



DEPARTMENT OF HEALTH & HUMAN SERVICES

APR 08 2016

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Re: Docket Nos. FDA-2012-P-1052 and FDA-2013-P-0298

Dear Petitioners:

This letter responds to two citizen petitions that request that the Food and Drug Administration (FDA or Agency) make changes to the labeling for metformin. On October 9, 2012, the Agency received 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). On March 12, 2013, the Agency received another petition that was submitted by Drs. Lipska and Inzucchi with Yale University's School of Medicine (Yale Petition)¹ (collectively referred to as the Metformin Petitions).

The Cornell Petitioners request that FDA take the following five actions on the labeling for metformin:

- (1) Eliminate the boxed warning regarding lactic acidosis associated with metformin

¹ In addition to the signatures of Drs. Lipska and Inzucchi, the Yale Petition includes 111 electronic signatures from individuals who support the petition. Yale Petition at 10-15.

- (2) Relax the contraindication against metformin use in renal impairment so that the contraindication does not apply to patients with a creatinine clearance (CrCL) greater than [or equal to] 30 milliliters (mL)/minute (min)
- (3) Revise the PRECAUTIONS section to emphasize close monitoring of renal function rather than strict avoidance of metformin in renal dysfunction
- (4) Revise the contraindication to metformin use with iodinated contrast so that it only applies to individuals with a baseline CrCL of < 60 mL/min
- (5) Revise the PRECAUTIONS section so that the recommendation to retest renal function after iodinated contrast exposure only applies to individuals with a baseline CrCL < 60 mL/min.

The Yale Petitioners request 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 \geq 60 mL/min/1.72 square meters (m^2).²
- (3) Revise the labeling to continue metformin use in individuals with an eGFR of 45 to <60 mL/min/1.72m², 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 m² 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/1.72m².

Because there are overlapping and related requests in the two petitions, we are addressing them together in this response. We have carefully reviewed the petitions and the supplements to the petitions, as well as other information available to the Agency. For the reasons explained in more detail below, we grant in part the Metformin Petitioners' requests for revisions to the CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS sections of the labeling related to metformin use in patients with renal impairment to the extent described in this response. In addition, for the reasons explained below, we believe that the Yale Petitioners' proposal to use the eGFR as a measurement of renal impairment to guide metformin use should be adopted.

² We note that the eGFR reporting units provided in the Yale Petition (i.e., "mL/min/1.72m²") are erroneous and should read "mL/min/1.73m²."

In addition, since the approval of the metformin new drug applications (NDAs), we have become aware of peer-reviewed medical literature, some of which are referenced in the Metformin Petitions, regarding the use of metformin in patients with renal impairment. As explained below in section I.D.2, we consider 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, today we issued letters to the holders of NDAs and applicable abbreviated new drug applications (ANDAs)⁴ for metformin notifying them that they are required to make revisions to their labeling related to the use of metformin in patients with renal impairment. In sum, these revisions include:

- The CONTRAINDICATIONS section of the metformin labeling should contraindicate metformin use in patients with severe renal impairment (e.g., eGFR <30 mL/min/1.73m²).
- 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 m²;
 - (3) Initiation of metformin is not recommended in patients with an eGFR between 30 - 45 mL/min/1.73 m²;
 - (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 m², 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 m²; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients that will be administered intra-arterial iodinated contrasts. Re-

³ 21 U.S.C. 355-1(b)(3).

⁴ Requirements under section 505(o)(4) apply to NDAs, biologics license applications, and ANDAs without a currently marketed reference listed drug approved under an NDA, *including discontinued products*, unless approval of an application has been withdrawn in the *Federal Register*. With respect to other ANDAs, the labeling for a generic drug product approved under an ANDA is required to be the same as the labeling for the generic drug product’s reference listed drug, with certain permissible differences not relevant here. See Section 505(j)(2)(A)(v) [21 U.S.C. 355(j)(2)(A)(v)], 21 CFR 314.94(a)(8)(iv); see also 21 CFR 314.127(a)(7). Therefore, the ANDA holders will be required to make the same labeling changes as the NDA holder for all generic versions of the drug.

evaluate eGFR 48 hours after the imaging procedure, and re-start metformin if renal function is stable.

