Peter Mathers
Jennifer Davidson
Kleinfeld Kaplan & Becker LLP
1850 M Street NW, Suite 800
Washington, DC 20036

July 22, 2022

Re: Docket No. FDA-2022-P-0155

Dear Mr. Mathers and Ms. Davidson:

This letter responds to the citizen petition submitted by Kleinfeld Kaplan & Becker LLP on behalf of Taiho Oncology, Inc. (Taiho), received on February 10, 2022 (2022 Petition). Taiho requests that the Food and Drug Administration (FDA, the Agency, or we) not permit applicants of abbreviated new drug applications (ANDAs) that reference Lonsurf, 15 milligrams (mg) trifluridine/6.14 mg tipiracil and 20 mg trifluridine/8.19 mg tipiracil, tablets (Lonsurf) (new drug application (NDA) 207981) as the reference listed drug (RLD) to omit certain labeling information. Taiho, represented by Foley & Lardner LLP, had previously submitted a citizen petition in 2020 (Docket No. FDA-2020-P-1312) (2020 Petition) making similar requests as the 2022 Petition. The 2020 Petition was denied with a non-substantive response on September 18, 2020.[1]

In the 2022 Petition, Taiho requests that FDA take the following actions:[2]

1. 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.

2. [R]equire 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.

On April 19, 2022, Hyman, Phelps & McNamara, P.C. (HPM) submitted a comment to the docket of the 2022 Petition on behalf of Natco Pharma Limited; MSN Laboratories Private Ltd

[1] Letter from P. Cavazzoni, Acting Director of FDA's Center for Drug Evaluation and Research (CDER), to D. Rosen, Foley & Lardner LLP, Docket No. FDA-2020-P-1312 (September 18, 2020).

[2] 2022 Petition at 2.

and MSN Pharmaceuticals Inc.; and Eugia Pharma Specialities Ltd., Aurobindo Pharma Ltd., and Aurobindo Pharma U.S.A. Inc.[3]

We have carefully reviewed the requests in the 2022 Petition, HPM's comments, and the administrative record. For the reasons explained below, we are granting the requests in the 2022 Petition.

I. FACTUAL BACKGROUND

A. Lonsurf and Its Original Approval

NDA 207981 for Lonsurf was originally 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-vascular endothelial growth factor (VEGF) biological therapy, and, if RAS wild-type,[4] an anti-endothelial growth factor receptor (EGFR) therapy. Lonsurf consists of two active ingredients: trifluridine and tipiracil hydrochloride.[5] Trifluridine is a thymidine-based nucleoside analog, which can be incorporated into DNA following phosphorylation and inhibit cell proliferation. Tipiracil is a thymidine phosphorylase inhibitor, which inhibits the degradation of trifluridine, leading to increased systemic exposure to trifluridine. Tipiracil is primarily eliminated by renal excretory mechanisms. At the time of this approval, the recommended dose of Lonsurf was 35 mg/m^2 up to a maximum of 80 mg per dose orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle until disease progression or unacceptable toxicity.

The primary study establishing the safety and efficacy of Lonsurf for the metastatic colorectal cancer indication was TPU-TAS-102-301 (RECOURSE), an international, randomized, double-blind, placebo-controlled study comparing TAS-102 (the alphanumeric descriptor used in clinical trials of Lonsurf) to placebo. Regarding renal impairment, an FDA review stated the following:[6]

> In Study RECOURSE, the mean values of the area under the curve (AUC) for trifluridine at steady state were 31% higher in patients with mild ([creatinine clearance (CLcr)] = 60-89 [milliliters (mL)/minute (min)], n =38) and 43% higher in patients with moderate (CLcr = 30 to 59 mL/min, n= 16) renal impairment than those in patients with normal (CLcr ≥ 90 mL/min, n=84) renal function. Similar effect of renal impairment on the tipiracil exposure was observed (34% higher in patients with mild and 68% 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. . . Since tipiracil

[3] On September 3, 2020, HPM submitted a comment to the docket of the 2020 Petition on behalf of Natco Pharma Limited.

[4] RAS is the most common mutated gene in colorectal cancer, and its occurrence is associated with primary and acquired resistance to anti-epidermal growth factor receptor (EGFR) blockade.

[5] Hereinafter, we will refer to "tipiracil hydrochloride" as "tipiracil."

[6] NDA 207981, Clinical Pharmacology and Biopharmaceutics Review(s) (February 24, 2015), at 8 (available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207981Orig1s000ClinPharmR.pdf).

> is a [pharmacokinetic (PK)] modulator increasing the systemic exposure of trifluridine by inhibiting [thymidine phosphorylase (TPase)], the increased exposure of trifluridine in patients with mild to moderate renal impairment could be the secondary effect mediated by the increased tipiracil exposures leading to increased inhibition of trifluridine metabolism (via TPase) in the same patients with renal impairment.

Based on population PK analyses in subjects who received TAS-102, FDA found that renal function was a primary intrinsic factor affecting the exposure to trifluridine and to tipiracil after TAS-102 administration.[7] This means FDA found that a patient's exposure to trifluridine and tipiracil after taking TAS-102 would vary based on the patient's renal function. FDA found that patients with renal impairment could have increased tipiracil exposure leading to increased trifluridine exposure due to increased inhibition of trifluridine metabolism by tipiracil, which may lead to more treatment-limiting severe toxicity.

FDA thus required Taiho to conduct a dedicated renal impairment study as a postmarketing requirement (PMR) pursuant to section 505(o)(3) of the FD&C Act to determine the appropriate dose of Lonsurf for patients with severe renal impairment. Specifically, the September 22, 2015, approval letter listed two PMRs that Taiho was required to conduct: PMR 2963-1 and 2963-2. PMR 2963-2 was described as:[8]

> 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."

Regarding labeling information on renal impairment, at the time of Lonsurf's original approval, subsection 8.7 (Renal Impairment) in Lonsurf's prescribing information stated the following:[9]

> No dedicated clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of LONSURF.
>
> In Study 1, patients with moderate renal impairment (CLcr = 30 to 59 mL/min, n= 47) had a higher incidence (difference of at least 5%) of ≥ Grade 3 adverse events, serious adverse events, and dose delays and reductions compared to patients with normal renal function (CLcr ≥ 90 mL/min, n= 306) or patients with mild renal impairment (CLcr = 60 to 89 mL/min, n= 178).
>
> No dose adjustment to the starting dose of LONSURF is recommended in patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min); however patients with

[7] Id. Body surface area was also considered a primary intrinsic factor affecting exposure of the two active ingredients.

[8] 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 2022 Petition and 2020 Petition.

[9] NDA 207981, Prescribing Information (September 22, 2015), available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207981s000lbl.pdf.

