Kleinfeld Kaplan Becker

1850 M Street NW, Suite 800
Washington, DC 20036

202.223.5120 › **kkblaw.com**

February 10, 2022

Via Electronic Submission – Regulations.gov

Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

CITIZEN PETITION

Dear Sir/Madam:

The undersigned, on behalf of Taiho Oncology, Inc. ("Taiho") submit this Citizen Petition pursuant to 21 C.F.R. §§ 10.30, 314.50(i), 314.52, 314.54, and Section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(b). As detailed below, Taiho is the holder of New Drug Application ("NDA") 207981 for Lonsurf® (trifluridine and tipiracil) tablets, for oral use.

The approved labeling for Lonsurf includes pharmacokinetic information on patients with severe renal impairment and corresponding required dosage reduction instructions for these patients. These sections of the label are based on a study conducted by Taiho demonstrating that severe renal impairment increased the steady-state AUC (dose-normalized) of trifluridine by 2.4 fold, and documenting that patients with severe renal impairment receiving a significantly modified dose of Lonsurf did not show a meaningful difference in safety profiles compared to patients with normal renal function or mild renal impairment. This Petition seeks to ensure applicants seeking to market generic versions of Lonsurf are not permitted to carve out this critical safety information in an attempt to circumvent the patent protections afforded to innovators such as Taiho through the Hatch-Waxman amendments to the FDCA.[1]

[1] A previous Citizen Petition addressing similar issues and requesting similar actions as the present petition was submitted on behalf of Taiho on April 28, 2020, Docket No. FDA-2020-P-1312. That Petition was the subject of non-substantive "denial" on September 18, 2020 because no generic applications were otherwise ready for approval at that time. Taiho attaches that previous petition as Exhibit 1 so that it becomes part of the record in this docket. Taiho submits this current petition to help assure that the issues raised in its previous petition are substantively addressed by the Agency in connection with its review of applications seeking approval to market generic versions of Lonsurf.

Action Requested

Taiho requests that the Food and Drug Administration take the following actions:

(a) Refuse to approve any abbreviated new drug application for generic trifluridine and tipiracil tablets that relies on Lonsurf as the reference listed drug ("RLD") that does not include in the proposed labeling those portions of the Lonsurf label describing pharmacokinetics in and dosage reduction instructions for patients with severe renal impairment, and other information from Taiho's dedicated renal impairment study; and

(b) require applicants seeking approval to market generic trifluridine and tipiracil tablets that rely on Lonsurf as the reference listed drug ("RLD") to submit a patent certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii) to United States Patent No. 10,456,399.

Statement of Grounds

I. Factual and Procedural Background

Lonsurf was originally approved on September 22, 2015 for treatment of patients with metastatic colorectal cancer who have been previously treated with certain other therapies.[2] In February 2019, FDA approved a supplement adding a second indication for treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior types of chemotherapy.[3]

The original NDA for Lonsurf did not include data from a dedicated pharmacokinetic study in patients with renal impairment. However, Taiho's pivotal study in patients with previously treated metastatic colorectal cancer had enrolled patients with mild and moderate renal impairment, and results from a population pharmacokinetic analysis of those data were included in the Clinical Pharmacology, Pharmacokinetics subsection of the initially approved label for Lonsurf.[4] In addition to reporting higher overall exposure to trifluridine and tipiracil in patients with mild and

---

[2] Approval Letter, NDA 207981 (Sept. 22, 2015), available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/207981Orig1s000ltr.pdf.

[3] Approval Letter, NDA 207981/S-008 (Feb. 22, 2019), available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/207981Orig1s008ltr.pdf.

[4] Package Insert, Lonsurf (trifluridine and tipiracil) tablets, for oral use, Section 12.3 (9/2015), available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207981s000lbl.pdf; Clinical Pharmacology Review, NDA 207981, pp. 8, 29, available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207981Orig1s000ClinPharmR.pdf.

moderate renal impairment, that original label also stated that the pharmacokinetics of trifluridine and tipiracil had not been studied in patients with severe renal impairment or end-stage renal disease.