The Metformin Petitions are granted to the extent that their requested labeling revisions are consistent with the labeling revisions outlined above. The Metformin Petitions are denied in all other respects.

I. BACKGROUND

A. Metformin

Metformin is a biguanide widely used in the treatment of type 2 diabetes mellitus (T2DM). Metformin has been commercially available in the United States since 1995. FDA has approved multiple NDAs to market metformin,⁵ which is indicated as an adjunct to diet and exercise to improve glycemic control in adults and children with T2DM. Metformin is available in multiple strengths, such as, 500 milligrams (mg), 750 mg, and 1 gram, and in multiple forms, including immediate release tablets,⁶ extended-release tablets,⁷ and an oral solution.⁸

Metformin improves glucose tolerance in patients with T2DM by lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not generally produce hypoglycemia in either patients with T2DM or in normal subjects and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting plasma insulin levels and day-long plasma insulin responses may actually decrease.⁹

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been

⁵ For example, Bristol Myers Squibb is the holder of the NDA for Glucophage (metformin hydrochloride) (NDA 20-357), which was approved on March 3, 1995; Ranbaxy is the holder of the NDA for Riomet (metformin hydrochloride) (NDA 21-591), which was approved on September 11, 2003; Andrx Labs, LLC is the holder of the NDA for Fortamet (metformin hydrochloride) (NDA 21-574), which was approved on April 28, 2004; and Santarus is the holder of the NDA for Glumetza (metformin hydrochloride) (NDA 21-748), which was approved on June 3, 2005.

⁶ See, e.g., labeling for Glucophage (Glucophage labeling), available at

http://www.accessdata.fda.gov/drugsatfda_docs/labeling/2008/020357s031,021202s016lbl.pdf.

⁷ See, e.g., labeling for Fortamet (Fortamet labeling), available at

http://www.accessdata.fda.gov/drugsatfda_docs/labeling/2008/021574s010lbl.pdf.

⁸ See, e.g., labeling for Riomet (Riomet labeling), available at

http://www.accessdata.fda.gov/drugsatfda_docs/labeling/2010/021591s005lbl.pdf.

⁹ See, e.g., Glucophage labeling, supra note 6; Riomet labeling, supra note 8; Fortamet labeling, supra note 7; and labeling for Glumetza (Glumetza labeling), available at

http://www.accessdata.fda.gov/drugsatfda_docs/labeling/2011/021748s010lbl.pdf.

identified in humans) or biliary excretion. Renal clearance of metformin is approximately 3.5 times greater than CrCL, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90 percent of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the metformin elimination half-life is approximately 17.6 hours.¹⁰

B. Biguanides, Lactic Acidosis, and the Role of the Kidney in Lactate Disposition

Biguanides are used to treat hyperglycemia in patients with T2DM; however, biguanides are also associated with lactic acidosis, a potentially fatal outcome. *Lactic acidosis* is defined as the acid-base disorder originating from accumulation of lactic acid in the body.¹¹ Biguanides are believed to predispose the body to lactic acidosis by increasing the body's production of lactate, an effect that may be correlated to the amount of drug in the circulation.

Patients with renal dysfunction are also predisposed to lactic acidosis because the kidneys play a major role in removing the body of excess acid.

Among the biguanides, phenformin and buformin have been withdrawn from most markets because of their unacceptably high tendency to cause lactic acidosis.¹² Metformin, the only biguanide still marketed in the United States, is also associated with lactic acidosis but at an appreciably lower rate than was observed for the other biguanides.

Renal excretion is the major route of elimination for biguanides and use of biguanides in patients with impaired renal function results in accumulation of these drugs in the circulation. Elevated circulating drug levels in turn may increase lactate production, a condition that could predispose the body to lactic acidosis.

The liver and the kidneys play important roles in removing the body of excess circulating lactate and the body's ability to eliminate lactate can be affected by impairment in both liver and kidney function.¹³ Importantly, it has been observed that in situations that cause excess acid

¹⁰ See Glucophage labeling, supra note 6, at 5; Riomet labeling, supra note 8, at 3; Fortamet labeling, supra note 7, at 5; and Glumetza labeling, supra note 9, at 10.

¹¹ Lactic acidosis. Nephrology Forum, Principal discussant: Nicolaos F. Madias. Kidney International, Vol. 29 (1986), pp. 752—774.

