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VIA ELECTRONIC SUBMISSION

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061, HFA-305
Rockville, MD 20852

CITIZEN PETITION

Foley & Lardner LLP on behalf of Taiho Oncology, Inc. (referred to as "Taiho" or the "Petitioner") submits this Petition under Section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FD&C Act") and 21 C.F.R. §§ 10.30, 314.50, 314.52, 314.54, 314.107, and 314.108.

The Petitioner respectfully requests that the Commissioner of Food and Drugs not permit companies to carve out of the labeling currently approved for Lonsurf® the language that relates to dose reductions in severely renally impaired patients. The carving out of dose reductions in severely renally impaired patients will result in labeling that will present an increased safety risk and that will render the proposed drug product less safe. The bases for this Petition are set forth below.

A. Action Requested

The Petitioner respectfully requests that the Commissioner of Food and Drugs:

1. Refrain from filing or approving any Abbreviated New Drug Application ("ANDA") or 505(b)(2) New Drug Application ("NDA") 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 the all of the patents listed in FDA's *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 FD&C Act (Section 21 CFR 314.94(8)(iv) of FDA's implementing regulations) stating that the applicant is not seeking approval of an application that contains an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the FD&C Act.

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.

B. Statement of Grounds

Lonsurf was approved by FDA under NDA No. 207981 on September 22, 2015. As a condition of approval, Taiho was required to conduct a post-marketing study to evaluate the safety, tolerability, and pK of Lonsurf's individual components (trifluridine and tipiracil) and the major metabolite of trifluridine in advanced solid tumor (except breast cancer) patients with varying degrees of renal impairment following single-dose and multiple-dose oral administration of the drug. Pharmacokinetic parameters were compared across patients with normal renal function and those with varying degrees of renal impairment.

Taiho requested a waiver from FDA from the completion of the study due to the difficulty in enrolling patients in the severely renal impaired cohort. Taiho and the FDA discussed the issues, agreed to a minor modification to the protocol and an extension of time to complete the post-marketing study.

Given that this study was an FDA mandated post-marketing requirement, the completion of the study and revision of the labeling to include a reduction of the dose in severe renally impaired patients was critical to safely dose Lonsurf in this patient subpopulation. FDA must not permit an ANDA applicant 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. Further discussion follows below.

1. Summary of Pharmacokinetic (PK) Studies Conducted to Support NDA Approval and to Satisfy Post Marketing Requirements

Lonsurf is a combination of trifluridine (FTD) and tipiracil hydrochloride (TPI) at a molar ratio 1:0.5 (weight ratio, 1:0.471). FTD is an antineoplastic thymidine-based nucleoside analog, which is incorporated into deoxyribonucleic acid (DNA) in tumor cells following phosphorylation. FTD after administration is predominantly metabolized to an inactive form, 5-trifluoromethyluracil (FTY) by thymidine phosphorylase (TPase) and then the inactive metabolites are excreted in urine and feces (see studies submitted to the NDA, Study AE-2350-3G, Study AE-6930-G, and Study TPU-TAS-102-108).

TPI is a specific inhibitor of TPase that inhibits degradation of FTD in the intestinal tract and liver. Absorbed TPI is mainly excreted in urine as an unchanged form, and partially converted to 6-hydroxymethyluracil (6-HMU) by a non-enzymatic reaction (see studies submitted to the NDA, Study AE-2350-2G, Study AE-6930-G, and Study TPU-TAS-102-108).

In a primate study, the absolute bioavailability of FTD alone was extremely low (3%) due to the first-pass metabolism by hepatic and intestinal TPase. However, when FTD was co-administered with TPI at a molar ratio 1:0.5, the overall exposure in plasma to FTD, as measured by area under the concentration-time curve (AUC) was increased by approximately 100-fold compared to FTD alone. These results demonstrate that co-administration of FTD with TPI in monkeys increased plasma FTD exposure and that TPI was the determinant of FTD pharmacokinetics (PK) following administration of Lonsurf (Study C-O149). Therefore, the effect of renal function on TPI elimination was also considered to have the potential to effect FTD exposure when FTD is given in combination with TPI. Actually, an animal study using a

rat model of chronic renal impairment showed that decreasing renal function caused significant increases in systemic exposure of FTD (100% increase) and TPI (400% increase) following administration of Lonsurf compared to a sham control group (Study 07DB43, on file at Taiho).

