FDA U.S. FOOD & DRUG ADMINISTRATION

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Re: Docket No. FDA-2013-P-0298

Dear Drs. Lipska and Inzucchi:

This letter responds to your petition for reconsideration received on May 4, 2016 (Reconsideration Petition). The Reconsideration Petition requests that the Food and Drug Administration (FDA or the Agency) reconsider certain aspects of its April 8, 2016, response (2016 Response) granting in part and denying in part your citizen petition received on March 12, 2013 (2013 Petition). The 2013 Petition requested that the Agency make certain changes to the labeling for metformin related to renal function in patients that are taking or may be prescribed metformin.

FDA has reviewed your Reconsideration Petition, and for the reasons described below, FDA reaffirms its decision to deny your request that the Precautions section of the metformin labeling specifically recommend use of a lower dose of metformin (up to half maximum dose, i.e., up to 500 mg of metformin twice daily) and monitoring of renal function frequently (every 3 months) in patients with an eGFR between 30-45 mL/min/1.73m^2.

I. BACKGROUND

On March 12, 2013, the Agency received your original petition requesting that FDA make revisions to the metformin labeling related to renal function in patients that are taking or may be prescribed metformin. Specifically, the 2013 Petition requested that FDA take the following five actions on the labeling for metformin:

(1) Remove the current creatinine-based contraindications from the metformin labeling.

(2) Revise the contraindications to metformin use so that metformin is not contraindicated based on renal function in individuals with an estimated glomerular filtration rate (eGFR) that is ≥ 60 mL/min/1.72 square meters (m^2).[1]

(3) Revise the labeling to continue metformin use in individuals with an eGFR of 45 to <60 mL/min/1.72m^2, monitoring renal function every 3 to 6 months.

(4) Revise the labeling to prescribe metformin with caution in individuals who have an eGFR of 30 to < 45 mL/min/1.72 m^2 using a lower dose of metformin (up to half the maximum dose), closely monitoring renal function every 3 months. Avoid starting new patients on metformin at this eGFR level.

(5) Revise the labeling to stop metformin use when an individual's eGFR is < 30 mL/min/1.72m^2.

Prior to the submission of the 2013 Petition, the Agency had received, on October 9, 2012, a citizen petition that was submitted by Drs. Flory and Furst with New York Presbyterian Hospital's Division of Endocrinology at Cornell University and by Drs. Razzaghi, Schutta, Rudnick, and Hennessy with the Perelman School for Medicine at the University of Pennsylvania (Cornell Petition), which also requested revisions to the metformin labeling related to renal impairment in patients.[2]

Because there were overlapping and related requests in the two petitions, we addressed them together in the 2016 Response. In the 2016 Response, FDA granted in part and denied in part the requests to revise the metformin labeling. We also noted that since the approval of the metformin new drug applications (NDAs), we had become aware of peer-reviewed medical literature, some of which were referenced in the 2013 Petition and Cornell Petition, regarding the use of metformin in patients with renal impairment. As explained in the 2016 Response, we considered this information to be *new safety information* as defined in section 505-1(b)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[3] Accordingly, concurrent with the issuance of the 2016 Response, we issued letters to the holders of NDAs and applicable abbreviated new drug applications (ANDAs) for metformin notifying them that they are required to make safety labeling changes (SLCs) to their labeling related to the use of metformin in patients with renal impairment. In sum, these revisions included:

- The CONTRAINDICATIONS section of the metformin labeling should contraindicate metformin use in patients with severe renal impairment (e.g., eGFR

[1] We note that the eGFR reporting units provided in the 2013 Petition (i.e., "mL/min/1.72m^{2}") are erroneous and should read "mL/min/1.73m^2."

[2] The Cornell Petitioners did not seek reconsideration of the 2016 Response, nor are the labeling revision requests in the Cornell Petition at issue in this Reconsideration Petition. Accordingly, we do not address the Cornell Petition further in this response.

[3] 21 U.S.C. 355-1(b)(3).

<30 mL/min/1.73m^2).

- The PRECAUTIONS section of the metformin labeling on *Renal Impairment* should state:

  (1) Before initiating metformin obtain an estimated glomerular filtration rate (eGFR);

  (2) Metformin is contraindicated in patients with an eGFR < 30 mL/min/1.73 m^2;

  (3) Initiation of metformin is not recommended in patients with an eGFR between 30 - 45 mL/min/1.73 m^2;

  (4) Obtain an eGFR at least annually in all patients taking metformin. In patients at risk for development of renal impairment (e.g., the elderly), renal function should be assessed more frequently; and

  (5) In patients taking metformin whose eGFR falls below 45 ml/min/1.73 m^2, assess the benefit and risk of continuing therapy.