¹² 44 FR 20967 (Apr 6, 1979) (providing notice of the withdrawal of the approval of the NDAs for phenformin). Buformin was never marketed and sold in the United States but was removed from the market in other countries because of the risk of lactic acidosis.

¹³ As explained in a review by Rinaldo Bellomo, the native kidney has a major role in lactate metabolism. Bellomo, R, Aug 2002, Bench-To-Bedside Review: Lactate and the Kidney, Crit Care, 6:4. The renal cortex appears to be the major lactate-consuming organ in the body after the liver. Under conditions of exogenous hyperlactatemia, the kidney is responsible for the removal of 25-30 percent of all infused lactate. Most of this lactate is removed through metabolism rather than through renal excretion. However, under conditions of marked hyperlactatemia, renal excretion of lactate is increased and can account for approximately 10-12 percent of lactate disposal by the renal route.

accumulation in the blood (i.e., acidosis) the ability of the liver to rid the body of excess lactate decreases while that of the kidney increases. Therefore patients with acidosis may rely more heavily on the kidneys for excess blood lactate removal. Patients with renal impairment who develop acidosis are therefore more likely to develop lactic acidosis because the pathways to eliminate circulating lactate through both the liver and kidneys are compromised.

In summary, patients with renal impairment treated with biguanides are more susceptible to developing lactic acidosis because biguanides accumulate in the blood and may increase lactate production and because, in the setting of acidosis, the ability of the body to remove excess lactate is compromised.

C. Current Labeling for Metformin

The current labeling for metformin includes a boxed warning for lactic acidosis. The warning states that lactic acidosis is a rare but serious metabolic complication that can occur due to metformin accumulation during treatment and that, when it occurs, is fatal in approximately 50 percent of cases. The warning also states, among other things, that the risk of lactic acidosis increases with the patient's age and with the degree of the patient's renal dysfunction; thus, the risk of lactic acidosis may be significantly decreased by regular monitoring of renal function in patients taking metformin.¹⁴

Metformin's current labeling also states that it is contraindicated in patients with:¹⁵

- Renal disease or renal dysfunction (e.g., as suggested by serum creatinine (SCr) levels \geq 1.5 mg/deciliters (dL) in males, by SCr levels \geq 1.4 mg/dL in females, or by an abnormal CrCL), which may result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia
- Known hypersensitivity to metformin hydrochloride
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma

The current metformin labeling does not specify the cut-point that defines "abnormal creatinine clearance," and it does not directly reference glomerular filtration rate (GFR) as a measure of renal function.

Metformin also is contraindicated in patients undergoing radiological studies involving administration of iodinated contrast materials because use of such products may result in acute alteration of renal function. The current labeling states that metformin should be temporarily

¹⁴ See Glucophage labeling, supra note 6, at 18-19; Riomet labeling, supra note 8, at 9; Fortamet labeling, supra note 7, at 9; and Glumetza labeling, supra note 9, at 1.

¹⁵ See Glucophage labeling, supra note 6, at 17; Riomet labeling, supra note 8, at 9; Fortamet labeling, supra note 7, at 9; and Glumetza labeling, supra note 9, at 3.

discontinued in such cases.¹⁶

In addition, the relevant portions of the WARNINGS and PRECAUTIONS sections of the current metformin labeling includes information both on monitoring renal function and on radiological studies involving the use of intravascular iodinated contrast materials.¹⁷ These two types of information are addressed in turn.

First, for monitoring renal function, the WARNINGS and PRECAUTIONS sections of the current metformin labeling explain that because metformin is excreted by the kidney, the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Accordingly, the labeling warns against the use of metformin in patients with renal impairment.

Second, the WARNINGS and PRECAUTIONS sections of the metformin labeling explain that metformin should be temporarily discontinued at the time of or prior to any radiological procedure, withheld for 48 hours subsequent to the procedure, and reinstated only after renal function has been reevaluated and found to be normal. This warning does not make a distinction between patients with varying degrees of renal impairment (as measured by SCr levels or other methods).