> moderate renal impairment may require dose modification for increased toxicity. No patients with severe renal impairment (CLcr < 30 mL/min) were enrolled in Study 1. *[see Clinical Pharmacology (12.3)]*

In subsection 12.3 (Pharmacokinetics, Specific Populations), Lonsurf's prescribing information when originally approved stated the following:[10]

> 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 [sic] 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)]*

B. Supplement 008

On February 22, 2019, FDA approved Supplement 008 to add a new indication for Lonsurf: 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.[11] This indication was supported by a multinational, double-blind, two-arm, parallel, randomized, phase 3 study evaluating the efficacy and safety of TAS-102 plus best supportive case versus placebo plus best supportive case in participants with metastatic gastric cancer who had previously received at least two prior regimens for advanced disease.[12] The median overall survival was 5.7 months in patients receiving TAS-102 and 3.6 months in patients receiving placebo (hazard ratio of 0.69). According to the "Approved Drug Products With Therapeutic Equivalence Evaluations" (the Orange Book), upon approval of the supplement, the application qualified for 3-year exclusivity (that expired on February 22, 2022) and orphan-drug exclusivity (expiring on February 22, 2026).[13]

C. PMR 2963-2 and Supplement 009

To fulfill PMR 2963-2, Taiho submitted the data and results of Study TAS-102-107, which evaluated the safety, tolerability, and pharmacokinetics of TAS-102 in advanced solid tumor

---

[10] Id.

[11] Supplement 008 of NDA 207981 Approval Letter, February 22, 2019, available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/207981Orig1s008ltr.pdf.

[12] See ClinicalTrials.gov Identifier: NCT02500043 for more information on the study.

[13] The exclusivity 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.

subjects with varying degrees of renal impairment.[14] A reduced dose of 20 mg/m^2 twice daily, instead of the recommended dose of 35 mg/m^2, was selected for patients with severe renal impairment. The trial results showed that severe renal impairment increased the steady-state AUC (dose-normalized) of trifluridine by 2.4-fold.[15] There was no meaningful difference found in the safety profile of TAS-102 in subjects with severe renal impairment who received the reduced dose of 20 mg/m^2 compared to subjects with normal renal function and mild renal impairment who received the recommended dose of 35 mg/m^2. Therefore, a dose of TAS-102 at 20 mg/m^2 twice daily was determined to be appropriate and tolerable for subjects with severe renal impairment. The trial results also showed that mild to moderate renal impairment had no clinically meaningful effects on the exposures of trifluridine.[16] In addition, the safety findings in these subjects from the trial were consistent with the known safety profile of Lonsurf in this population. Therefore, no dose adjustment was found to be needed for subjects with mild and moderate renal impairment.

Based on the data and results of this trial, on January 1, 2020, FDA approved Lonsurf's Supplement 009 for labeling updates or additions to subsection 2.3 (Dosage and Administration, Recommended Dosage for Renal Impairment); subsection 8.6 (Use in Specific Populations, Renal Impairment); and subsection 12.3 (Clinical Pharmacology, Pharmacokinetics) of the prescribing information to incorporate data from the trial used to fulfill PMR 2963-2.[17]

The labeling approved in this supplement added subsection 2.3 (Recommended Dosage for Renal Impairment), which describes that the recommended dosage for patients with severe renal impairment is 20 mg/m^2 twice daily with food on Days 1 through 5 and Days 8 through 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.[18]

Additionally, subsection 8.6 on Renal Impairment was updated, in part, to include a recommendation for patients with severe renal impairment as follows:[19]

> No dose adjustment is recommended for patients with mild or moderate renal impairment (CLcr of 30 to 89 mL/min as determined by the Cockcroft-Gault formula). Reduce the dose of LONSURF for patients with severe renal impairment (CLcr of 15 to 29 mL/min) *[see Dosage and Administration (2.3)]*. The pharmacokinetics of trifluridine and tipiracil have not been studied in patients with end stage renal disease.

---

[14] See generally, Supplement 009 of NDA 207981, Clinical Pharmacology Review (December 19, 2019), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/207981Orig1s009.pdf.

[15] Id. at 2.

[16] Id.

[17] Supplement 009 of NDA 207981 Approval Letter (January 1, 2020), available at: https://www.accessdata.fda.gov/drugsatfda_docs/appetter/2020/207981Orig1s009ltr.pdf.

[18] Supplement 009 of NDA 207981, Prescribing Information (January 1, 2020), available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/207981s009lbl.pdf.

[19] Id.

Subsection 12.3 on Pharmacokinetics, Patients with Renal Impairment, was updated to describe the total exposure (AUC) of trifluridine and tipiracil in patients with varying levels of renal impairment:[20]

> 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 ≥ 90 mL/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.

D. Patents for Lonsurf listed in the Orange Book

Currently, there are five unexpired patents listed in the Orange Book for Lonsurf.[21]

- Two of the patents are listed as drug substance and drug product patents: 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.[22]

- The other three patents are listed as method-of-use patents:

    - U.S. Patent No. 10,456,399 ('399 patent) (expires February 3, 2037), with U-2642 patent use code of "Method of treating cancer by detecting a creatinine clearance of a patient and administering Lonsurf"

    - U.S. Patent No. 10,960,004 ('004 patent) (expires on February 3, 2037), with the same U-2642 patent use code

    - U.S. Patent No. RE46284 (expires December 16, 2026), with U-1751 patent use code of "Treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy," and U-2503 patent use code of "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"[23]

[20] Id.

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

[22] Id.

[23] Id.

II. LEGAL AND REGULATORY BACKGROUND

A. Abbreviated Approval Pathway for Generic Drugs

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the FD&C Act. The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure for pioneer drugs first approved after 1962" with new incentives for drug development in the form of marketing exclusivity and patent term extensions.[24] Section 505(j) of the FD&C Act establishes an abbreviated approval pathway for a drug product that is the same as a previously approved drug (the reference listed drug or RLD) with respect to active ingredient; dosage form; route of administration; strength; and, with certain exceptions, labeling and conditions of use. An ANDA applicant also must demonstrate that its proposed product is bioequivalent to the RLD. An applicant that meets the requirements under section 505(j) for approval may reference the Agency's finding of safety and effectiveness for the RLD and need not repeat the nonclinical and clinical investigations required for approval of an NDA submitted under section 505(b)(1) of the FD&C Act.

B. Patent Listing Requirements and Patent Certification Requirements

Section 505(b)(1)(A)(viii) of the FD&C Act requires NDA applicants to file as part of the NDA:[25]

> the patent number and expiration date of each patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug, and that (I) claims the drug for which the applicant submitted the application and is a drug substance (active ingredient) patent or a drug product (formulation or composition) patent; or (II) claims a method of using such drug for which approval is sought or has been granted in the application.

FDA is required to publish the patent information provided by the NDA holder for drugs approved under section 505(c) and does so in the Orange Book.[26] For each unexpired patent listed in the Orange Book, the ANDA applicant must submit either a paragraph III certification (certifying the date on which such patent will expire and delaying approval until such date), a paragraph IV certification (certifying that such patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted), or, with respect to a method of use patent, a statement that the patent does not claim a use for which the ANDA

[24] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

[25] Section 505(c)(2) of the FD&C Act requires submission of patent information within 30 days of NDA approval. Section 505(c)(2) also imposes an additional patent submission requirement on holders of approved NDAs when those NDA holders subsequently obtain new patent information that could not have been submitted with the NDA.