The Clinical Pharmacology Review of the original NDA indicated that the increased exposure in patients with mild and moderate renal impairment might be confounded by the lower body weights of those patients, and recommended completion of a dedicated study in patients with renal impairment to investigate potential treatment-limiting severe toxicity.[5] The Clinical Pharmacology Review further stated that no dosing adjustment was recommended for patients with mild or moderate renal impairment.[6] Accordingly, the approved label recommended the same starting dose for all patients – 35 mg/m^2.[7]

As referenced in the Clinical Pharmacology Review, at the time of initial approval of Lonsurf, FDA determined that there was a need to assess signals of a serious risk of impaired renal function on the pharmacokinetics of Lonsurf resulting in excessive toxicity including myelosuppression. The Agency concluded that only a clinical trial would be sufficient for this assessment, and therefore imposed the following postmarketing requirement ("PMR"):

> 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."[8]

Taiho completed the study and submitted a supplemental NDA proposing to update the Lonsurf label to incorporate data and information from the study. FDA approved the supplement on January 1, 2020, adding a new subsection 2.3 to the Dosage and Administration section of the label, *Recommended Dosage for Renal Impairment.* This new subsection directs that patients with severe renal impairment take a substantially lower dose of Lonsurf – 20 mg/m^2, rather than 35 mg/m^2, as recommended for other patients in section 2.1 of the labeling. The new subsection

---

[5] *See* Clinical Pharmacology Review, NDA 207981, pp. 8, 6, available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207981Orig1s000ClinPharmR.pdf.

[6] *Id.,* p. 32.

[7] Package Insert, Lonsurf (trifluridine and tipiracil) tablets, for oral use. Section 2.1 (9/2015), available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207981s000lbl.pdf.

[8] Approval Letter, NDA 207981 (Sept. 22, 2015), available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/207981Orig1s000ltr.pdf.

further advises to reduce the dose to 15 mg/m^2 in patients with severe renal impairment who are unable to tolerate a dose of 20 mg/m^2. In contrast, the lowest dose recommended for other patients is 20 mg/m^2. Finally, new subsection 2.3 states that Lonsurf should be permanently discontinued in patients with severe renal impairment who are unable to tolerate a dose of 15 mg/m^2.[9]

The required dose reduction in patients with severe renal impairment was also added to the Highlights of Prescribing Information section of the Lonsurf label: "Renal Impairment: Reduce LONSURF dose in patients with severe renal impairment. (8.6)."

As reflected in the new Highlights language, the January 1, 2020 supplemental approval also modified subsection 8.6 of the Lonsurf label. Subsection 8.6 now instructs prescribers to reduce the dose of Lonsurf in patients with severe renal impairment, cross referencing new subsection 2.3. Further, this subsection states that the pharmacokinetics of trifluridine and tipiracil have not been studied in patients with end stage renal disease.

Finally, the Clinical Pharmacology, Pharmacokinetics subsection of the Lonsurf label (12.3) was revised to include data from Taiho's dedicated study in patients with renal impairment:

> Patients with Renal Impairment
> In a dedicated renal impairment study, all patients received LONSURF 35 mg/m^2 twice daily except for patients with severe renal impairment who received 20 mg/m^2 twice daily. Mild renal impairment (CLcr of 60 to 89 mL/min as determined by the Cockcroft-Gault formula) had no clinically important effect on steady-state $AUC_{0\text{-last}}$ of trifluridine and tipiracil. Moderate renal impairment (CLcr of 30 to 59 mL/min) increased steady-state $AUC_{0\text{-last}}$ of trifluridine by 56% and tipiracil by 139% compared to normal renal function (CLcr ≥ 90mL/min) . Severe renal impairment (CLcr of 15 to 29 mL/min) increased the dose-normalized steady-state $AUC_{0\text{-last}}$ of trifluridine by 140% and tipiracil by 614% compared to normal renal function. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with end stage renal disease.

---

[9] Package Insert, Lonsurf (trifluridine and tipiracil) tablets, for oral use (12/2019), available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/207981s009lbl.pdf. For patients without severe renal impairment, the recommended dosage of LONSURF is 35 mg/m2 up to a maximum of 80 mg per dose. *Id.* at Section 2.1. Modifications for this population are addressed in Section 2.2 of the label, *Dosage Modifications for Adverse Reactions.* Specifically, in the event of specified adverse events LONSURF is to be resumed at a dose 5 mg/m^2/dose lower than the previous dose. This section further states that a "maximum of 3 dose reductions are permitted. Permanently discontinue LONSURF in patients who are unable to tolerate a dose of 20 mg/m2 orally twice daily. Do not escalate LONSURF dosage after it has been reduced."