D. Regulations on Warnings in Prescription Drug Labeling

1. CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and Boxed Warnings

FDA regulations state that the WARNINGS and PRECAUTIONS sections of prescription drug and biological product labeling must describe clinically significant adverse reactions, other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these situations occur.¹⁸ Labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association of the hazard with the product.¹⁹ For products described in § 201.56(b) (21 CFR 201.56(b)), a summary of the most clinically significant warnings and precautions information must be included in the Highlights of Prescribing Information for the product.²⁰

Under § 201.57(c)(1), a boxed warning (sometimes referred to as a black box warning) may be required for certain contraindications or serious warnings, particularly those that may lead to death or serious injury.²¹ A boxed warning must contain, in uppercase letters, a heading that

¹⁶ See, e.g., Riomet labeling, supra note 8, at 9.

¹⁷ See, e.g., Glucophage labeling, supra note 6, at 19-20; Riomet labeling, supra note 8, at 11; Fortamet labeling, supra note 7, at 10-11; and Glumetza labeling, supra note 9, at 4-5.

¹⁸ Section 201.57(c)(6)(i) (21 CFR 201.57(c)(6)(i)); see § 201.80(e) and (f) (21 CFR 201.80(e) and (f)).

¹⁹ § 201.80(e).

²⁰ Section 201.57(a)(10).

²¹ See § 201.80(e).

includes the word *Warning* and conveys the general focus of the information in the box § 201.57 (21 CFR 201.57(c)(1)). A boxed warning briefly explains the risk and refers to more detailed information in the CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS sections of the labeling.²² A summary of a boxed warning (with the heading *Warning* and other words identifying the subject of the warning) must be included in the Highlights of Prescribing Information both in a box and in bold type.²³

FDA's guidance for industry, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format* (Warnings Guidance),²⁴ states that a boxed warning ordinarily is used to highlight for prescribers one of the following situations:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using a drug, or
- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation), or
- FDA approved the drug with restrictions to assure safe use because FDA concluded that the drug can be safely used only if its distribution or use is restricted.

The Warnings Guidance (at 11) also states that there may be other situations in which a boxed warning may be appropriate to highlight information that is especially important to a prescriber.

2. *Labeling Changes Based on “New Safety Information”*

Section 505(o)(4) authorizes FDA to require holders of approved drug and biological product applications to make safety labeling changes for an approved drug based on “new safety information” that becomes available after the approval of the drug.²⁵ As defined in section 505-1(b)(3) of the FD&C Act, *new safety information* is information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3)), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis

²² Section 201.57(c)(1).

²³ Sections 201.56(d)(1) and 201.57(a)(4).

²⁴ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended but not required.

²⁵ Section 505(o)(4) of the FD&C Act.

system under section 505(k) of the Act; or other scientific data deemed appropriate by the Agency about, among other things, a serious or an unexpected serious risk associated with use of the drug that the Agency has become aware of (that may be based on a new analysis of existing information) since the drug was approved.

II. DISCUSSION

In section II.A of this response, we address the Yale Petitioners' request that the Agency revise the metformin labeling by removing the creatinine-based contraindications and using instead eGFR measurements for renal function. As explained in this section, we grant the Yale Petitioners' request to remove the current creatinine-based contraindications in the metformin labeling and to revise the labeling regarding use of metformin in patients with renal impairment based on eGFR measurements.

In section II.B of this response, we address the Cornell Petitioners' request that the Agency remove the boxed warning on lactic acidosis from the metformin labeling and revise the labeling related to metformin use in patients with renal impairment or undergoing radiological studies involving administration of iodinated contrast media. As explained in this section, we deny the Cornell Petitioners' request to remove the boxed warning on lactic acidosis, and we grant in part the Cornell Petitioners' request to revise the labeling related to metformin use in patients with renal impairment or undergoing radiological studies involving administration of iodinated contrast media.

The Yale Petitioners do not request removal of the metformin boxed warning on lactic acidosis, but in support of their petition, they raise points similar to the Cornell Petitioners regarding the use of metformin and the risk of lactic acidosis. Accordingly, where applicable, we address the similar points in section II.B of this response.