[26] Section 505(b)(1), (c)(2), and (j)(7) of the FD&C Act; 21 CFR 314.53(e).

applicant is seeking approval.[27]

An applicant submitting a paragraph IV certification is required to give notice of the paragraph IV certification to the NDA holder for the RLD and each owner of the patent that is the subject of the certification. Notice of a paragraph IV certification is intended to provide an opportunity for "any legal disputes regarding the scope of the patent and the possibility of infringement [to] be resolved as quickly as possible."[28] The submission of an ANDA "for a drug claimed in a patent or the use of which is claimed in a patent" is an act of patent infringement that can establish jurisdiction for patent infringement litigation.[29]

An ANDA applicant seeking to omit from the use(s) for which it seeks approval an approved use of the RLD covered by a listed method of use patent need not file a paragraph III or IV certification for that patent. Instead, the applicant may submit a "section viii statement" acknowledging that a given method of use patent has been listed but stating that the patent at issue does not claim a use for which the applicant seeks approval.[30] Such a statement requires the ANDA applicant to omit or "carve out" from its labeling any information pertaining to the protected use.[31] Section 314.94(a)(12)(iii)(A) states that:

> If patent information is submitted under section 505(b) or (c) of the [FD&C Act] and § 314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include an indication or other condition of use that is covered by the method-of-use patent, a statement explaining that the method-of-use patent does not claim a proposed indication or other condition of use.

If an ANDA applicant submits a section viii statement to a patent-protected method of use, and, as described further in the next subsection, FDA determines that any differences between the proposed ANDA labeling and the RLD labeling do not render the ANDA product less safe or effective than the RLD for all remaining, nonprotected conditions of use, the patent(s) claiming the protected method of use will not serve as a barrier to ANDA approval.[32] If FDA determines that such differences in labeling would render the ANDA product less safe or effective than the RLD for all remaining, nonprotected conditions of use, the ANDA sponsor must address the patent(s) by submitting a certification described in section 505(j)(2)(A)(vii) of the FD&C Act.[33] Any ANDA applicant that fails to submit such certification will not be approved under section 505(j) of the FD&C Act.[34]

---

[27] Section 505(j)(2)(A)(vii) through (viii) of the FD&C Act; see also section 505(j)(5)(B) of the FD&C Act.

[28] *Torpharm, Inc. v. Thompson*, 260 F. Supp. 2d 69, 71 (D.D.C. 2003).

[29] 35 U.S.C. 271(e)(2)(A).

[30] Section 505(j)(2)(A)(viii) of the FD&C Act.

[31] 21 CFR 314.92(a)(1) and 314.94(a)(12)(iii)(A).

[32] See section 505(j)(2)(A)(viii) of the FD&C Act; 21 CFR 314.127(a)(7).

[33] See also 21 CFR 314.94(a)(12)(i)(A).

[34] See also 21 CFR 314.127(a)(7).

C. Labeling Requirements for Products Approved as ANDAs

Section 505(j)(2)(A)(i) of 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 [generic] drug have been previously approved for a [listed drug]." Section 505(j)(2)(A)(v) also requires that an ANDA contain "information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the FD&C Act] or because the new [generic] drug and the listed drug are produced or distributed by different manufacturers."[35] A parallel provision appears in section 505(j)(4)(G) of the FD&C Act.[36]

Section 505(j)(2)(A)(v) and (j)(4)(G) of the FD&C Act does not require that a generic drug's labeling be identical to that of the listed drug it references in every respect. Interpreting the statutory exception in section 505(j)(2)(A)(v) and (j)(4)(G) that allows certain labeling differences due to the fact that the proposed ANDA and the listed drug are "produced or distributed by different manufacturers," § 314.92(a)(1) states that an ANDA for a proposed generic drug product may omit "conditions of use for which approval cannot be granted because of exclusivity or an existing patent." Section 314.94(a)(8)(iv) more explicitly sets forth examples of permissible differences in labeling that may result because the generic drug product and listed drug are produced or distributed by different manufacturers. Permissible differences include, but are not limited to, the following:[37]

> . . . [D]ifferences 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)(5)(F) of the [FD&C Act].

However, § 314.127(a)(7) provides an important limitation to the circumstances under which FDA can approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are protected by patent, or by exclusivity." To approve such an ANDA, this regulation requires FDA to find that the omissions "do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use."[38] Thus, under the statute and regulations, a proposed generic drug cannot omit an aspect of labeling of the RLD protected by patent if the omission would render the proposed generic drug

---

[35] See also 21 CFR 314.92(a)(1), 314.94(a)(4)(i) and (a)(8)(iv), and 314.127(a)(2) and (a)(7).

[36] Section 505(j)(4)(G) of the FD&C Act provides that FDA shall approve an ANDA unless, among other things, the "information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved under [an ANDA suitability petition] or because the drug and the listed drug are produced or distributed by different manufacturers."

[37] 21 CFR 314.94(a)(8)(iv) (emphasis added).

[38] "[T]he statute expresses the legislature's concern that the new generic be safe and effective for each indication that will appear on its label." *Bristol Myers Squibb v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996).

less safe or effective than the RLD for the nonprotected conditions of use that remain in the labeling.

D. Postmarketing Requirements

FDA approves NDAs for drug products based on a demonstration that the drug product is safe and effective when used under the conditions specified in the proposed labeling. In some instances, FDA may be aware of information and/or data at the time of approval or become aware of data and/or information in a postapproval setting that requires further assessment. Section 505(o)(3) of the FD&C Act authorizes FDA to require postmarketing studies or clinical trials (i.e., PMRs) to (1) assess a known serious risk related to the use of the drug, (2) assess signals of serious risk related to the use of the drug, and (3) identify an unexpected serious risk when available data indicate the potential for a serious risk.[39] FDA may issue such PMRs at the time of approval on the basis of scientific data identified preapproval or after approval if FDA becomes aware of new safety information (as defined in section 505-1(b)(3) of the FD&C Act).

III. DISCUSSION

The 2022 Petition requests that FDA not approve any ANDAs for generic trifluridine/tipiracil tablets referencing Lonsurf as the RLD that "omit[s] 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."[40,41] Taiho asserts that this information is necessary for the safe use of Lonsurf for patients with severe renal impairment that cannot be omitted from the labeling of generic drugs.[42] Taiho claims that the statements concerning patients with severe renal impairment are protected by the '399 patent. Because an ANDA applicant of generic trifluridine/tipiracil tablets cannot omit this information on patients with severe renal impairment, Taiho maintains that a section viii statement to the

[39] See also draft guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019) (PMR Guidance). When final, this guidance will represent FDA's current thinking on this topic. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[40] 2022 Petition at 2.