As described in the NDA supporting the approval of Lonsurf in metastatic colorectal cancer, pharmacokinetic studies in humans replicated the findings in animals. When the PK of a single-dose of FTD administered in combination with TPI as Lonsurf was compared to the PK of a single dose of FTD alone in patients with advanced solid tumors, the plasma exposure of FTD was approximately 37-fold higher following administration of Lonsurf than following administration of FTD alone (Study TPU-TAS-102-102). These results indicated the poor bioavailability of FTD when administered alone, consistent with the results observed in monkeys (Study C-O149). Furthermore, the results demonstrate the contribution of TPI, in the combination of FTD and TPI (Lonsurf), in effectively inhibiting the degradation of FTD by TPase and permitting effective anti-tumor activity.

The effect of renal function on PK of FTD and TPI following administration of Lonsurf was assessed in a population PK (PopPK) analysis in patients (Study 12DA025). The analysis identified that renal function, as measured by creatinine clearance (CLcr), was a primary intrinsic factor significantly effecting exposures of FTD and TPI. In Study TPU-TAS-102-103, the mean values of AUC at steady state for FTD were 31% higher in patients with mild renal impairment (CLcr 60-89 mL/min) and 43% higher in patients with moderate renal impairment (CLcr 30-59 mL/min) than that for patients with normal renal function (CLcr ≥ 90 mL/min) (Additional analysis for Response to Clinical questions from the Agency). A similar effect of renal impairment on the TPI exposure was observed. Furthermore, an analysis of PK/pharmacodynamic (PD) relationships in patients with refractory colorectal cancer (Study TPU-TAS-102-301), demonstrated that greater systemic exposure to FTD was associated with longer overall survival and greater risk of safety events (Study TPU-TAS-102-301 PK/PD). Consistent with the results of the PK/PD analysis, the safety analysis across clinical studies (Study J003 and Study TPU-TAS-102-301) suggested that patients with moderate renal impairment (based on baseline CLcr) had a higher incidence of severe (≥Grade 3) adverse events compared to the normal renal function and mild renal impairment subgroups. Similar results were observed for renal function subgroups based on baseline estimated glomerular filtration rate

(eGFR) (CTD m2.7.4 Table 31 and Table 32). Thus, based on animal and human data there is a clear effect of renal impairment on the PK, efficacy, and safety of Lonsurf. (The studies referred to in the above paragraph were submitted in the NDA.)

Given that a formal renal impairment study in patients was not conducted as part of the Lonsurf development plan in support of approval in metastatic colorectal cancer, and given that patients with severe renal impairment were not included in Lonsurf clinical studies which contributed to the population PK analysis, the FDA required a formal renal impairment study of Lonsurf as a post-marketing requirement following the initial approval of Lonsurf in 2015. This study, TO-TAS-102-107, examined the effect of varying degrees of renal impairment (normal function, mild, moderate and severe renal impairment) on Lonsurf PK in patients. Following administration of Lonsurf, overall exposure as measured by $AUC_{0\text{-last}}$ at steady state for FTD and TPI in patients with moderate renal impairment was approximately 1.56- and 2.39-fold higher than that in patients with normal renal function. Severe renal impairment increased $AUC_{0\text{-last}}$ at steady state for FTD and TPI by 1.37- and 4.08-fold respectively compared to normal renal function even though the Lonsurf dosage was adjusted downward (FTD: from 35 mg/m^2 to 20 mg/m^2). These results demonstrated that severe renal impairment had the expected effect of greatly increasing the TPI exposure leading to an increased FTD exposure. Based on the results, the post marketing commitment for a formal renal impairment study was met and FDA approved a change to product labeling recommending that Lonsurf be administered at a starting dose of 15 mg/m^2 to patients with severe renal impairment.

2. Severe Renal Impairment Significantly Alters Lonsurf's Pharmacokinetics

To emphasize what is noted above, severe renal impairment significantly alters Lonsurf's pharmacokinetics. Severe renal impairment (CLcr of 15 to 29 mL/min) increased the dose-normalized steady-state AUC0-last of trifluridine by 140% and tipiracil by 614% compared to normal renal function.