Originally, Section 12.3 of the label provided different pharmacokinetic data on patients with mild and moderate renal impairment, gathered in Taiho's pivotal study in patients with previously treated metastatic colorectal cancer, which had enrolled patients with mild and moderate renal impairment:

> Renal Impairment
> In Study 1, the estimated mean AUC of trifluridine at steady state was 31% higher in patients with mild renal impairment (CLcr = 60 to 89 mL/min, n= 38) and 43% higher in patients with moderate renal impairment (CLcr = 30 to 59 mL/min, n= 16) than that in patient with normal renal function (CLcr ≥ 90 mL/min, n= 84) based on the population pharmacokinetic analysis. The estimated mean AUC of tipiracil was 34% higher in patients with mild renal impairment and 65% higher in patients with moderate renal impairment than that in patients with normal renal function. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with severe renal impairment (CLcr < 30 mL/min) or end-stage renal disease. [see Use in Specific Populations (8.7)][10]

Among the patents listed in the Orange Book for Lonsurf is U.S. Patent 10,456,399 ("the '399 Patent"), the use code for which reads, "method of treating cancer by detecting creatinine clearance of a patient and administering Lonsurf." Based on comments submitted to the Docket for Taiho's previous petition on this matter, Docket No. FDA-2020-P-1312, as well as communications or the lack of communications from other generic applicants, Taiho believes that at least three generic companies have submitted or will be submitting a statement under section 505(j)(2)(A)(viii) of the FDCA and 21 C.F.R. § 314.94(8)(iv) to the '399 Patent seeking to carve out the dosage reduction instructions and related pharmacokinetic information in sections 2.3, 8.6, 12.3, and the Highlights section of the Lonsurf label and to use superseded information from the original Lonsurf labeling. For the reasons discussed below, such a carve out of this critical safety information should not be permitted.

II. Argument

A. Generic Drugs Must Have The Same Labeling as, and Must Submit Certifications to all Listed Patents for, the Pioneer Products They Reference, Except In Limited Circumstances

To obtain approval of an Abbreviated New Drug Application ("ANDA"), an applicant must identify the listed drug on which it seeks to rely for approval (the "RLD"). With respect to each patent submitted by the NDA applicant for the RLD and listed in the Orange Book, the ANDA applicant generally must submit to FDA

---

[10] Package Insert, Lonsurf (trifluridine and tipiracil) tablets, for oral use, Section 12.3 (9/2015), available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207981s000lbl.pdf.

one of four specified certifications under section 505(j)(2)(A)(vii) of the Act. For unexpired patents, the options are a paragraph III certification, indicating that the applicant does not seek approval before expiration of the patent, or a paragraph IV certification, indicating that the generic applicant asserts that the patent is invalid or will not be infringed by the generic drug for which approval is being sought.

A generic applicant must also show that the labeling proposed for the generic drug is the same as the labeling approved for the RLD, "except for changes required…because the new drug and the listed drug are produced or distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v). *See also* 21 U.S.C. § 355(j)(4)(G). Furthermore, FDA regulations narrowly define the acceptable variations between the two labels, which are limited to "differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act." 21 C.F.R. § 314.94(a)(8)(iv).[11] Additionally, FDA regulations at 21 C.F.R. § 314.92(a)(1) provide that a generic drug product must have the same conditions of use as the reference listed drug "except that conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted."

FDA has repeatedly emphasized that "the exceptions to the requirement of 'same labeling' are limited."[12] Accordingly, FDA regulations provide that approval of an ANDA that omits an "aspect of labeling protected by patent" is conditioned on an affirmative finding by the FDA that the "differences do not render the proposed drug product *less safe or effective* than the listed drug for all remaining, non-protected conditions of use." 21 C.F.R. § 314.127(a)(7) (emphasis added).

Only if the Agency makes such an affirmative finding may a generic applicant omit certifications to the subject patent, and instead submit a so-called section viii statement, indicating that the patent is listed for the RLD, but that the patent does not claim a use for which the applicant seeks approval. 21 U.S.C. § 505(j)(2)(A)(viii).

---

[11] The reference in this regulation to differences in "bioavailability or pharmacokinetics" between the RLD and generic labeling applies only when the generic product has different bioavailability or pharmacokinetics than the RLD. *See, e.g.*, 21 C.F.R. § 320.1(e). It does not contemplate omission of truthful information about pharmacokinetics which applies to both the RLD and the proposed generic.

