David L. Rosen
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3000 K Street, NW, 6th Floor
Washington, DC 20007-5109

September 18, 2020

Re: Docket No. FDA-2020-P-1312

Dear Mr. Rosen:

This letter responds to the citizen petition submitted to the Food and Drug Administration (FDA, the Agency, or we) and received on April 28, 2020 (Petition), on behalf of Taiho Oncology, Inc. (Taiho), concerning Lonsurf tablets, 15 milligrams (mg) trifluridine/6.14 mg tipiracil and 20 mg trifluridine/8.19 mg tipiracil (Lonsurf), approved under new drug application (NDA) 207981. In the Petition, you ask FDA to:

(1) Refrain from filing or approving any abbreviated new drug application (ANDA) or 505(b)(2) application for a generic version of Lonsurf tablets, 15 mg trifluridine/6.14 mg tipiracil and 20 mg trifluridine/8.19 mg tipiracil, that does not reference Lonsurf and include certifications to all of the patents listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) for Lonsurf;

(2) Refrain from approving any ANDA or 505(b)(2) application for a generic version of Lonsurf tablets, 15 mg trifluridine/6.14 mg tipiracil and 20 mg trifluridine/8.19 mg tipiracil product, if the application includes a statement pursuant to Section 505(j)(2)(A)(viii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (see also 21 CFR 314.94(8)(iv)) stating that the applicant is not seeking approval of an application that contains an indication or other aspect of labeling protected by patent or exclusivity under section 505(j)(5)(F) of the FD&C Act; and

(3) Require the labeling for any generic version of Lonsurf tablets, 15 mg trifluridine/6.14 mg tipiracil and 20 mg trifluridine/8.19 mg tipiracil product, to include all information related to Warnings, Precautions and other safety related information that is included in the Lonsurf labeling, including relevant dose adjustments in severe renally impaired patients needed to prevent unnecessary toxicity.[1]

[1] Petition at 1-2.

We have carefully considered the information submitted in the Petition.[2] The Petition is denied for the reasons stated below.

I. BACKGROUND

A. Lonsurf

NDA 207981 for Lonsurf was approved on September 22, 2015, for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF (vascular endothelial growth factor) biological therapy, and if RAS wild-type, an anti-EGFR (estimated glomerular filtration rate) therapy. The drug product consists of two active ingredients: trifluridine and tipiracil. Trifluridine is a thymidine-based nucleoside analog, which can be incorporated into deoxyribonucleic acid (DNA) following phosphorylation and inhibit cell proliferation. Tipiracil is a thymidine phosphorylase inhibitor, which contributes to the action of Lonsurf by inhibiting degradation of trifluridine, leading to increased systemic exposure to trifluridine.

B. PMR 2963-2 and Supplement 009

The September 22, 2015, approval letter described two postmarketing requirements (PMRs) that Taiho was required to conduct: PMR 2963-1 and 2963-2. PMR 2963-2 was described as:

> Complete the ongoing clinical pharmacokinetic trial to determine an appropriate dose of Lonsurf (trifluridine and tipiracil) in patients with severe renal impairment in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."[3]

To satisfy PMR 2963-2, Taiho submitted the data and results of Study TAS-102-107, which evaluated the safety, tolerability, and pharmacokinetics (PK) of TAS-102 (the alphanumeric descriptor used in clinical trials of Lonsurf) in advanced solid tumor patients with varying degrees of renal impairment (RI).[4] Based on the data and results of this trial, on January 1, 2020, FDA approved a supplement for updates to the Dosage and Administration, Recommended Dosage for Renal Impairment subsection (2.3), Use in Specific Populations, Renal Impairment subsection (8.6), and the Clinical Pharmacology, Pharmacokinetics subsection (12.3) of the

[2] We also reviewed a comment that was submitted to the docket dated September 3, 2020, by Hyman, Phelps & McNamara, P.C.