[41] The '004 patent has the same patent use code (U-2642) of "Method of treating cancer by detecting a creatinine clearance of a patient and administering Lonsurf" as the '399 patent. Because the petitioner's requested actions only concern the '399 patent, we are only addressing that patent in this petition response; however, we note that the same reasoning and result would be applicable to the '004 patent. For the purposes of this petition response, we are assuming that the '399 patent protects information in Lonsurf's labeling concerning patients with severe renal impairment (i.e., the new dose reduction and related PK information for such patients with severe renal impairment added to the labeling by the approval of Supplement 009 to sections 2.3, 8.6, and 12.3) since neither Taiho nor HPM appears to contest that the '399 patent protects such information. For purposes of this response, it is not necessary to decide whether the U-2642 patent use code covers information in the labeling beyond such dose reduction and related PK information for patients with severe renal impairment. Even assuming the use code covers solely dose reduction and related PK information for patients with severe renal impairment and does not cover other information related to Taiho's dedicated renal impairment study, we do not believe a carve out of such information would be appropriate for the reasons described in this petition response.

[42] 2022 Petition at 7.

'399 patent is inappropriate, and thus any ANDA applicant must address this patent by submitting a certification pursuant to section 505(j)(2)(A)(vii) of the FD&C Act.[43]

In its comments to the 2022 Petition, HPM asserts that omitting Lonsurf's labeling on its use in patients with severe renal impairment would not render a proposed generic drug referencing Lonsurf "less safe or effective than Lonsurf for the remaining conditions of use, i.e., the other approved patient populations (those with normal renal function and mild or moderate renal impairment)."[44] HPM states generic drug labeling that does not contain information for severe renal impairment patients but does for mild or moderate impairment patients would indicate "that the product is not intended for use in patients with severe renal impairment. Such a label would, in fact, remove patients with severe renal impairment from the approved patient population."[45] HPM further claims that omitting this information from generic drug labeling "would essentially be identical to the originally approved Lonsurf label."[46] Therefore, HPM concludes that FDA is permitted to approve an ANDA containing a section viii statement to the '399 patent with labeling that omits the patent-protected information.[47]

After a careful review of the 2022 Petition, HPM's comments, and the administrative record, FDA concludes that omitting patent-protected information concerning patients with severe renal impairment from labeling would render generic trifluridine/tipiracil tablets less safe than Lonsurf for all remaining, nonprotected conditions of use. Therefore, FDA agrees with Taiho that labeling of generic trifluridine/tipiracil tablets must retain the patent-protected dose reduction and related PK information for patients with severe renal impairment. Accordingly, FDA also agrees that a section viii statement to the '399 patent is not permissible because the associated labeling information currently protected by that patent cannot be omitted without rendering an ANDA product less safe than Lonsurf for all remaining, nonprotected conditions of use. Thus, a generic applicant must address this patent by submitting a certification described in section 505(j)(2)(A)(vii) of the FD&C Act. As discussed further below, FDA is granting the requests in the 2022 Petition.

A. Omitting dose reduction and related PK information on patients with severe renal impairment from the labeling of generic trifluridine/tipiracil tablets would render these drugs less safe than Lonsurf for the remaining, nonprotected conditions of use.

FDA's regulations permit ANDA applicants to omit from labeling patent- or exclusivity-protected conditions of use and obtain approval for the remaining, nonprotected conditions of use, provided that the differences between the RLD and generic drug labeling would not render the generic drug product less safe or effective than the RLD for the remaining, nonprotected

[43] Id. at 11.

[44] HPM Comment to 2022 Petition at 2.

[45] Id. at 12.

[46] Id. at 9; see also id. at 13.

[47] Id. at 2.

conditions of use.[48] FDA generally assesses "the same labeling requirement" by comparing the proposed ANDA labeling against the most recently approved RLD labeling.[49] FDA evaluates any proposed labeling differences between the ANDA labeling and the RLD labeling on a case-by-case basis to determine whether the proposed differences are permissible under the applicable statute and regulations as this inquiry is fact-specific.[50]

FDA has long recognized that patients with varying levels of renal impairment may need different dosing recommendations compared to patients with normal renal function.[51] FDA recommends that applicants conduct dedicated PK studies in patients with impaired renal function when the drug is likely to be used in such patients and "when impaired renal function is likely to alter the [pharmacokinetics] of the drug or its active metabolites because they are substantially eliminated by the renal route."[52] The primary goal of these studies in patients with impaired renal function is to assess whether the pharmacokinetics are altered such that the recommended dosage for renally impaired patients should be altered from the dose(s) established in the pivotal trials. Pursuant to section 505(o)(3) of the FD&C Act, FDA may require application holders to conduct PMRs that include PK studies or clinical trials that evaluate the pharmacokinetics of the drug in the labeled population or in a subpopulation at potential risk for high drug exposures that could lead to toxicity, such as studies designed to "[d]etermine the optimal dose for maintenance therapy in patients with chronic renal disease, a population at risk for drug accumulation."[53] For all approved drugs, FDA generally recommends that a summary of essential information about the effect of renal function on the pharmacokinetics (and pharmacodynamics if known) of the drug be described in the prescribing information to inform health care professionals on the safe and effective use of the drug in patients with impaired renal function.[54]

As stated above, tipiracil, one of the active ingredients in Lonsurf, is primarily eliminated by renal excretory mechanisms, and FDA recognized at the time of its initial approval that patients with renal impairment could have increased tipiracil exposure, leading to increased trifluridine exposure due to increased inhibition of trifluridine metabolism by tipiracil. Increased trifluridine exposure may lead to more severe toxicity and adverse events (e.g., myelosuppression,[55] nausea,

[48] See generally 21 CFR 314.92(a)(1), 314.94(a)(8)(iv), 314.127(a)(7).

[49] But see section 505(j)(10) of the FD&C Act.

[50] FDA has stated that omission of a precaution, warning, or similar information about a condition of use that is not proposed for inclusion in the labeling of a generic product can, but does not necessarily, render the generic drug less safe for its remaining, nonprotected conditions of uses. See, e.g., letter from Janet Woodcock, CDER Director, to Philip Honerkamp, Jazz Pharmaceuticals, Inc., Docket No. FDA-2016-P-2672 (January 17, 2017) (Xyrem Petition).

[51] Draft guidance for industry, *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing,* Revision 2 (September 2020) (Renal Study Guidance). When final, this guidance will represent FDA's current thinking on this topic.

[52] Id. at 2-3.

[53] PMR Guidance at 15.

[54] Renal Study Guidance at 14.

