



Meenal Kheterpal, M.D.

(b) (6)

Re: Docket No. FDA-2020-P-1831

MAR 27 2023

Dear Dr. Kheterpal:

This letter responds to your citizen petition received by the Food and Drug Administration (FDA, the Agency, or we) on August 31, 2020 (Petition). In the Petition, you ask FDA to require that all Hedgehog inhibitor drug products have FDA-approved labeling that carries a warning regarding musculoskeletal reactions and requirements for creatine kinase (CK) monitoring¹ as an indicator of muscle damage.² The Petition specifies that the request applies to “all those currently approved [Hedgehog inhibitor drug products] and any approved in the future.”³

We have carefully considered your Petition and other information available to the Agency. For the reasons stated below, the Petition is granted in part and denied in part.

I. BACKGROUND

A. Hedgehog Inhibitor Drug Products

The Hedgehog signaling pathway regulates cell differentiation and self-renewal in the developing human embryo, but not in adult tissues.⁴ Mutations leading to an inappropriate activation of the Hedgehog signaling pathway may lead to the development of several types of cancer, including basal cell carcinoma. Hedgehog inhibitors bind to and inhibit Smoothened, a transmembrane protein involved in Hedgehog signal transduction.

FDA has approved three Hedgehog inhibitor drug products for varying cancer indications. On January 30, 2012, FDA approved Erivedge (vismodegib) oral capsule under new drug application (NDA) 203388.⁵ Erivedge is indicated for the treatment of adults with metastatic basal cell carcinoma or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery and who are not candidates for radiation. Subsequently on July 24, 2015, FDA approved Odomzo (sonidegib phosphate) oral capsule,

¹ “CK monitoring” is also at times referred to as creatine phosphokinase (CPK) monitoring. These terms are synonymous.

² Petition at 1.

³ Petition at 8.

⁴ See Cross Discipline Team Leader Review, January 13, 2012 (Reference ID: 3072126), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203388Orig1s000CrossR.pdf.

⁵ Labeling for Erivedge (vismodegib) (July 2020), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203388s016lbl.pdf.

NDA 205266.⁶ Odomzo is indicated for the treatment of adult patients with locally advanced basal cell carcinoma that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy. Daurismo (glasdegib maleate) was approved by FDA on November 21, 2018, NDA 210656, and is indicated, in combination with low-dose cytarabine, for the treatment of newly-diagnosed acute myeloid leukemia in adult patients who are ≥ 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.⁷

B. Prescription Drug Labeling

Under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and FDA regulations, the Agency makes decisions on the approval of marketing applications, including supplemental applications, for drug products based on a comprehensive scientific evaluation of the drug product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling (see section 505(d) of the FD&C Act (21 U.S.C. 355(d))). An NDA is “required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the NDA that is received or otherwise obtained by the applicant from any source” (§ 314.50 (21 CFR 314.50)). An NDA also must contain the applicant’s proposed text of the labeling, including “annotations to the information in the summary and technical sections of the NDA that support the inclusion of each statement in the labeling” (§ 314.50(c)(2)(i)).

FDA-approved drug product labeling summarizes the essential information needed for the safe and effective use of the drug (see § 201.56(a) (21 CFR 201.56(a))). The primary purpose of FDA-approved labeling for prescription drugs is to provide health care practitioners with the essential scientific information needed to facilitate prescribing decisions, thereby enhancing the safe and effective use of prescription drug products and reducing the likelihood of medication errors. Prescription drug labeling is directed to health care practitioners but may also include additional FDA-approved labeling directed at the patient or caregiver (commonly referred to as patient labeling).

Once approved, application holders have an ongoing obligation to ensure that their drug product labeling is accurate and up-to-date.⁸ When new information becomes available that causes information in labeling to be inaccurate, false, or misleading, the application holder must take steps to change the content of its labeling.⁹ For example, the labeling “must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely

⁶ Labeling for Odomzo (sonidegib phosphate) (May 2019), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/205266s006lbl.pdf.

⁷ Labeling for Daurismo (glasdegib maleate) (March 2020), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210656s002s004lbl.pdf.

⁸ See *Wyeth v. Levine*, 555 U.S. 555, 570–71 (2009) (“It is a central premise of the [FD&C Act] and the FDA’s regulations that the manufacturer bears responsibility for the content of its label[ing] at all times”); see also section 505(o)(4)(I) of the FD&C Act and § 201.56(a)(2) of the regulations.