[3] NDA 207981 Approval Letter, available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/207981Orig1s000ltr.pdf. Of the two PMRs issued at the time of approval, PMR 2963-2 is the only one relevant to Taiho's requests in the Petition.

[4] See generally, Supplement 9 of NDA 207981, Clinical Pharmacology Review, December 19, 2019 (2019 Clin Pharm Review).

package insert to incorporate data from the trial used to fulfill PMR 2963-2.[5] The labeling approved in this supplement added Section 2.3, which describes that the recommended dosage for patients with severe renal impairment is 20 mg/m^2 twice daily with food on Days 1-5 and Days 8-12 of each 28-day cycle; that the dose could be reduced to 15 mg/m^2 twice daily in patients with severe renal impairment who cannot tolerate a dose of 20 mg/m^2; and that Lonsurf should be permanently discontinued in patients who are unable to tolerate a dose of 15 mg/m^2 twice daily.[6] Additionally, subsection 8.6 was updated, in part, to include a recommendation to "[r]educe the dose of LONSURF for patients with severe renal impairment (CLcr of 15 to 29 mL/min)," and subsection 12.3 was updated, in part, to describe the total exposure (area under the curve or AUC) of trifluridine and tipiracil in patients with varying levels of renal impairment.[7]

C. Supplement 008

Prior to the approval of supplement 009, on February 22, 2019, FDA approved supplement 008 for a new indication: for the treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and, if appropriate, HER2/neu-targeted therapy.[8] According to the Orange Book, the supplement qualified for 3-year exclusivity (expiring February 22, 2022) and orphan drug exclusivity (expiring February 22, 2026).[9]

D. Patents for Lonsurf Listed in the Orange Book

Currently, there are four unexpired patents listed in the Orange Book for Lonsurf.[10] Two of these patents have been listed as drug substance and drug product patents.[11] The other two patents have been listed as method-of-use patents.[12]

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[5] Supplement 9 of NDA 207981 Approval Letter, January 1, 2020, available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/207981Orig1s009ltr.pdf.

[6] Supplement 9 of NDA 207981 Prescribing Information, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/207981s009lbl.pdf.

[7] Id.

[8] Supplement 8 of NDA 207981 Approval Letter, February 22, 2019, available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/207981Orig1s008ltr.pdf.

[9] The code associated with 3-year exclusivity is I-794: Treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy, and if appropriate, HER2/NEU-targeted therapy. The code associated with orphan drug exclusivity is ODE-229: Treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy, and if appropriate, HER2/NEU-targeted therapy.

[10] See Orange Book listing for Lonsurf, https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm.

[11] See Orange Book listing for Lonsurf, which lists U.S. Patent Nos. 9,527,833 (expires June 17, 2034) and 10,457,666 (expires June 17, 2034), with "DS" (drug substance) and "DP" (drug product) notations.

[12] See Orange Book listing for Lonsurf, which lists U.S. Patent No. 10,456,399 (expires February 3, 2037), with U-2642 patent use code: Method of treating cancer by detecting a creatinine clearance of a patient and administering

E. Section 505(q) of the Federal Food, Drug, and Cosmetic Act

Section 505(q) of FD&C Act 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 (Public Law 112-144, 126 Stat. 993). Section 505(q), as originally added by 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 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 such a petition no later than 150 days after the date on which the petition is submitted.

III. DISCUSSION

While the Petition's requested actions, which are described above, are broad in scope, the substance of the Petition generally focuses on Taiho's completion of Study TAS-102-107 and the approvability of generic versions[13] of Lonsurf that "carve out" or omit labeling information related to dose adjustments in severely renally impaired patients. The Petition asserts that the completion of Study TAS-102-107 "and revision[s] of the labeling to include a reduction of the dose in severe renally impaired patients [were] critical to safely dose Lonsurf in this patient subpopulation."[14] In discussing this study, the Petition notes one patent listed in the Orange Book in particular, namely U.S. Patent No. 10,456,399, for which Taiho submitted to FDA the following patent use code description: "method of treating cancer by detecting a creatinine clearance of a patient and administering Lonsurf."[15]