[55] Myelosuppression is a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets. Low red blood cell counts (anemia), leads to insufficient supply of oxygen to

vomiting) in an already severely ill cancer population. Because of this serious risk, FDA required Taiho to conduct PMR 2963-2 in accordance with FDA guidance to determine the appropriate dose of Lonsurf for patients with severe renal impairment. Pending the completion of Taiho's PMR study, FDA originally approved Lonsurf with labeling intended to inform prescribers that no dedicated clinical studies had been conducted to evaluate the effect of renal impairment on the pharmacokinetics of Lonsurf and that no patients with severe renal impairment were enrolled in the study conducted to support original approval.[56] Following the study's completion, subsections 2.3, 8.6, and 12.3 of Lonsurf's labeling were updated with information based on the findings from PMR 2963-2. As a result, the current labeling of Lonsurf now contains information showing that the exposures of Lonsurf's two active ingredients are significantly increased in patients with severe renal impairment and recommends that patients with severe renal impairment may be prescribed the drug but with a reduced dose of 20 mg/m^2 twice daily, compared to the dose for patients with mild to moderate renal impairment or normal renal function of 35 mg/m^2 twice daily. The labeling also recommends that the dose of Lonsurf could be further 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.

As discussed above, Lonsurf is indicated for patients with metastatic colorectal cancer and gastric or gastroesophageal junction adenocarcinoma who have disease progression on or after prior therapy. Standard of care for patients with metastatic colorectal cancer and gastric or gastroesophageal junction adenocarcinoma who have disease progression on or after prior therapy would include the use of cytotoxic drugs and antibodies (e.g., platinum compounds, bevacizumab, cetuximab), which can potentially cause renal impairment. In addition to prior therapy that may have caused renal impairment,[57] age and comorbidities associated with these cancers may be present, which are additional factors contributing to the presence of renal impairment. A patient with an indicated cancer may have acceptable renal function at the time of treatment initiation but may develop renal disease or experience worsening of their renal disease and develop severe renal impairment during the course of cancer treatment (e.g., due to a treatment regimen with other potentially nephrotoxic therapies). Severe renal impairment can develop without advance warning, and once a patient has severe renal impairment, an appropriate dose reduction, as described in the Lonsurf labeling, is needed. As a patient's renal function may change over time and any patient could develop severe renal impairment during treatment for the indicated cancers, the dose reduction and related PK information on increased drug exposure for patients with severe renal impairment is necessary information for health care professionals to know in the treatment of any patient. Although the dose reduction and related PK information in labeling directly pertains to patients with severe renal impairment, it also

---

tissues, which translates clinically into fatigue and if severe, potential cardiac failure, organ failure, and death. Low white cell counts, particularly neutrophils (neutropenia), increase the risk of serious infections that could lead to death. Low platelet counts (thrombocytopenia), increase the risk of bleeding, which may sometimes be fatal. See also section 5.1 of Lonsurf prescribing information for warning and precaution related to severe myelosuppression.

[56] See supra fn. 7-8 and accompanying text.

[57] See, e.g., Camptosar (irinotecan hydrochloride) prescribing information (Jan. 27, 2022), available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/020571Orig1s053lbl.pdf (stating in section 5.5 Renal Failure/Renal Impairment "Renal impairment and acute renal failure have been identified, usually in patients who became volume depleted from severe vomiting and/or diarrhea.").

provides an important signal to health care professionals as they treat patients *without* severe renal impairment. It alerts health care professionals that the renal function of patients *without* severe renal impairment needs closer and systematic monitoring, particularly when creatinine clearance is decreasing, because once severe renal impairment develops, a dose reduction is necessary. Because of these considerations, omission of such dose reduction and related PK information for patients with severe renal impairment would render the generic less safe than Lonsurf for the remaining, nonprotected conditions of use.[58]

We do not consider other sections of Lonsurf's prescribing information, such as subsections 2.1 and 2.2, to be sufficient to ensure that a generic drug with the proposed labeling carve out is as safe as Lonsurf for the remaining, nonprotected conditions of use. Subsection 2.1 of Lonsurf's prescribing information on the recommended dosage states: "The recommended dosage of LONSURF is 35 mg/m^2 up to a maximum of 80 mg per dose (based on the trifluridine component) orally twice daily with food on Days 1 through 5 and Days 8 through 12 of each 28-day cycle until disease progression or unacceptable toxicity."[59] Subsection 2.2 on dose modifications for adverse events states: "After recovery, resume LONSURF after reducing the dose by 5 mg/m^2/dose from the previous dose, if the following occur" and lists certain adverse events.[60] Section 2.2 also states: "A maximum of 3 dose reductions are permitted. Permanently discontinue LONSURF in patients who are unable to tolerate a dose of 20 mg/m^2 orally twice daily. Do not escalate LONSURF dosage after it has been reduced."[61] There is no mention of renal function in these subsections. These subsections alone would not adequately signal to health care professionals that closer and systematic monitoring of renal function is needed, particularly when creatinine clearance is decreasing in their patients who have no renal impairment or only mild or moderate renal impairment, given that once severe renal impairment develops, a dose reduction is necessary. Without the signal to health care professionals to monitor closely patients with decreasing creatinine clearance, a patient may develop severe renal impairment that is not detected before the patient suffers adverse events. Because of these considerations, we have determined that other sections of Lonsurf's prescribing information cannot ensure that a generic drug product with labeling containing the proposed carve out is as safe as Lonsurf for the remaining, nonprotected, conditions of use.

HPM claims that omission of information on patients with severe renal impairment from the labeling of generic drugs referencing Lonsurf would not pose safety concerns for the remaining, nonprotected conditions of use.[62] FDA disagrees. Although the dose reduction and related PK information directly pertains to patients with severe renal impairment, if a generic drug's

[58] Taiho asserts that Lonsurf's current labeling provides necessary dose reduction instructions for patients with severe renal impairment and that the "clinical importance of this information is reflected by its placement in the Lonsurf package insert," for example, in the Dosage and Administration section and the Highlights section, which contains important information for prescription drugs. Id. We note that the placement of protected labeling information does not necessarily determine whether that information may not be omitted from labeling.

[59] Supplement 009 of NDA 207981, Prescribing Information (January 1, 2020), available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/207981s009lbl.pdf.

[60] Id.

[61] Id.

[62] HPM Comment to 2022 Petition at 12.

labeling were to omit such information from subsections 2.3, 8.6, and 12.3, we believe that such drug would be less safe for use in patients *without* severe renal impairment for the reasons explained above. HPM also maintains that such omission would indicate "the product is not intended for use in patients with severe renal impairment. Such a label would, in fact, remove patients with severe renal impairment from the approved patient population."[63] Whether a carve out of patients with severe renal impairment in generic labeling "removes" that group from the approved patient population is not relevant to the applicable inquiry here, which is whether the carve out would render the generic drug product less safe than Lonsurf *for the remaining, nonprotected conditions of use*. As explained above, a patient with an indicated cancer may have acceptable renal function at the time of treatment initiation but may develop renal disease or experience worsening of their renal disease and develop severe renal impairment during the course of treatment; once a patient has severe renal impairment, an appropriate dose reduction, as described in the Lonsurf labeling, is needed. Without the dose reduction and related PK information for patients with severe renal impairment to signal to health care professionals that it is necessary to monitor closely patients' renal function, particularly in those with decreasing creatinine clearance, a patient may develop severe renal impairment that is not detected before the patient suffers adverse events. Thus, the proposed carve out would render the generic drug product less safe than Lonsurf for the remaining, nonprotected conditions of use.