⁹ See §§ 201.56(a)(2) and 314.70 (21 CFR 314.70).

established.”¹⁰ A drug is misbranded in violation of the FD&C Act when its labeling is false or misleading or does not provide adequate warnings.¹¹

After FDA has approved an NDA, for most substantive changes to product labeling, an application holder is required to submit a prior approval supplement and receive approval for the proposed labeling changes before distributing revised product labeling.¹²

1. WARNINGS AND PRECAUTIONS

The WARNINGS AND PRECAUTIONS section of prescription drug labeling must describe “clinically significant adverse reactions,” other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these situations occur when “reasonable evidence of a causal association” between the drug and such hazards exists.¹³ FDA regulations require that the labeling “must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established.”¹⁴ FDA adopted that standard in part to “prevent overwarning” of potential risks, which, if included in the WARNINGS AND PRECAUTIONS section, could dilute other “more important warnings” or “deter appropriate use” of the drug.¹⁵ FDA typically reserves this section for a “discrete set” of hazards serious enough to affect prescribing decisions.¹⁶ FDA regulations provide that a “specific warning relating to a use not provided for under the INDICATIONS AND USAGE section may be required by FDA in accordance with sections 201(n) [21 U.S.C. 331(n)] and 502(a) [21 U.S.C. 352(a)] of the [FD&C Act] if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard.”¹⁷

2. ADVERSE REACTIONS

The ADVERSE REACTIONS section of prescription drug labeling describes “the overall adverse reaction profile of the drug.”¹⁸ FDA’s regulations define an adverse reaction, for purposes of prescription drug labeling, as “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.”¹⁹ The threshold for including an adverse reaction in this section

¹⁰ § 201.57(c)(6)(i) (21 CFR 201.57 (c)(6)(i)).

¹¹ See sections 301(a) and (b) and 502(a), (f), and (j) of the FD&C Act (21 U.S.C. 331(a) and (b) and 352(a), (f), and (j)).

¹² § 314.70(b).

¹³ § 201.57(c)(6)(i).

¹⁴ Id.

¹⁵ Preamble to final rule, “Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices” (73 FR 49603 at 49605–49606, August 22, 2008).

¹⁶ See FDA guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format* (October 2011), available at <https://www.fda.gov/media/71866/download> (Warnings Guidance). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatoryinformation/search-fda-guidance-documents>.

¹⁷ § 201.57(c)(6)(i).

¹⁸ § 201.57(c)(7).

¹⁹ Id.

is lower than that for the WARNINGS AND PRECAUTIONS section: An adverse reaction must be listed if “some basis” exists “to believe there is a causal relationship between the drug and the occurrence of the adverse event.”²⁰

II. DISCUSSION

The Petition requests that all Hedgehog inhibitors, including currently approved and any future Hedgehog inhibitors, be required to have FDA-approved labeling that carries a warning regarding musculoskeletal reactions and requirements for creatine kinase (CK) monitoring as an indicator of muscle damage.²¹ In support of this request, the Petition states that

[a]ll currently approved Hedgehog inhibitors have the same mechanism of action; they selectively bind to and inhibit Smoothened to interrupt Hedgehog signal transduction, and have comparable safety data supporting their respective approvals.²²

Specifically, the Petition states, “the data and safety profile for vismodegib and sonidegib are similar or slightly better for sonidegib; therefore, both Hedgehog inhibitors should have similar prescribing information warnings regarding musculoskeletal adverse reactions.”²³ Additionally, the Petition states that various clinical and safety studies conducted for vismodegib resulted in reported adverse events associated with muscle spasms, and in one study, “380 (31%) patients discontinued vismodegib due to an AE; the most common AE resulting in discontinuation was muscle spasms (85 [7%] patients).”²⁴ For glasdegib maleate, the Petition notes that “the pivotal clinical trial for glasdegib (administered in combination with cytarabine), 66 (79%) patients experienced a serious AE, with 30 (36%) patients discontinuing the study due to AEs.”²⁵ The Petition further states that “[w]ithin the first 90 days of treatment with glasdegib and cytarabine, 13 (15%) patients experienced muscle spasms and 38 (16%) had increased CK levels.”²⁶

For the reasons set forth below, your Petition is granted in part and denied in part. Today, we approved changes to the labeling for vismodegib to include information on musculoskeletal adverse reactions in the DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS sections of the labeling and recommendations for obtaining baseline serum CK and monitoring of CK levels in the WARNINGS AND PRECAUTIONS section of the labeling. Today, we also approved changes to the labeling for glasdegib maleate to include musculoskeletal adverse reactions and recommendations for obtaining baseline serum CK and monitoring of CK levels in the WARNINGS AND PRECAUTIONS section of the labeling.