A. The Yale Petition

In their petition, the Yale Petitioners request that the Agency remove the current creatinine-based contraindications in the metformin labeling and revise the labeling in the following ways:

- There should be no contraindications to metformin use based on renal function in individuals with an eGFR ≥ 60 mL/min/1.72 m².
- Metformin use should be continued in individuals with an eGFR of 45 to <60 mL/min/1.72 m², monitoring renal function every 3 to 6 months.
- Prescribe metformin with caution in those with an eGFR of 30 to <45 mL/min/1.72 m², using a lower dose (up to half maximum dose), closely monitoring renal function every 3 months. Avoid starting new patients on metformin at this eGFR level.

- Stop metformin when eGFR is <30 mL/min/1.72 m².²⁶

In support of the use of the eGFR measurements in the metformin labeling, the Yale Petitioners state that:

- Metformin is often already used in practice outside the current labeling contraindications and is prescribed in full knowledge of the relevant SCr cut-points.
- Considering the imperfect reflection of actual renal function by SCr levels, metformin is likely used even more frequently in patients with an impaired GFR, including patients with mild to moderate chronic kidney disease (CKD), than suggested by the studies cited in their petition.
- Several U.S. practice guidelines substantially differ in their recommendations for metformin use related to renal status from the prescribing information for metformin on the current labeling and clinical guidelines outside the U.S. already incorporate eGFR for determination of metformin safety.
- The current serum creatinine cut-points in the metformin labeling have limitations in measuring renal impairment because it is unknown how well these values reflect the patient's ability to effectively clear metformin.²⁷

We address each of these points in turn below.

1. Use of Metformin Outside Current Labeling Contraindications and in Patients With Mild to Moderate CKD

The Yale Petitioners state that metformin is often already used in practice outside of the current labeling contraindications and is prescribed in full knowledge of the relevant cut-points.²⁸ Based on published clinical trials, population-based studies, and retrospective case series in the United States and abroad, some of which are cited in the Metformin Petitions, we agree that there is evidence that metformin is being used outside of the current labeling contraindications. However, it is unclear how extensive this use is.

- Across these studies, when the SCr values for metformin users were reported, only the mean SCr levels, not the distribution levels, were reported. Of note, the mean SCr levels (e.g., 1.8 mg/dL) were at times above the cut-points specified in the labeling.²⁹

²⁶ Yale Petition at 1-2.

²⁷ Id. at 3-6.

²⁸ Id. at 4.

²⁹ See, e.g., Yale Petition at 4, note 20 (citing Horlen, C, et al., May 2002, Frequency of Inappropriate Metformin Prescriptions, JAMA, 287(19):2504-2505)).

- Most of the retrospective studies cited in the Yale Petition on the prevalence of metformin use outside of the labeling (ranging from 3 to 4.5 percent) were based on a one-time SCr value, so it is unclear if the SCr value represented an isolated elevation above the cut-point. The extent to which the creatinine value exceeded the cut-point also was not reported.

Only a few of the studies assessed the continued use of metformin after developing an out-of-range SCr value. The incidence of out-of-range SCr values varied widely (from 4.8% to 75%) across studies.³⁰

In addition, although we agree that there is evidence that metformin is being used outside the current labeled contraindications, it is unclear whether this is with the prescriber's full knowledge of the relevant cut-points. Although the Yale Petitioners' cited studies report the use of metformin outside the current contraindications, it is difficult to infer the prescriber's knowledge of the contraindications or rationale for use of metformin. Specifically, these studies do not directly address whether metformin was being used because elevated SCr levels went unrecognized or because the prescriber decided the benefit of metformin therapy outweighed any potential risk.

The Yale Petitioners also say that when one considers the imperfect reflection of actual renal function by SCr levels, metformin is likely used even more frequently in patients with an impaired GFR than that suggested by the studies cited in their petition.³¹ The Yale Petitioners cite two studies to support this position, and these studies, together with another study not cited by the Yale Petitioners,³² show that a substantial portion of metformin recipients have normal SCr values combined with reduced eGFR values. This finding supports the Yale Petitioners' assertion that more metformin recipients show impaired renal function when determined by eGFR compared to when serum creatinine is used to determine renal function.