Tumor patients are often elderly and therefore have a high rate of renal impairment. Furthermore, tumor patients receiving Lonsurf are often receiving other antitumor agents as

pretreatment. For colorectal cancer, for which Lonsurf is effective, fluorouracil (FU), platinum, taxane and irinotecan may be administered as standard therapies such as infusional 5-fluorouracil (5-FU)/leucovorin with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI. These other products may increase the likelihood of causing kidney damage.

3. Post-Marketing Study Requirements

Taiho utilized diligent effort and significant resource to execute the renal impairment study, requiring several years to do so. Even though patient recruitment was very difficult and Taiho requested to modify or stop the study, the study was required to continue and be completed, because it was important to evaluate the impact of renal disease on the pK of the drug and to update the labeling to provide safe dosing modifications in this severely renally impaired patient population. The results of that study have indicated in order for Lonsurf to be administered safely in patients with severe renal impairment, the dosing must be modified. The dose modification in patient with severe renal impairment was incorporated into the current version of the Lonsurf labeling that was approved by FDA in January, 2020.

Taiho has been granted US patents with claims covering Lonsurf that are including in FDA's list of Approved Drug Products with Therapeutic Equivalence Evaluations (the "FDA's Orange Book"). Among those patents is US Patent 10,456,399 that provides for a method of treating cancer by detecting creatinine clearance of a patient and administering Lonsurf.

4. Current FDA Approved Lonsurf Labeling Includes Critical Information for Dose Modification in Severe Renally Impaired Patients

As seen in the current FDA approved Lonsurf labeling (included as an attachment to this Citizen Petition) there is critically important information for healthcare practitioners that provides for modification of the dose in patients with severe renal impairment. The dosing modification in this patient population affords patients with metastatic colorectal cancer or metastatic gastric or gastroesophageal junction adenocarcinoma the opportunity to continue to receive the benefits of this combination drug product treatment when they might be otherwise taken off the drug due to inability to tolerate the product or due to adverse events they may be experiencing.

C. FDA's Authority to Approve an ANDA That Omits Labeling Protected by Exclusivity or Patent

The FD&C Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]" and "information ... to show that the labeling proposed for the new drug is the same as the labeling approved for the listed, drug..." (Section 505(j)(2)(A)(i) and (v)). The FD&C Act provides the following two exceptions for when ANDA labeling may differ from that of the listed drug: (1) because changes reflect differences approved pursuant to an ANDA suitability petition; or (2) because the drugs are produced or distributed by different manufacturers (section 505(j)(2)(A)(v)).

FDA regulations implementing the statutory exceptions to the same labeling requirement state that "... differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include ... 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 CFR 314.94(a)(8)(iv)). The regulations further provide, however, that to approve an ANDA that omits an aspect of labeling protected by patent or exclusivity, FDA must find 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 CFR 314.127(a)(7)).

D. FDA Must Not Approve a Generic Version of Lonsurf that Carves Out Dose Adjustments in Severely Renally Impaired Patients

As noted above, Taiho expended tremendous resources developing Lonsurf Tablets, 15 mg trifluridine/6.14 mg tipiracil and 20 mg trifluridine/8.19 mg tipiracil. As a condition of approval Lonsurf Tablets (see approval letter dated September 22, 2015), FDA required Taiho to conduct a post marketing study to evaluate the safety, tolerability, and pharmacokinetics of the drug in patients with advanced solid tumors and varying degrees of renal impairment. Taiho completed the study, submitted a supplement to NDA 207981 dated June 21, 2019. Revised labeling for Lonsurf was submitted to FDA dated June 24, 2019. The labeling supplement, which included revisions for dosing adjustments in severe renally impaired patients, was approved by FDA on January 1, 2020.

This post-marketing requirement is consistent with FDA Guidance for Industry entitled, "Pharmacokinetics in Patients with Impaired Renal Functions: Study Design, Data Analysis, and Impact on Dosing and Labeling.[1]" The labeling section of the guidance includes the following statement:

> The labeling should reflect the data pertaining to the effect of renal function on the pharmacokinetics and pharmacodynamics (if known) obtained from studies conducted. The various permutations of intrinsic drug characteristics and the effect of renal impairment on drug performance preclude precise specification of how such drugs should be labeled. The following comments offer general suggestions on which sections of the labeling should include standardized information and how such information should be structured…
>
> FDA Guidance at 12.

It is clear that it dosing information in severe renally impaired patients is critically important to ensure the safe use of drug products in this patient population.