Taiho states that FDA should not allow applicants that reference Lonsurf "to carve-out this important information out of the labeling as the resultant labeling will make the proposed generic product less safe and effective than the reference product, Lonsurf."[16] Taiho maintains that if the labeling of a drug product approved through an ANDA or 505(b)(2) application that references Lonsurf could omit dosing information concerning severely renally impaired patients,

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Lonsurf; and U.S. Patent No. RE46284 (expires December 16, 2026), with U-1751 patent use code: Treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, as if RAS wild-type, an anti-EGFR therapy, and U-2503 patent use code: Treatment of adults with metastatic gastric or GJA previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/NEU-targeted therapy.

[13] The Petitioner seems to use the term "generic versions" to refer both to ANDAs that reference Lonsurf as the reference listed drug and 505(b)(2) applications that rely on Lonsurf as a listed drug.

[14] Petition at 3.

[15] Petition at 6.

[16] Id.

"prescribers would be deprived of vital information required for the safe prescription of generic versions of Lonsurf to patients with severe renal impairment."[17] Taiho further asserts that:

> [S]evere renally impaired patients who do not tolerate the drug and where the labeling did not provide appropriate dose reductions, would likely experience a higher rate and severity of adverse events, including neutropenia, anemia, febrile neutropenia, fatigue/asthenia, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting and pyrexia.[18]

Furthermore, the Petition states:

> [I]f the dose reduction in severe renally impaired patients is permitted to be carved out of the labeling, patients may be taken off the drug, when in fact, if there was a reduction in dose, patients with metastatic colorectal cancer or metastatic gastric or gastroesophageal junction adenocarcinoma they [sic] could continue to receive the benefits of this combination drug product.[19]

Therefore, the Petitioner maintains that allowing the omission of dosing information for severe renally impaired patients would make a product approved through an ANDA or 505(b)(2) application that references Lonsurf less safe and effective than Lonsurf.

As described above, 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 the Petition regarding the approvability of an ANDA or 505(b)(2) application referencing or relying on Lonsurf.

FDA has not made a final determination on whether to approve or not approve any ANDA or 505(b)(2) application referencing or relying on Lonsurf.[20] FDA's decision to approve or not approve a specific application will be based on the particular facts that are applicable to that application at the time of the decision. The patents and periods of exclusivity described above for Lonsurf may have different implications with respect to any individual application and its labeling depending on the particulars of an ANDA or 505(b)(2) application and/or the timing of its eligibility for approval. Such decisions are made by the Agency on a case-by-case basis in the normal course of the review process.

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

[17] Petition at 9.

[18] Id.

[19] Id.

[20] Under applicable statutory and regulatory provisions, we are generally prohibited from disclosing any determinations regarding the receipt or approvability of any pending NDA or ANDA before we have reached a final decision on whether to approve or not approve the ANDA or NDA.

of ANDAs and 505(b)(2) 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 in part 314 (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 (section 505(c) and (j) of the FD&C Act; § 314.105) or may not be approved (section 505(c), (d), and (j) of the FD&C Act; §§ 314.125 and 314.127), or identifies the deficiencies in the application and the steps an applicant may take to respond to the deficiencies (§ 314.110). 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 (section 505(c)(1)(B) and (d) of the FD&C Act; § 314.200). 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.[21] 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. 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 150-day 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. Accordingly, we deny without comment the specific requests in the Petition regarding the approvability of an ANDA or 505(b)(2) application referencing or relying on Lonsurf.

IV. CONCLUSION

For the reasons stated above, the Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
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Patrizia Cavazzoni, M.D.
Acting Director
Center for Drug Evaluation and Research

[21] Section 505(c)(1)(B) and (d) of the FD&C Act; and § 314.200.