The Yale Petitioners also cite studies³³ that indicate that use of metformin in patients with mild to moderate CKD is not uncommon and state that there is evidence that metformin use is safe and effective in patients with CKD.³⁴ Although it is difficult to infer whether CKD was present

³⁰ See, e.g., (1) Yale Petition at 4-5, note 22 and Cornell Petition at 2, note 6 (citing Emslie-Smith, AM, et al., 2001, Contraindications to Metformin Therapy in Patients With Type 2 Diabetes—A Population-Based Study of Adherence to Prescribing Guidelines, *Diabet Med*, 18:483-488 (Emslie-Smith, 2001)) and (2) Yale Petition at 4-5, note 21 (citing Calabrese, AT, et al., 2002, Evaluation of Prescribing Practices: Risk of Lactic Acidosis With Metformin Therapy, *Arch Intern Med*, 162:434-437 (Calabrese, 2002)).

³¹ Yale Petition at 4.

³² Warren, RE, et al., 2007, Introducing Estimated Glomerular Filtration Rate (eGFR) Into Clinical Practice in the UK: Implications for the Use of Metformin, *Diabet Med*, 24:494-497.

³³ As the Yale Petitioners recognize, their first study cited to support the positions that metformin is safe and effective in patients with CKD and that cardiovascular benefits may extend to patients with moderate CKD had limitations that include a lack of information on diabetes duration, HbA1c values, and duration of therapy. Yale Petition at 5-6, note 29 (citing Roussel, R, et al., Nov 2010, Metformin Use and Mortality Among Patients With Diabetes and Atherothrombosis, *Arch Intern Med*, 170(21): 1892-1899 (Roussel, 2010)).

³⁴ Yale Petition at 5. The Yale Petitioners also say that these studies indicate that there are cardiovascular benefits of metformin use and that these benefits may extend to patients with established atherosclerosis and moderate CKD.

at the time metformin therapy was initiated (due to the design of these studies), we agree with the Yale Petitioners that based on the cited publications, metformin is used in patients with mild to moderate CKD.

2. *Certain Practice Guidelines Recommend Use of eGFRs*

The Yale Petitioners state that several U.S. practice guidelines substantially differ in their recommendations for metformin use related to renal status from the prescribing information for metformin. Currently, the labeling proscribes use at or above the 1.4 to 1.5 mg/dL levels in women and men, respectively.³⁵ The Yale Petitioners also say that clinical guidelines outside the United States incorporate eGFR for determination of metformin safety.³⁶

We do not believe that U.S. practice guidelines substantially differ in their recommendations for metformin use related to renal status from the currently approved labeling because these guidelines do not contain an outright endorsement of GFR-based guidelines.³⁷ We acknowledge,

Yale Petition at 5-6. They also note, however, that there are no randomized clinical trials that specifically evaluate the safety of metformin use and potential cardiovascular benefits in patients with CKD. Yale Petition at 6. We believe that the evidence provided neither suggests a beneficial nor a detrimental effect on cardiovascular disease in patients with renal impairment. The two cited studies (Yale Petition at 5-6) supporting the assertion of cardiovascular benefit are observational studies, and study limitations preclude definitive conclusions. Thus, we do not believe that a cardiovascular benefit has been established for metformin beyond the benefit of improved glycemic control and therefore cannot agree with the Yale Petitioners' assertion that there are cardiovascular benefits that extend to patients with established atherosclerosis and moderate CKD. As noted by the Yale Petitioners, we also found no published clinical trials specifically designed to explore the efficacy in CKD and therefore cannot agree that there is evidence of efficacy with CKD.

³⁵ The Yale Petitioners reference the consensus statement of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) that reports that metformin appears safe unless a patient's eGFR falls below 30 mL/min/1.73m² and that endorses GFR-based guidelines consistent with the guidelines of the United Kingdom's National Institute for Health and Clinical Excellence (NICE). Yale Petition at 6, note 32 (citing the 2010 NICE guidelines on managing T2DM).

³⁶ Yale Petition at 6.

³⁷ Both the 2012 joint position statement of the ADA and the EASD (ADA-EASD) regarding the management of hyperglycemia in T2DM, which was cited in the Yale Petition (Yale Petition at 7, note 37 (citing Inzucchi, SE, et al., 2012, Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach, *Diabetes Care*, 35:1364-1379)(ADA-EASD joint statement))), and the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) entitled "Clinical Practice Guideline for Diabetes and CKD: 2012 Update" (available at <https://www.kidney.org/sites/default/files/docs/diabetes-ckd-update-2012.pdf>) (KDOQI guideline) contain information on the creatinine-based thresholds used in U.S. labeling.