[12] Abbreviated New Drug Application Regulations, Proposed Rule, 54 Fed. Reg. 28872, at 2881 (July 10, 1989) ("Consistent labeling for duplicate versions of a drug product, insofar as this is possible, will avoid differences that might confuse health care professionals who prescribe and dispense prescription drug products or might create omissions of significant information.").

B. Omission of Dosage Reduction Instructions for Patients with Severe Renal Impairment and other Information from Taiho's Dedicated Renal Impairment Study would Render Generic Products Less Safe than Lonsurf for the Remaining Conditions of Use

The dosage reduction instructions and information on the study informing those necessary dosage reductions is critical safety information necessary for the safe and effective use of the drug in patients with severe renal impairment that cannot lawfully be carved out of the labels for generic versions of Lonsurf. The current label for Lonsurf provides necessary dosage reduction instructions for these patients; specifically patients with severe renal impairment must be started on a substantially lower dose than other patients, and should be administered an even lower dose if unable to tolerate the recommended starting dose. The clinical importance of this information is reflected by its placement in the Lonsurf package insert. For instance, the dosage reduction instructions are contained in the Dosage and Administration section, reflecting that it is "information needed for safe and effective dosing and administration."[13] The need for dosage reduction in patients with severe renal impairment is also discussed in the Highlights of Prescribing Information section of the package insert. As explained in the Agency's guidance on prescription drug labeling, the Highlights section summarizes "crucial prescribing information" to which "practitioners most commonly refer and regard as most important."[14] FDA has elsewhere explained that the need for dosage adjustments in specific populations, including those with renal impairment, is just the type of "important" information that must be included the Highlights section.[15] Allowing a generic label to omit such clinically meaningful information would significantly increase the risk to patients with severe renal impairment, and render the generic product less safe than Lonsurf.

These circumstances are the same as those in which FDA has determined that a carve out would render a generic product less safe for the remaining, non-protected conditions of use and is therefore impermissible. For example, FDA refused to allow generic versions of Xyrem to carve out dosage reduction instructions based on a drug interaction study finding that coadministration of Xyrem with divalproex sodium increased mean systemic exposure to sodium oxybate (AUC) by approximately 25%,

---

[13] Guidance for Industry Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format (2010), p. 1, 3-4, available at: https://www.fda.gov/media/72142/download.

[14] *See* Guidance for Industry Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements (2013), p. 6, available at: https://www.fda.gov/media/71836/download.

[15] Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, Final Rule, 71 Fed. Reg. 3922, 3939 (Jan. 24, 2006).

though Cmax was comparable.[16] Based on this study, the dosage and administration section of the Xyrem label was revised to recommend an at least 20% lower dose of Xyrem in patients taking both drugs. FDA concluded that information on this specific interaction and the resulting dosing recommendations are important to prevent an exacerbation of serious adverse events associated with Xyrem. FDA reached this conclusion despite the fact that the Xyrem label discussed, in general terms, the risks when taking Xyrem with other CNS depressant medications, including sedating anti-epileptic drugs, and makes a general recommendation to consider dose reduction.

FDA reached a similar decision in the case of Colcrys, concluding that the drug interaction information and dosing adjustments added to the label based on the sponsor's studies could not be carved out of the label for generic versions of Colcrys.[17] FDA made this determination despite the fact that published literature described the relevant interactions in general terms, identifying CYP3A4 substrates and inhibitors as well as P-gp inhibitors as drugs with potentially dangerous interactions with colchicine that could result in serious colchicine toxicity. Nevertheless, FDA explained that, before the labeling for Colcrys was updated with the sponsor's study data, "there were no widely-accepted specific recommendations for dose reduction in the setting of potential concomitant use of drugs with known interactions, other than avoidance when possible and caution when necessary, with vigilant monitoring of clinical signs of toxicity." The sponsor's drug-drug interaction studies provided quantitative pharmacokinetic information on the effect of co-administration with certain drugs and informed specific recommended dose reductions in the labeling for Colcrys. The Agency thus concluded that drug-drug interaction information and corresponding dose adjustments was required in the labels of all single-ingredient colchicine products.

Comments on Taiho's previous petition, Docket No. FDA-2020-P-1312, argue that omission of dosage reduction instructions and related information from Taiho's dedicated renal impairment study is acceptable, on the assumption that removal of these sections of the label would also result in removal of patients with severe renal impairment from the approved patient population. This is not the case. Lonsurf was originally approved for use in adults with a specific type of cancer, without regard to renal function, and is now indicated for use in adults with two types of cancer, again without regard to renal function. Removal of specific dosage adjustments for patients with severe renal impairment and related pharmacokinetic data would not remove these patients from the approved patient population or otherwise change that approved patient population. Rather, these patients would still remain within the approved patient population, but the label would be silent as to the significantly lower dose of trifluridine and tipiracil that must be used to safely treat them.