HPM further asserts that "[t]he resulting generic labels essentially would be identical to the originally approved Lonsurf label, which was used by physicians to safely treat patients with normal renal function and mild or moderate renal impairment for four and a half years."[64] FDA disagrees that any similarity between the originally approved labeling and labeling with a carve out of severe renal impairment information means a generic would be as safe as Lonsurf for all remaining, nonprotected conditions of use. When Lonsurf was first approved, FDA determined that its benefit in treating patients with metastatic colorectal cancer, which is a serious and life-threatening disease with a poor prognosis, outweighed the risk of temporarily having incomplete information of the manner in which it would affect renal function. At that time, Lonsurf's labeling stated that the pharmacokinetics of trifluridine and tipiracil had not been studied in patients with severe renal impairment. However, because of the serious risk associated with increased trifluridine exposure in patients with impaired renal function, upon approval, FDA required Taiho to conduct PMR 2963-2. This study showed that in patients with severe renal impairment, the exposures of Lonsurf's two active ingredients are significantly increased. The Agency now knows that a safer way to prescribe Lonsurf for patients with severe renal impairment is to decrease the dose of Lonsurf. With this new safety information changing the risk-benefit profile of Lonsurf, FDA has determined that a generic drug that would omit the dose reduction and related PK information for patients with severe renal impairment in Lonsurf's

[63] Id.

[64] Id. at 9. FDA notes that while there would be similarities between ANDA labeling that proposes to carve out information regarding severe renal impairment and the originally approved Lonsurf labeling, a carve out of information on severe renal impairment would not result in identical labeling since a carve out is executed with respect to the current RLD labeling, which has changed since Lonsurf was first approved.

approved labeling would be less safe than Lonsurf for the remaining, nonprotected conditions of use.[65]

B. FDA's prior decisions support retaining information on patients with severe renal impairment for the safe use of trifluridine/tipiracil tablets.

Although HPM points to several prior decisions by FDA about labeling carve outs to support its position, none are directly on point, and they can be distinguished from the Lonsurf matter. For instance, HPM cites[66] a 2006 citizen petition response concerning labeling omissions for Oxandrin (oxandrolone)[67] as support for HPM's assertion that Lonsurf's dosing information intended to address the drug's use in patients with severe renal impairment could be omitted from the labeling of a proposed generic drug referencing Lonsurf without rendering such drug less safe and effective than Lonsurf for all remaining, nonprotected conditions of use. In the Oxandrin matter, the petitioner claimed that protected geriatric use information added to the Oxandrin labeling could not be omitted from the labeling for generic oxandrolone products because the information was necessary to ensure the safe and effective use of the generic drugs. FDA disagreed and concluded that "all of the safety and effectiveness issues addressed in the new geriatric use information are of concern within the general adult population and, as a

[65] Taiho states that 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." 2022 Petition at 9. HPM asserts "Taiho vehemently argues that a contraindication would be inappropriate here. See Petition at 9. Whether in the form of a contraindication or simply omitting instructions as to the use of the product in patients with severe renal impairment, a generic label would (in both circumstances) provide information directing use only in mild or moderate renal impairment patients without regard to the type of cancer to be treated." HPM Comment to 2022 Petition at 12. It is unclear whether HPM thinks a contraindication would be appropriate and does not attempt to demonstrate that the standard for a contraindication would be met here. However, we note that even though FDA has determined that a generic drug product that omits from its labeling dose reduction and related PK information regarding severe renal impairment would be less safe than Lonsurf for the remaining, nonprotected conditions of use under 21 CFR 314.127(a)(7) for the reasons explained in this petition response, we do not believe the different standard regarding a contraindication would be met. See, e.g., 21 CFR 201.57(c)(5). A drug should be contraindicated only in those clinical situations for which the risk from use "clearly outweighs any possible therapeutic benefit." Id.; Guidance for Industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format at 8 (October 2011). As explained in that guidance, "In rare cases, when the risks of the drug clearly outweigh any possible therapeutic benefit and the drug should never be used in a selected patient subset, a contraindication for use of the drug in that subset should also be described in the CONTRAINDICATIONS section." Id. at 9 fn. 7. It is not the case that generic trifluridine/tipiracil tablets should never be used in patients with severe renal impairment because the risks of the drug clearly outweigh any possible therapeutic benefit. Despite heightened risk of experiencing increased toxicity and adverse events like myelosuppression, we do not believe the risk is such that this product should never be used in severely renally impaired patients. The risk of use at the higher dose of 35 mg/m^2 for patients with severe renal impairment does not clearly outweigh any possible therapeutic benefit because these patients could still achieve a possible benefit in their cancer treatment. What is more, PMR 2963-2 demonstrated that patients with severe renal impairment can achieve benefit with adjusted dosing and demonstrated adverse event profiles similar to those with normal renal function or mild renal impairment, when dosage was appropriately reduced. Accordingly, in this particular situation, we do not believe that it would be appropriate to include a contraindication as a potential means of permitting the carve out in the generic labeling. See, e.g., 21 CFR 201.57(c)(5); section 505(j)(2)(A)(v) and (j)(4)(G) of the FD&C Act; 21 CFR 314.94(a)(8)(iv) and 314.127(a)(7).

[66] HPM Comment to 2022 Petition at 11.

[67] Letter from Steven Galson, CDER Director, to Edward Allera and Theodore Sullivan, Buchanan Ingersoll P.C., Docket No. FDA-2005-P-0368 (December 1, 2006) (Oxandrin Response).

consequence, are adequately addressed elsewhere in the label."[68] Although the geriatric studies showed that geriatric patients may have greater sensitivity to edema and liver toxicities, the Agency concluded that the labeling for generic oxandrolone products would still contain information on these two adverse events if the new, protected geriatric information were omitted.[69] Regarding the dosing, the Agency remarked that the recommended dose for geriatric patients (5 mg twice daily) was within the range of nonprotected dosing information (2.5 mg to 20 mg given in 2 to 4 divided doses), and that dosing information would provide adequate guidance to health care professionals on safe and effective dosing of oxandrolone.[70] Therefore, FDA determined that omission of the protected geriatric use information would not affect the safety and effectiveness of the generic drugs. Unlike the Oxandrin matter, here information on severe renal impairment is addressed only in subsections 2.3, 8.6, and 12.3 (i.e., those sections containing patent-protected information) of Lonsurf's labeling, and we do not consider other sections of the labeling to address FDA's safety concerns adequately. For example, as explained above, subsections 2.1 and 2.2 of Lonsurf's prescribing information alone would not adequately signal to health care professionals that closer and systematic monitoring of renal function is needed, particularly when creatinine clearance is decreasing in their patients without severe renal impairment, given that once severe renal impairment develops, a dose reduction is necessary.