Prior to today’s actions, sonidegib phosphate was the only Hedgehog inhibitor product to include information about musculoskeletal adverse reactions in all three sections of the labeling: WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION. Moreover, sonidegib phosphate was the only Hedgehog inhibitor product

²⁰ Id.

²¹ Petition at 1.

²² Petition at 1.

²³ Petition at 7.

²⁴ Petition at 5.

²⁵ Petition at 6.

²⁶ Petition at 6.

to recommend obtaining baseline serum CK and monitoring of CK levels in both the WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION sections of the labeling.

We agree with the Petition that there is reasonable evidence of a causal association between the Hedgehog inhibitor class and musculoskeletal adverse reactions and that CK elevation is an adverse reaction that should be monitored. With respect to CK elevation, we evaluated postmarketing cases of CK elevation and rhabdomyolysis (i.e., release of myoglobin when muscle fibers break down), which serve as indirect markers of muscle damage, with vismodegib, sonidegib phosphate, and glasdegib maleate use. We also evaluated clinical and nonclinical data reviewed prior to approval of the Hedgehog inhibitor drug products for evidence of a causal association to each of these products. While the postmarketing data linking CK increase or rhabdomyolysis to vismodegib or glasdegib maleate use was limited, the clinical trial data together with nonclinical findings provide reasonable evidence of a causal association between CK increase or rhabdomyolysis and vismodegib or glasdegib maleate use, and suggest that these events may represent a class effect related to the mechanism of action of the Hedgehog inhibitors. For example, the data from clinical trials as already described in various sections of the labeling for these products show musculoskeletal adverse reactions and/or CK increase with use of all three Hedgehog inhibitor products (vismodegib, glasdegib maleate, and sonidegib phosphate).²⁷

Additionally, although musculoskeletal reactions, CK elevation and rhabdomyolysis were not previously identified in the WARNINGS AND PRECAUTIONS section of the labeling for the entire drug class, musculoskeletal adverse reactions, CK elevation and/or rhabdomyolysis were referenced in various parts of the labeling (i.e., DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS, and/or WARNINGS AND PRECAUTIONS) for all three Hedgehog inhibitor drugs, which further support a potential class effect. For example, the labeling for vismodegib under the ADVERSE REACTIONS section referenced a post-approval clinical trial finding of CK elevation in a subset of patients with baseline values for CK reported. For glasdegib maleate, the DOSAGE AND ADMINISTRATION section of the labeling recommends obtaining serum CK levels prior to initiating treatment and as indicated clinically thereafter (e.g., if muscle symptoms are reported). However, prior to today's actions, the labeling for vismodegib and glasdegib maleate did not include musculoskeletal adverse reactions and recommendations for obtaining baseline serum CK and monitoring levels in the WARNINGS AND PRECAUTIONS section.

Based on our review, we have determined that CK elevation is an adverse reaction that should be monitored by measuring CK levels to potentially avoid serious outcomes, such as renal failure or rhabdomyolysis for the Hedgehog inhibitor class. Additionally, we agree with the Petition that musculoskeletal adverse reactions should be identified in the WARNINGS AND PRECAUTIONS section of the labeling across the class. To align the labeling more closely

²⁷ See Clinical Trials Experience Section 6.1 of the labeling for Erivedge (vismodegib) (July 2020), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203388s016lbl.pdf and Clinical Trials Experience Section 6.1 of the labeling for Daurismo (glasdegib maleate) (March 2020), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210656s002s004lbl.pdf.

across the Hedgehog inhibitor class, today we approve the labeling for vismodegib and glasdegib maleate to include further information on musculoskeletal adverse reactions and CK monitoring.²⁸

The following sections of the vismodegib labeling have been updated to read:

2 DOSAGE AND ADMINISTRATION

2.3 Dosage Modifications for Adverse Reactions

Withhold ERIVEDGE for up to 8 weeks for intolerable adverse reactions until improvement or resolution. Treatment durations shorter than 8 weeks prior to interruptions have not been studied.