---

[16] Response to Citizen Petition of Jazz Pharmaceuticals, Inc., Docket No. FDA-2016-P-2672 (Jan. 17, 2017).

[17] Response to Citizen Petition of Mutual Pharmaceutical Company, Inc., Docket No. FDA-2010-P-0614 (May 25, 2011).

The only potential means of permitting a carve out without materially increasing the risk to patients with severe renal impairment would be to add a contraindication to the label of generic versions of Lonsurf instructing that those drug products not be used in patients with severe renal impairment. Although applicable FDA regulations refer only to omission of label information protected by patent or exclusivity,[18] in the past FDA has also permitted minor additions to generic labels to facilitate readability in conjunction with a carve out. For example, in response to a petition addressing the potential carve out of the protected allergic rhinitis indication from generic versions of Xyzal, FDA determined that 21 C.F.R. § 314.94(a)(8)(iv) permits not only omissions of words or phrases from the reference listed drug's labeling, but also "minor attendant changes to ensure that the language of the labeling reads properly." FDA concluded that pooled safety information from studies of various indications including allergic rhinitis could not be carved out of generic labeling, but could remain with "selective deletions of the references to allergic rhinitis and *de minimis* modifications in the labeling."[19] FDA reached the same conclusion in a petition addressing the carve out of protected seizure and pain indications from the labeling for generic versions of Lyrica, stating that required safety information could remain in the labeling with selective omissions and "*de minimis* modifications" or "minor attendant changes to ensure that the language of the labeling reads properly."[20]

The types of minor additions FDA has found acceptable to implement a carve out in the past are not of the character or significance of a contraindication or other

---

[18] *See* 21 C.F.R. §§ 314.92(a)(1), 314.94(a)(8)(iv), 314.127(a)(7).

[19] Response to Citizen Petition of UCB, Inc., Docket No. FDA-2010-P-0545 (Feb. 24, 2011).

[20] Response to Citizen Petition of Sandoz, Inc., Docket No. FDA-2010-P-0087 (July 30, 2010). In a later decision, FDA stated, without citation in support, that its authority was not limited to "minor attendant changes" but nevertheless defended as *de minimis* the addition of words to effectively carve out a first line indication from Velcade's broad indication for "treatment of patients with mantel cell lymphoma." FDA concluded it could add words to essentially revert to the prior approved second-line indication for Velcade: "treatment of patients with mantel cell lymphoma who have received at least one prior therapy." In support, FDA noted that it could have added the first-line therapy indication with a separate clause, rather than combining the two into the more concise "treatment of patients with mantle cell lymphoma" and the Agency did not believe that the pioneer's exclusivity should be broadened due to FDA's choice to use concise language to encompass both indications. Response to Citizen Petition of Millenium Pharmaceuticals, Docket No. FDA-2017-P- 3672 (Nov. 6, 2017). The Agency's reasoning in the Velcade case is inapplicable to Lonsurf. Even if the Agency were authorized and willing to make more than *de minimis* changes to facilitate a carve out, the decisions on Xyrem and Colcrys indicate that adding a contraindication to facilitate a carve out is impermissible.

language warning against use in a subset of the approved patient population. We have identified no precedent in which FDA determined that a contraindication or other language precluding use in a particular subset of patients could be added to a generic label in order to address safety or efficacy questions that would otherwise be raised by a carve-out. Indeed, were FDA of the view that addition of a contraindication to facilitate a carve out was appropriate and within its statutory authority, the Agency could have reached contrary decisions on the Xyrem and Colcrys petitions. In both cases, a carve out of drug/drug interaction data and associated dosage adjustments could theoretically have been implemented if the generic labels were further revised to include contraindications in patients taking the relevant concomitant medications.