In addition, Taiho has conducted a post-marketing surveillance study, in which the company investigated the safety and efficacy of trifluridine/tipiracil in patients with metastatic colorectal cancer in a real-world setting, particularly hematological drug reactions classified according to the baseline renal and hepatic functions. This study has been written up in a paper that has been submitted for publication in an academic journal.[2] The following conclusion is expected to be stated:

> ….patients with renal impairment had higher incidences of adverse drug reactions than those with normal renal function.

It was observed that patients with moderate and severe renal impairment have higher rates of adverse events. This suggests that if Lonsurf or a generic version is administered to the

[1] https://www.fda.gov/files/drugs/published/Pharmacokinetics-in-Patients-with-Impaired-Renal-Function.pdf

[2] Post-Marketing Surveillance Study of Trifluridine/Tipiracil in Patients with Metastatic Colorectal Cancer, submitted for publication in a peer-reviewed medical journal.

patients with severe renal impairment, without the appropriate modifications in dosing, the rate and severity of adverse event will be much higher. This emphasizes that appropriate dosing modifications for severe renally impairment patients must be included in any generic version of Lonsurf in order to provide physicians with critical dosing information for safe use of the drug product.

The Petitioner requests that FDA not permit generic companies to carve out of the labeling information on the reduction in dose in severe renally impaired patients. The carving out of important reduction in dosing information in severely renally impaired patients will make the generic product less safe if the product is prescribed without appropriate dosing instructions in renally impaired patients. If this dose reduction were to be 'carved out' by a generic sponsor, prescribers would be deprived of vital information required for the safe prescription of generic versions of Lonsurf to patients with severe renal impairment. In this scenario, severe 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.

In addition, if 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 could continue to receive the benefits of this combination drug product.

The Lonsurf dosing adjustment in severe renally impaired patients is very important to the safe use of the product. Lonsurf is often the last line of therapy for these patients. Currently there are very limited or no other treatment options for these patients. Permitting generic companies to carve out information on the dose reduction in severely renally impaired patients would cause confusion to physicians and put the health and safety of the patients at risk.

Thus, the Petitioners firmly believe that if FDA were to permit such a labeling carve out of information pertaining to the dose reduction in severe renally impaired patients, this would

render the language remaining in the package insert to be less safe than the reference listed drug, Lonsurf.

FDA has not permitted the carving out of information protected by patent(s) or exclusivity where the omission of information would make the proposed product less safe and effective than the reference product. See FDA response dated September 20, 2004 to Docket FDA-2003-P-0518 (the "Rapamune response") and FDA response dated May 25, 2011to Docket FDA-2010-P-0614 (the Colcrys response"). In the Rapamune situation, FDA stated that without the cyclosporine withdrawal language, thereby limiting the indication to the remaining narrow subset of renal transplant patients at high risk of infection, could be potentially unsafe and confusing." See Rapamune response at page 4. In the Colcrys situation, FDA stated "that product labeling for any single-ingredient oral colchicine product needs to include adequate information on drug-drug interactions, *including relevant dosage adjustments needed to prevent unnecessary toxicity*." See the Colcrys response at page 3 (*emphasis added*.)

In conclusion, with respect to Lonsurf, the carving out of information pertaining to the dose reduction in severe renally impaired patients would render the language remaining in the package insert to be less safe than the reference listed drug, Lonsurf. FDA should not and cannot permit 505(b)(2) or ANDA applicants to carve out important labeling information that could result in a less safe and confusing situation.

E. Environmental Impact

The Petitioners claim a categorical exclusion under 21 CFR § 25.31.

F. Economic Impact

The health and safety of cancer patients with severe renal impairment is at issue. Without appropriate dosing adjustments, this population could experience more significant and severe adverse events would increase the cost of care for these patients. In addition, if severely renally impaired patients discontinue the use of 15 mg trifluridine/6.14 mg tipiracil and 20 mg

trifluridine/8.19 mg tipiracil tablets because there is no dosing adjustment in the labeling, other courses of therapy could be more expensive, present different safety concerns and be less effective. If patients are taken off generic versions of Lonsurf, the prognosis for these patients will likely worsen because this is generally a last line of therapy. The healthcare system will bear increased costs to care for these patients.

G. 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: September 18, 2018. 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

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Attachment:
Current Lonsurf Labeling

Cc: Taiho Oncology, Inc.