HPM also references[71] a 2002 citizen petition response regarding protected titration-dosing for a tramadol-intolerant subpopulation that the Agency found could be omitted from generic drug labeling without rendering it less safe or effective compared to the RLD for the remaining, nonprotected conditions of use.[72] Ultram (tramadol hydrochloride), the RLD, had been approved for a 10-day titration schedule consisting of 50 mg increments every 3 days until an effective dose (not exceeding 400 mg per day) was achieved. Subsequently, Ultram was approved for a new, even slower 16-day titration schedule consisting of 25 mg increments every 3 days until a 100 mg dose was reached, followed by a dose increase in 50 mg increments, as tolerated, every 3 days to reach 200 mg/day. The clinical investigations demonstrated that for patients who had been shown to be tramadol-intolerant, the new titration schedule resulted in a statistically significant reduction in discontinuations due to nausea and vomiting and fewer discontinuations due to any cause.[73] FDA concluded that this new, exclusivity-protected 16-day titration schedule could be omitted from the labeling of generic drugs without rendering the generic drugs less safe or effective than the RLD for the remaining, nonprotected conditions of use (i.e., the general population who were not intolerant to the higher dose of tramadol). The Agency stated that the study supporting the 16-day titration schedule did not test whether it would result in better tolerance or fewer discontinuations due to nausea and vomiting than the 10-day titration schedule in patients who have not previously reacted adversely to tramadol.[74] Information regarding the

[68] Oxandrin Response at 13.

[69] Id. at 13-15.

[70] Id. at 16.

[71] HPM Comment to 2022 Petition at 11.

[72] Letter from Janet Woodcock, CDER Director, to Marcy McDonald, et al., Docket Nos. FDA-2001-P-0413, FDA-2002-P-0003, FDA-2002-P-0291 (June 11, 2002) (Ultram Response).

[73] Id. at 8.

[74] Id.

10-day titration schedule would remain in the labeling along with information about the side effects of tramadol such that physicians could still use the information to evaluate patient treatment options and understand that titration reduces discontinuation due to adverse events. The Ultram decision is distinguishable from Lonsurf. For Ultram, FDA concluded that "the utility of the information granted exclusivity for doctors prescribing tramadol to patients who have not previously shown tramadol intolerance is limited."[75] In contrast, here in the context of Lonsurf, the dose reduction and related PK information for patients with severe renal impairment is important to the safe use and treatment of patients *without* severe renal impairment. Such information alerts health care professionals that the renal function of patients without severe renal impairment needs closer and systematic monitoring, particularly when creatinine clearance is decreasing, because once severe renal impairment develops, a dose reduction is necessary. As explained above, without such a signal to health care professionals, a patient may develop severe renal impairment that is not detected before the patient suffers adverse events. Accordingly, the utility of the protected information to health care professionals prescribing trifluridine/tipiracil tablets to patients who, at the time of initiation of therapy, do not have severe renal impairment is not limited, but rather is significant.

HPM also discusses[76] a citizen petition decision on Prandin (repaglinide)[77] as support for HPM's assertion that if a patient needs a drug for a use that is omitted from the labeling of a generic drug, that patient can take the RLD product consistent with its labeling, including for conditions that are progressive in nature. Prandin was approved in combination with metformin for adults with type 2 diabetes (non-insulin mellitus). The metformin combination regimen was protected by a patent, and an ANDA applicant had submitted a section viii statement indicating that it was proposing to omit this regimen from its labeling. The Agency concluded that despite the progressive nature of type 2 diabetes, carving out the metformin combination regimen from generic repaglinide labeling would not render the product less safe or effective for the remaining, nonprotected conditions of use (i.e., as a monotherapy and in combination with thiazolidinediones (TZDs)).[78] To support this determination, FDA stated that the contribution of efficacy that Prandin made to the combination of Prandin plus metformin was comparable to Prandin monotherapy. Further, FDA found no safety data from the Prandin plus metformin trial were included in Prandin's labeling, so none of the safety data would need to be carved out of the generic drug's labeling.[79] Again, Prandin is distinguishable from Lonsurf. Analogous safety information was not at issue in Prandin because no safety data from the Prandin plus metformin trial were included in Prandin's labeling. While our position was that Prandin could be prescribed instead of generic repaglinide if a patient needed the metformin combination regimen, the safe and effective use of repaglinide by patients as a monotherapy and in combination with TZDs remained unaffected by the carve out. That is not the case for Lonsurf where the safe use by patients *without* severe renal impairment would be jeopardized by the proposed carve out. As explained above, without the signal to health care professionals to monitor closely patients' renal

[75] Id.

[76] HPM Comment to 2022 Petition at 12.

[77] Prandin Response at 13.

[78] Id.

[79] Id. 13-14.

function, particularly in those with decreasing creatinine clearance, a patient may develop severe renal impairment that is not detected before the patient suffers adverse events.

Additionally, HPM cites a 2008 citizen petition response regarding the drug Camptosar (irinotecan)[80] to support its position that omitting information on patients with severe renal impairment would result in generic drug labeling that would "be essentially the same as what was in the labeling with which Lonsurf was originally approved — Taiho safely marketed Lonsurf with only this dosing information ***for more than four years*** and continues to include this dosing information in its labeling today."[81] FDA determined that generic drugs referencing Camptosar could omit information regarding first-line therapy cancer treatment and would continue to include information regarding second-line cancer treatment. By limiting the indication to second-line cancer treatment, there was no impact on the safe and effective use of generic irinotecan for second-line therapy. The indications were distinct, and treatment of one population did not affect the other. Lonsurf is distinguishable because the proposed carve out would be of information that is relevant to the monitoring and treatment of the entire patient population. It is true that a generic version of Lonsurf with a labeling carve out would have labeling sections on Dosing and Administration, Renal Impairment, and Pharmacokinetics – Special Population similar to Lonsurf's original approved labeling if the dose reduction and related PK information for patients with severe renal impairment were omitted from a generic drug's labeling. However, as explained above, now dose reduction and related PK information is known to the agency because of PMR-2963-2 and described in Lonsurf's currently approved labeling. With this new safety information changing the risk-benefit profile of Lonsurf, FDA has determined that a generic drug that would omit the dose reduction and related PK information for patients with severe renal impairment in Lonsurf's approved labeling would be less safe for patients than Lonsurf for the remaining, nonprotected conditions of use. This was not the case for Camptosar, where there was no impact on the safe and effective use of generic irinotecan for second-line therapy as a result of the applicable carve out.

To support its position that information on patients with severe renal impairment cannot be omitted from the labeling of generic drug products referencing Lonsurf, Taiho references the Agency's responses to two citizen petitions.[82] In the Xyrem (sodium oxybate) decision,[83] FDA refused to approve any generic drug product that omitted from its labeling protected information related to a specific dose reduction recommendation of Xyrem when coadministered with divalproex sodium. Xyrem, a central nervous system depressant used to treat narcolepsy, can cause serious adverse events such as respiratory depression, coma, or death.[84] Based on a drug interaction study, the dosage and administration section of Xyrem's labeling was updated to recommend that the initial sodium oxybate dose should be reduced by at least 20 percent when

[80] Letter from Janet Woodcock, CDER Director, to Ernest Lengle, Watson Laboratories, Inc., Docket No. FDA-2008-P-0069 (July 28, 2008).