- The "Radiological studies with contrast" subsection of the Precautions section of the metformin labeling should state that metformin should be stopped at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients that will be administered intra-arterial iodinated contrasts. Re-evaluate eGFR 48 hours after the imaging procedure, and re-start metformin if renal function is stable.

In response to the 2016 Response, you submitted this Reconsideration Petition requesting that the Precautions section of the metformin labeling specifically recommend use of a lower dose of metformin (up to half maximum dose, i.e., up to 500 mg of metformin twice daily) and monitoring of renal function frequently (every 3 months) in patients with an eGFR between 30-45 mL/min/1.73m^2, as originally requested in the 2013 Petition (Reconsideration Petition at 2).

II. DISCUSSION

A. FDA Regulations on Requests for Reconsideration

The regulations on administrative reconsideration of an action state that the Commissioner may at any time reconsider a matter, on the Commissioner's own initiative or on the petition of an interested person (21 CFR 10.33(a)). A petition for reconsideration may not be based on information and views not contained in the administrative record on which the decision was made (21 CFR 10.33(e)).

After determining to reconsider a matter, the Commissioner shall review and rule on the

merits of the matter. The Commissioner may reaffirm, modify, or overrule the prior decision, in whole or in part, and may grant such other relief or take other action as warranted (21 CFR 10.33(i)).

B. Relief Requested in your Reconsideration Petition

In your Reconsideration Petition, you request that the Precautions section of the metformin labeling specifically recommend use of a lower dose of metformin (up to half maximum dose, i.e., up to 500 mg of metformin twice daily) and monitoring of renal function frequently (every 3 months) in patients with an eGFR between 30-45 mL/min/1.73m^2 (Reconsideration Petition at 2), as originally requested in the 2013 Petition.

In support of your request, you state that because metformin is eliminated predominantly by the kidneys and because both lactate and metformin levels accumulate with severe renal impairment, "dose adjustment is required" for metformin (Reconsideration Petition at 2). You state that the omission from the metformin labeling of the dose adjustment recommendation for patients with an eGFR between 30-45 mL/min/1.73m^2 raises safety concerns because in these patients creatinine clearance is compromised to some degree. You say that this suggests that both metformin and lactate are eliminated less efficiently, and continuing a full dose of metformin in patients with this degree of renal dysfunction may increase metformin accumulation and the risk of lactic acidosis (Reconsideration Petition at 2).

In the Reconsideration Petition, you also state that in the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) guidelines generally allow use of metformin down to an eGFR of 30 ml/min, but with dose reduction advised at 45 ml/min (Reconsideration Petition at 2).

In addition, you acknowledge that evidence on the dosing of metformin is limited and you suggest that a cautious approach of reduced dosing of metformin is likely to be the safest until more data are available (Reconsideration Petition at 3).

C. Review of your Reconsideration Petition

We have reviewed your Reconsideration Petition and reconsidered the administrative record underlying our 2016 Response to your 2013 Petition. In sum, we do not believe that revising the metformin labeling to recommend your suggested dose adjustment and specific monitoring intervals for patients with an eGFR between 30-45 mL/min/1.73 m^2 is warranted. As explained below, we reaffirm our decision to deny your request because the data to support your proposed revisions are limited.

As you note in the Reconsideration Petition, metformin is eliminated predominantly by the kidneys and metformin levels accumulate with severe renal impairment (Reconsideration Petition at 2). We also believe that the kidneys play a role in lactate

removal and lactate levels may accumulate in patients who lose kidney function.[4] The Warnings and Precautions statement described in our April 8, 2016, Safety Labeling Change notification adequately communicates these concepts by stating that the risk of metformin-associated lactic acidosis increases with the severity of renal impairment in clinical situations that affect metformin and lactate clearance. This general conceptual understanding, however, is inadequate to establish that the specific dose adjustment that you recommend will improve the balance of benefit and risk in patients with an eGFR between 30-45 mL/min/1.73 m^2. While renal function is compromised in patients with an eGFR between 30-45 mL/min/1.73 m^2, available data are inadequate to support a conclusion that the specific dose adjustment you are petitioning us to recommend would reduce the risk of lactic acidosis. There remain many unknowns with respect to the risk of metformin-associated lactic acidosis, for example, it is unclear if the risk of metformin associated lactic acidosis increases with exposure in the recommended dosage range, or occurs above a specific threshold of exposure, or occurs predictably in all individuals at the same level of metformin exposure.