Permanently discontinue ERIVEDGE if patients experience severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or drug reaction with eosinophilia and systemic symptoms (DRESS) [see Warnings and Precautions (5.2)].

Interrupt ERIVEDGE for severe or intolerable musculoskeletal adverse reactions. Permanently discontinue ERIVEDGE for recurrent, severe or intolerable musculoskeletal adverse reactions [see Warnings and Precautions (5.3)].

5 WARNINGS AND PRECAUTIONS

5.3 Musculoskeletal Adverse Reactions

Musculoskeletal adverse reactions, which may be accompanied by serum creatine phosphokinase (CPK) elevations, have occurred with ERIVEDGE and other drugs which inhibit the hedgehog (Hh) pathway. In the pooled safety population in clinical trials of ERIVEDGE, musculoskeletal and connective tissue adverse reactions occurred in 78% of patients treated, with 7% (9/138) reported as Grade 3. The most frequent manifestations of musculoskeletal and connective tissue adverse reactions (all grades) reported were muscle spasms (72%) and arthralgias (16%). In a post-approval clinical trial of 1232 patients, Grade 3 or 4 elevations in serum CPK laboratory values occurred in 2.4% of the 453 patients who had any CPK measurement [*see Adverse Reactions (6.1)*].

Obtain baseline serum creatine phosphokinase (CPK) and creatinine levels and as clinically indicated (e.g., if muscle symptoms are reported). Depending on the severity of symptoms, temporary dose interruption or discontinuation may be required for musculoskeletal adverse reactions or serum CPK elevation [*see Dosage and Administration (2.3)*].

²⁸ Prior to today's action, muscle spasms were already included in the labeling for all Hedgehog inhibitors under ADVERSE REACTIONS. In addition, the ADVERSE REACTIONS section of the labeling also includes information about arthralgias (vismodegib), musculoskeletal pain (sonidegib phosphate and glasdegib maleate), and myalgia (sonidegib phosphate).

The following section of the glasdegib maleate labeling has been updated to read:

5 Warnings and Precautions
5.3 Musculoskeletal Adverse Reactions

Musculoskeletal adverse reactions, which may be accompanied by CPK elevations, have occurred with DAURISMO and other drugs which inhibit the hedgehog (Hh) pathway. In BRIGHT AML 1003, musculoskeletal adverse reactions occurred in 45% of patients treated, with 2% (7/79) reported as Grade 3 or higher. The most frequent manifestations of musculoskeletal adverse reactions reported were musculoskeletal pain (30%) and muscle spasms (15%). Increased CPK laboratory values occurred in 16% of patients [*see Adverse Reactions (6.1)*].

Obtain baseline CPK levels prior to initiating DAURISMO and as clinically indicated (e.g., if muscle symptoms are reported). Obtain CPK and serum creatinine levels at least weekly in patients with musculoskeletal adverse reactions with concurrent CPK elevation greater than 2.5 times ULN until resolution of clinical signs and symptoms. Depending on the severity of symptoms, temporary dose interruption, dose reduction, or discontinuation of DAURISMO may be required for musculoskeletal adverse reactions or serum CPK elevation [*see Dosage and Administration (2.2)*].

To the extent that all currently approved Hedgehog inhibitor drug products (i.e., vismodegib, glasdegib maleate, and sonidegib phosphate) now include a warning regarding musculoskeletal reactions and recommendations to obtain baseline serum CK and monitoring of CK levels, your Petition is granted. While the labeling across the currently approved Hedgehog inhibitor class will be aligned to include language in the Warnings and Precautions sections of the labeling, there will continue to be variations in the labeling due to differences in these products, including differences in indication and dosage.

Regarding the Petition's request that FDA require a warning regarding musculoskeletal reactions and information on CK monitoring for all future, not-yet-approved Hedgehog inhibitor drug products, we are denying that request at this time. Any safety data for future Hedgehog inhibitor products will be reviewed for any potential signals that may be applicable to that particular drug product.

III. CONCLUSION

In sum, for the reasons stated above, your Petition is granted in part and denied in part.

Sincerely,

Douglas C.
Throckmorton -S

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