In the case of Lonsurf, a contraindication in patients with severe renal impairment is inappropriate for the additional reason that it would be inconsistent with FDA regulations and false. Taiho's dedicated renal impairment study showed that patents with severe renal impairment can achieve efficacious exposure with acceptable safety, provided the dose is adjusted significantly downward, as instructed in the Lonsurf label. The Agency's review of Taiho's supplement concludes, "[p]atients with severe RI who received 20 mg/m^2/dose did not show a meaningful difference in safety profiles compared to the normal renal function and mild RI cohorts. Therefore a dose of TAS-102 at 20 mg/m^2 BID is appropriate and tolerable for patients with severe RI."[21]

A contraindication should be included in a drug label only when "the drug should not be used because the risk of use . . . clearly outweighs any possible therapeutic benefit." 21 C.F.R. § 201.57(c)(5).[22] That is plainly not the situation here. Indeed, the most recently approved label adding the dosage reduction instructions for patients with severe renal impairment continues to state "Contraindications None" reflecting an affirmative Agency finding that there are no known circumstances warranting a contraindication. 21 C.F.R. § 201.57(c)(5).[23] Accordingly, the addition of language to

---

[21] *See* Clinical Pharmacology Review, NDA 207981/S-009, p. 16, attached hereto as Exhibit [ ].

[22] *See* Guidance for Industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format (2001), p. 8, available at: https://www.fda.gov/media/71866/download ("[a] drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit.").

[23] *Id.* ("If there are no known contraindications for a drug, this section must state "None.""); Package Insert, Lonsurf (trifluridine and tipiracil) tablets, for oral use. Section 4 (12/2019), available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/207981s009lbl.pdf. Moreover, FDA regulations also require that the dosage and administration section of the label include "modification of dosage needed . . . in special patient populations (e.g., . . . in patients with renal or hepatic disease"). 21 C.F.R. § 201.57(c)(3)(H); *see also* Guidance for Industry, Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling, pp. 13-14 (May 1998) (if impaired renal function requires

the label for a generic version of Lonsurf stating that the product should not be used in patients with severe renal impairment would be inconsistent with FDA regulations and render that label false and misleading, and would misbrand those products. *See* 21 U.S.C. § 352(a); 21 C.F.R. § 201.56(a)(2)

For all of these reasons, omission of the dosage reduction instructions for patients with severe renal impairment and other information from Taiho's dedicated renal impairment study would render a generic product less safe than Lonsurf for the remaining conditions of use, and is therefore impermissible.

C. A Certification to Patent No. 10,456,399 is Required

Because a generic applicant cannot lawfully omit dosage reduction instructions for patients with severe renal impairment or other information from Taiho's dedicated renal impairment study, a section viii statement to Patent No. 10,456,399 is impermissible. Generic applicants must therefore address this patent in a certification under 21 U.S.C. § 355(j)(2)(A)(vii).

Environmental Impact

Petitioner claims a categorical exclusion from the requirements of an environmental assessment or environmental impact statement pursuant to 21 C.F.R. § 25.31.

Economic Impact

An economic impact statement will be submitted if requested by the Commissioner, pursuant to 21 C.F.R. § 10.30(b).

Certification

I certify that, to my best knowledge and belief: (a) this Petition includes all information and views upon which the Petition relies; (b) this Petition includes representative data and/or information known to the Petitioner which are unfavorable to the Petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date:

February 5, 2016: Date the application for United States Patent No. 10,456,399 was filed with the U.S. Patent and Trademark Office.

---

dosage adjustment or results in clinically important changes in pharmacokinetics, these should described in labeling).

March 26, 2019: Date when results of study renal study TAS-102-107 were available to Taiho.

June 24, 2019: Date when Taiho filed NDA 207981/S-009.

October 29, 2019: Date of issuance of United States Patent No. 10,456,399.

November 7 and 12, 2019: Date on which Taiho received a Paragraph IV certification for patents listed in the Orange Book for Lonsurf that did not include a certification to United States Patent No. 10,456,399.

November 8, 2019: Date that information on United States Patent No. 10,456,399 was submitted to FDA.

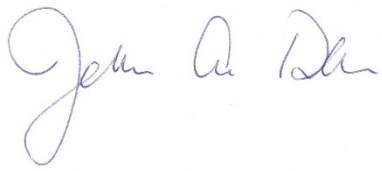
January 2, 2020: Date of FDA approval of NDA 207981/S-009.

April 28, 2020: Date of submission of citizen petition, FDA-2020-P-1312.

September 18, 2020: Date of issuance of non-substantive denial of citizen petition, FDA-2020-P-1312.

If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Taiho Oncology Inc. and Taiho Pharmaceutical Ltd. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this Petition.

Respectfully submitted,



Peter R. Mathers
Jennifer A. Davidson
Counsel to Taiho Oncology Inc.