Moreover, while we agreed in the 2016 Response that published literature described the use of metformin in some patients with a degree of renal impairment outside of the recommended use, this literature was limited and did not provide specific evidence with regard to dose adjustment for patients with an eGFR between 30-45 mL/min/1.73 m^2. We are therefore unable to conclude that the dose adjustment of metformin you are proposing would appreciably decrease the risk of lactic acidosis in patients with an eGFR between 30-45 mL/min/1.73 m^2.

With respect to the NICE guidelines, while we agree that the NICE guidelines generally provide for use of metformin down to an eGFR of 30 mL/min/1.73 m^2, they do not recommend a specific dose when eGFR falls below 45 mL/min/1.73 m^2, but instead make non-specific recommendations to health care providers to "review" the dose and to "prescribe metformin with caution." The NICE recommendations with regard to metformin dosing are essentially unchanged from the 2008 version that we reviewed and considered when we responded to your 2013 Petition, except that the threshold relying on serum creatinine has since been removed from these recommendations. The recommendations in the most recent version of the NICE guidelines are as follows:

"In adults with type 2 diabetes, review the dose of metformin if the estimated glomerular filtration rate (eGFR) is below 45 mL/minute/1.73 m^2:

- Stop metformin if the eGFR is below 30 mL/minute/1.73 m^2
- Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 mL/minute/1.73 m^2"

This language does not make specific dose recommendations for patients with an eGFR

[4] Bellomo, R., August 2002, Bench-to-bedside review: Lactate and the kidney, Critical Care, (6) 4.

below 45 mL/min/1.73 m^2. We believe the language captures the uncertainty around the science and serves a similar purpose as the SLC language being added to the U.S. prescribing information (i.e., "assess the benefit and risk of continuing therapy"), which advises prescribers to weigh the benefit and risk of continuing metformin therapy in individuals with an eGFR between 30-45 mL/min/1.73 m^2.

We are not persuaded that your dosage adjustment recommendations represent the "safest approach" at this time. For some patients with an eGFR between 30-45 mL/min/1.73 m^2, stopping the drug altogether may be the safest approach and the clinical decision to continue (i.e., at the same or a lower dose) or stop the drug should be individualized and left to the prescriber's best knowledge and judgment. We are also concerned that specific dosage recommendations for patients with an eGFR between 30-45 mL/min/1.73 m^2 could be detrimental to public health if prescribers over prescribe metformin in these patients based on a false assurance that dose recommendations in the product labeling were demonstrated to effectively mitigate the risk. As stated previously, it is unknown whether the dose recommendations you suggest would achieve their intended goal of mitigating the risk of metformin-associated lactic acidosis in these patients.

As noted in the metformin labeling, a variety of factors can influence the risk of metformin-associated lactic acidosis. Our recommendation to not initiate metformin in patients with an eGFR between 30-45 mL/min/1.73 m^2, and to consider the benefit-risk of continuing therapy in patients whose eGFR later falls below 45 mL/min/1.73 m^2, directs the prescriber to take into account all factors pertinent to the individual patient in their prescribing decisions (i.e., the benefit of continued treatment and all factors in the individual that may predispose them to the risk).

With regard to specifying a three month interval for monitoring of renal function, note that the updated metformin labeling recommends that eGFR be obtained prior to initiation, at least annually while on treatment, and more frequently in patients at increased risk for the development of renal impairment. This recommendation communicates the need for close monitoring of patients, while also providing for flexibility and allowing for the clinician's ability to tailor the monitoring interval to their individual patients.

As previously stated, after determining to reconsider a matter, the Commissioner may reaffirm, modify, or overrule the prior decision, in whole or in part, and may grant such other relief or take other action as warranted (21 CFR 10.33(i)). Based on the discussion above, we conclude that our decision to deny your request that the Precautions section of the metformin labeling specifically recommend use of a lower dose of metformin (up to half maximum dose, i.e., up to 500 mg of metformin twice daily) and monitoring of renal function frequently (every 3 months) in patients with an eGFR between 30-45 mL/min/1.73m^2 was warranted. Therefore, we reaffirm our decision to deny your request.

III. CONCLUSION

For the reasons described in this response, we reaffirm our decision to deny your request to revise the metformin labeling for the PRECAUTIONS section to specifically recommend use of a lower dose of metformin (up to half maximum dose, i.e., up to 500 mg of metformin twice daily) and monitoring of renal function frequently (every 3 months) in patients with an eGFR between 30-45 mL/min/1.73m^2.

Sincerely,

Leslie Kux
Associate Commissioner for Policy