious or even fatal course in non-immune patients taking corticosteroids, including DRUG-X. In corticosteroid-treated patients who have not had these diseases or are non-immune, particular care should be taken to avoid exposure to varicella and measles:

- If a DRUG-X-treated patient is exposed to varicella, prophylaxis with varicella zoster immune globulin may be indicated. If varicella develops, treatment with antiviral agents may be considered.
- If a DRUG-X-treated patient is exposed to measles, prophylaxis with immunoglobulin may be indicated.

Hepatitis B Virus Reactivation

Hepatitis B virus reactivation can occur in patients who are hepatitis B carriers treated with immunosuppressive dosages of corticosteroids, including DRUG-X. Reactivation can also occur infrequently in corticosteroid-treated patients who appear to have resolved hepatitis B infection.

Screen patients for hepatitis B infection before initiating immunosuppressive (e.g., prolonged) treatment with DRUG-X. For patients who show evidence of hepatitis B infection, recommend consultation with physicians with expertise in managing hepatitis B regarding monitoring and consideration for hepatitis B antiviral therapy.

Fungal Infections

Corticosteroids, including DRUG-X, may exacerbate systemic fungal infections; therefore, avoid DRUG-X use in the presence of such infections unless DRUG-X is needed to control drug reactions. For patients on chronic DRUG-X therapy who develop systemic fungal infections, DRUG-X withdrawal or dosage reduction is recommended.

Amebiasis

Corticosteroids, including DRUG-X, may activate latent amebiasis. Therefore, it is recommended that latent amebiasis or active amebiasis be ruled out before initiating DRUG-X in patients who have spent time in the tropics or patients with unexplained diarrhea.

Strongyloides Infestation

Corticosteroids, including DRUG-X, should be used with great care in patients with known or suspected Strongyloides (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Cerebral Malaria

Avoid corticosteroids, including DRUG-X, in patients with cerebral malaria.

Kaposi's sarcoma

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement of Kaposi's sarcoma.

Alkindi Sprinkle (hydrocortisone) oral granules is a synthetic glucocorticoid that was approved on September 29, 2020, as a replacement therapy in pediatric patients with adrenocortical insufficiency (AI). Unlike other approved glucocorticoids, supraphysiologic doses for the treatment of various inflammatory/immunologic conditions in patients with normal adrenal function are not recommended in the labeling. Based on the Alkindi-specific indication (treatment of AI) and recommended doses (low physiologic doses) FDA has determined that the new safety information that should be included in the labeling for Alkindi should differ from the information that should be included in the labeling of the other approved corticosteroids. In particular, since latent infections and Kaposi's sarcoma are not associated with low replacement doses used as recommended in patients with AI, the labeling should include the statement that latent infection is more likely to occur in patients when supraphysiologic doses are used. Further, a list of individual infections should not be included in the WARNINGS AND PRECAUTIONS section. Lastly, the labeling should not include a statement that the drug has to be discontinued if these adverse reactions develop, since the discontinuation of the drug in a patient with inadequate production of cortisol will lead to life-threatening adrenal crisis. Accordingly, we have notified the application holder for Alkindi that we believe new safety information should be included in the labeling as follows:

Immunosuppression and Increased Risk of Infection with Use of a Dosage Greater Than Replacement

Use of the recommended dosage of ALKINDI SPRINKLE [see Dosage and Administration (2.1, 2.2)] as a replacement therapy in pediatric patients with adrenocortical insufficiency is not expected to cause immunosuppression or increase the risk of infection. The use of a greater than replacement dosage can suppress the immune

system and increase the risk of infection with any pathogen, including viral, bacterial, fungal, protozoan, or helminthic pathogens. The use of ALKINDI SPRINKLE at greater than replacement dosage can:

- Reduce resistance to new infections
- Exacerbate existing infections
- Increase the risk of disseminated infections
- Increase the risk of reactivation or exacerbation of latent infections
- Mask some signs of infection

Infections associated with the use of corticosteroids at a greater than replacement dosage range from mild to severe or fatal and the rate of infectious complications increases with increasing corticosteroid dosages.

Monitor for the development of infection and consider ALKINDI SPRINKLE dosage reduction as needed.

Risk of Kaposi's Sarcoma with Use of a Dosage Greater Than Replacement

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions at a dosage greater than replacement (supraphysiologic dosage). If patients take a supraphysiologic chronic dosage of ALKINDI SPRINKLE, they are at increased risk of developing Kaposi's sarcoma.