[81] HPM Comment to 2022 Petition at 13 (emphasis in the original).

[82] 2022 Petition at 7-8.

[83] Xyrem Response at 5.

[84] Id. at 5.

the two drugs are coadministered.[85] FDA concluded that information on this specific dose reduction recommendation is important to prevent an exacerbation of serious adverse events associated with Xyrem. HPM claims that the Xyrem decision is distinguishable from the Lonsurf matter because "the drug-drug interaction information related to divalproex sodium . . . is part of an approved Risk Evaluation Mitigation Strategy ("REMS") that requires ***all*** physicians prescribing Xyrem to 'attest to having read and understood' the [prescribing information], including the drug-drug interaction information, and to counsel ***all*** patients about using divalproex sodium with Xyrem." HPM states that Lonsurf's labeling does not include "additional risks or warning information for patients with severe renal impairment or include any REMS requirements to instruct on such a risk."[86] The Agency's decision in Xyrem that the omission of information related to the specific dose reduction recommendation from the prescribing information would render the ANDA less safe was not predicated on the Xyrem REMS requirements. Instead, the decision was based on the fact that in the absence of the applicable information in the Xyrem labeling, a prescriber would not know that coadministering divalproex sodium and sodium oxybate would result in a net increase in overall exposure to sodium oxybate such that the initial dose of sodium oxybate should be reduced to prevent adverse events. Omission of the relevant dose adjustment recommendation in labeling for generic sodium oxybate products would result in a safety issue that could not be adequately addressed by the remaining sections of a generic drug's labeling. Thus, the labeling for generic versions of Xyrem with a carve out would be less safe for the remaining, nonprotected conditions of use. The Agency's decision in Xyrem is similar to that for Lonsurf. Here, the patent-protected information similarly concerns dose reduction and information on increased drug exposure, although for patients with severe renal impairment. As explained above, if such information is omitted from ANDA product labeling, a patient may develop severe renal impairment that is not detected before the patient suffers adverse events.

Another citizen petition cited by Taiho[87] to support their petition involved a proposed carve-out from the labeling for Colcrys (colchicine).[88] The protected information at issue in the Colcrys petition related to the dosing regimen for colchicine for treatment of acute gout flares. Specifically, the labeling information, which qualified for 3-year exclusivity,[89] was supported by a study that demonstrated that a lower dose of a single-ingredient colchicine product for the treatment of acute gout flares was as effective as the higher dose regimen, but resulted in significantly fewer adverse events, when colchicine was coadministered with certain drugs. Although the exclusivity related to the treatment of acute gout flares, FDA considered whether omission of the protected information from the labeling of a generic drug would render it less safe or effective for a nonprotected condition, the prophylaxis of gout flares, in the event that a health care professional determined that it was necessary to use colchicine for the treatment of an

[85] Id.

[86] HPM Comment to 2022 Petition at 14.

[87] 2022 Petition at 8.

[88] Letter from Janet Woodcock, CDER Director, to Gary Veron, Sidley Austin LLP, Docket No. FDA-2010-P-0614 (May 25, 2011) (Colcrys Response).

[89] Section 505(c)(3)(E)(iii) of the FD&C Act; see also 21 CFR 314.108(b)(4).

acute gout flare in a patient receiving colchicine for prophylaxis.[90] The Agency concluded that the protected information (relating to the treatment of acute gout flares) could not be omitted from the labeling of a single-ingredient colchicine product without rendering it less safe or effective than Colcrys for a remaining, nonprotected condition of use (the prophylaxis of gout flares).[91] HPM claims that the Colcrys decision is inapplicable to the Lonsurf matter because the protected labeling information on the dosing of patients with severe renal impairment is not necessary for the safe or effective use of the drug in patients with normal renal function and mild or moderate renal function. We disagree with HPM. We have explained above that the dose reduction and related PK information for patients with severe renal impairment is, in fact, necessary for the safe use of the drug in patients without severe renal impairment (and without such information, the drug is less safe for all remaining, nonprotected conditions of use).

Although the Agency's decision on the Rapamune (sirolimus) citizen petition[92] was not cited by either Taiho or HPM, that decision is also consistent with our determination for the Lonsurf matter. Rapamune is an immunosuppressive agent indicated for the prophylaxis of organ rejection in patients receiving renal transplants. It was determined that the combination of Rapamune and cyclosporine could cause an increased risk of renal function impairment. A clinical study, which qualified the application for 3-year exclusivity, showed that the benefits of withdrawing cyclosporine outweighed risks of immune system reactions. The petitioner requested that FDA refrain from approving any ANDAs for sirolimus that carved out from labeling information regarding cyclosporine withdrawal.[93] FDA agreed and determined that the cyclosporine withdrawal information was necessary for the safe and effective use of sirolimus and could not be omitted from the labeling of generic drugs.[94] FDA found that the protected labeling in question contained critical prescribing information pertaining to cyclosporine withdrawal that any physician should receive to appropriately determine treatment for all indications for sirolimus; patients treated with sirolimus for whom the cyclosporine-sparing regime might not be relevant at first could be reclassified in such a manner that could benefit from such information. Similarly, with respect to Lonsurf, as explained above, since a patient's renal function may change over time, due to nephrotoxic therapies, age, and other comorbidities, and any patient could develop severe renal impairment during treatment for the indicated cancers, the dose reduction and related information on increased drug exposure for patients with severe renal impairment is important information for health care professionals to know in the treatment of any patient.

In summary, we conclude that the Agency's prior decisions support the determination that omission from generic drug labeling of information regarding dose reduction and related PK information for patients with severe renal impairment would render generic trifluridine/tipiracil tablets less safe than Lonsurf for the remaining, nonprotected conditions of use.

---

[90] Colcrys Response at 19.

[91] Id. at 19-20.

[92] Letter from Steven Galson, CDER Acting Director, to Michael Labson and Elizabeth Walsh, Docket No. FDA-2003-P-0002 (September 20, 2004) (Rapamune Response).

[93] Id. at 1, 3.

[94] Id. at 4.

C. A section viii statement to the '399 patent is not permissible, and generic applicants must address this patent by submitting a certification described in section 505(j)(2)(A)(vii) of the FD&C Act.

Because we agree with Taiho that information regarding dose reduction and related PK information for patients with severe renal impairment protected by the '399 patent cannot be omitted from the labeling of generic trifluridine/tipiracil tablets that reference Lonsurf, without rendering the generic product less safe than Lonsurf for all remaining, nonprotected conditions of use, we also agree with Taiho that a section viii statement to the '399 patent would not be permissible. Generic applicants must therefore address the '399 patent by submitting a certification described in section 505(j)(2)(A)(vii) of the FD&C Act. Any generic applicant that fails to submit such certification will not be approved under section 505(j) of the FD&C Act.

IV. CONCLUSION

In summary, for the reasons stated above, the 2022 Petition requests are granted.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
Date: 2022.07.22 11:09:49 -04'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research