Tarpeyo (budesonide) is an oral corticosteroid granted accelerated approval on December 15, 2021, and converted to traditional approval on December 20, 2023. It is indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy at risk of rapid disease progression. The recommended duration of therapy is 9 months, with a dosage of 16 mg administered orally once daily. Based on attributes of Tarpeyo that are different from other approved corticosteroids, FDA has determined that the new safety information that should be included in the labeling should be individualized for Tarpeyo based on the following:

- The concept of dosage reduction does not apply for Tarpeyo; there's a single recommended dose (and a specified taper at the end).
- Based on assessment of benefit-risk for Tarpeyo, which is different from other corticosteroids approved for different indications, Tarpeyo was approved with and should continue to include labeling recommending it should not be used in patients with latent tuberculosis or tuberculin reactivity, systemic fungal infections, or parasitic infestation.
- The term "prolonged" may be confusing for prescribers as the Tarpeyo label describes a specified 9-month course of therapy.
- Controlling drug reactions is not applicable to the Tarpeyo indication and Tarpeyo is not a chronic therapy.

Accordingly, we have notified the applicant for Tarpeyo that we believe the new safety information should be included in the labeling as follows:

Corticosteroids, including TARPEYO, suppress the immune system and increase the risk of infection with any pathogen, including viral, bacterial, fungal, protozoan, or helminthic pathogens. Corticosteroids can:

- Reduce resistance to new infections
- Exacerbate existing infections
- Increase the risk of disseminated infections
- Increase the risk of reactivation or exacerbation of latent infections
- Mask some signs of infection

Corticosteroid-associated infections can be mild but can be severe and at times fatal. The rate of infectious complications increases with increasing corticosteroid dosages.

Monitor for the development of infection and consider TARPEYO withdrawal as needed.

Tuberculosis

If TARPEYO is used to treat a condition in patients with latent tuberculosis or tuberculin reactivity, reactivation of tuberculosis may occur. In patients with latent tuberculosis or tuberculin reactivity TARPEYO should be discontinued.

Varicella Zoster and Measles Viral Infections

Varicella and measles can have a serious or even fatal course in non-immune patients taking corticosteroids, including TARPEYO. In corticosteroid-treated patients who have not had these diseases or are non-immune, particular care should be taken to avoid exposure to varicella and measles:

- If a TARPEYO-treated patient is exposed to varicella, prophylaxis with varicella zoster immune globulin may be indicated. If varicella develops, treatment with antiviral agents may be considered.
- If a TARPEYO-treated patient is exposed to measles, prophylaxis with immunoglobulin may be indicated.

Hepatitis B Virus Reactivation

Hepatitis B virus reactivation can occur in patients who are hepatitis B carriers treated with immunosuppressive dosages of corticosteroids, including TARPEYO. Reactivation can also occur infrequently in corticosteroid-treated patients who appear to have resolved hepatitis B infection.

Screen patients for hepatitis B infection before initiating immunosuppressive treatment with TARPEYO. For patients who show evidence of hepatitis B infection, recommend consultation with physicians with expertise in managing hepatitis B regarding monitoring and consideration for hepatitis B antiviral therapy.

Fungal Infections

Corticosteroids, including TARPEYO, may exacerbate systemic fungal infections; therefore, avoid TARPEYO use in the presence of such infections.

Amebiasis

Corticosteroids, including TARPEYO, may activate latent amebiasis. Therefore, it is recommended that latent amebiasis or active amebiasis be ruled out before initiating TARPEYO in patients who have spent time in the tropics or patients with unexplained diarrhea.

Strongyloides Infestation

Corticosteroids, including TARPEYO, should be discontinued in patients with known or suspected *Strongyloides* (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to *Strongyloides* hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Cerebral Malaria

Avoid corticosteroids, including TARPEYO, in patients with cerebral malaria.

Kaposi's sarcoma

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement of Kaposi's sarcoma.

Letters notifying the application holders of the required labeling changes described above were issued based on our authority to require safety labeling changes under section 505(o)(4) of the FD&C Act. Under section 505(o)(4) of the FD&C Act, the application holders are required, within 30 days following notification, either (1) to submit a supplement containing proposed labeling changes, or (2) to notify the Agency that they do not believe labeling changes are warranted and submit a statement detailing the reasons they believe such changes are not warranted.

C. Request To Review the Labeling of All Glucocorticosteroids and Require Additional Labeling Changes

Your Petition requests that FDA review the labeling of all glucocorticosteroids and “as appropriate, require additional label changes to ensure that other important information regarding the use and safety of these medications is presented in a consistent manner across all labels” (Petition at 1 and 4).

The Agency has reviewed the labeling examples specified by your Petition, and additional samples of systemic corticosteroid labeling, and we agree that there are differences in the information provided regarding risks and precautions in the labeling. The Agency believes, subject to the determinations regarding safety labeling changes described above, current corticosteroid labeling includes the essential scientific information needed for the safe and effective use of the drugs (§ 201.56(a)(1)). To the extent that the Petitioner identified specific adverse events of concern, the Agency has addressed them. The Agency is declining to prioritize review of all corticosteroid labeling since specific safety concerns have not been identified.

III. CONCLUSION

For the reasons discussed in this response, your Petition is granted in part and denied in part.

Sincerely,

Douglas C.

Throckmorton -

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C. Throckmorton -S
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Patrizia Cavazzoni, M.D.

Director

Center for Drug Evaluation and Research

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