For instance, the ADA-EASD joint statement notes that the NICE guideline recommends metformin use down to a GFR of 30 mL/min and advises a dose reduction at 45 mL/min/1.73 m². See Yale Petition at 6. The ADA-EASD joint statement also notes that, "[g]iven the current widespread reporting of estimated GFR, these guidelines appear very reasonable." Similarly, the KDOQI guideline notes that the British National Formulary and the Japanese Society of Nephrology guidelines recommend metformin use down to a GFR \geq 30 mL/min/1.73 m² and advise that "metformin use be reevaluated when [the] GFR is < 45 mL/min/1.73 m²." The KDOQI guideline does not state a position on whether such use of metformin is advisable.

However, after describing the creatinine-based thresholds referenced in U.S. labeling, the KDOQI guideline indicates that "it is also reasonable to consider a GFR cut-point for metformin use as well, since serum creatinine can translate into different eGFR levels depending on weight, race or age." Nathan, DM, et al., 2009, *Medical*

however, that the U.S. guidelines note that there is a controversy about the thresholds in metformin labeling and whether the thresholds are too restrictive. We also note that the U.S. guidelines indicate that it is reasonable to use a GFR-based cut-point.

We agree that there are guidelines outside of the U.S. that incorporate eGFR, although some also include CrCl levels. For example, the Canadian Diabetes Association 2013 Clinical Practice Guideline for the Prevention and Management of Diabetes in Canada, the 2009 NICE guidelines on the management of type 2 diabetes in adults and the 2009 Australian Guideline titled “National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes” have incorporated eGFR as a measure of kidney function to guide metformin use.³⁸ While the Canadian Diabetes Association Guideline refers to eGFR and CrCl-based thresholds for dosing metformin, other guidelines such as the 2009 Australian Guideline and the 2009 NICE guideline only refer to eGFR. Of note, the Yale Petitioners do not distinguish between these two estimates of kidney function (GFR versus CrCl) or the difference in units employed by these estimating equations (mL/min vs. mL/min per 1.73m²) in their discussion of the guidelines.

3. Serum Creatinine Measurements Alone Have Limitations in Measuring Renal Impairment

The Yale Petitioners say that the creatinine cut-points for contraindication to metformin use were set at 1.4 mg/dl in women and 1.5 mg/dl in men based on the calculated ability to remove 3 grams of metformin at steady-state levels within 24 to 48 hours.³⁹ They also say that “the ability to comfortably remove metformin extends up to creatinine levels of 1.8-2.0 mg/dl, but the cut-points chosen were intentionally set lower to ensure that those patients who may be lost to follow-up and whose creatinine levels increase over time would not be at risk for appreciable drug accumulation.”⁴⁰

The Yale Petitioners also state that it is unknown how well the current serum creatinine cut-points reflect the ability to effectively clear metformin, and they describe the limitations of the estimation of renal function with creatinine.⁴¹ Specifically, the Yale Petitioners say that serum creatinine can only be used reliably in patients with stable kidney function; and, variation in creatinine production may differ among and within individuals over time, especially if there are

Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy, *Diabetes Care*, 32(1):193-203.

³⁸ See Colagiuri, S, et al., 2009, National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes, Diabetes Australia and the National Health and Medical Research Council, Canberra (available at <http://static.diabetesaustralia.com.au/s/fileassets/diabetes-australia/659c89a3-dcc2-4a2e-86e5-cc1d09956c60.pdf>); Canadian Diabetes Association, 2013, Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada, *Canadian Journal of Diabetes*, 37(Suppl 1):S1-S212; and National Institute for Health and Care Excellence (NICE), May 2009, NICE Guidelines [CG87], Type 2 diabetes in adults: management (updated Dec. 2015, NICE Guidelines [NG28]).

³⁹ Yale Petition at 2.

⁴⁰ Id.

⁴¹ Id. at 3.

significant changes in muscle mass or physical activity. The Yale Petitioners also say that variability in creatinine secretion, extra-renal creatinine excretion, assay method, and equipment can all affect serum measurements.⁴²

Based on the literature cited in the Yale Petition, we agree with the Yale Petitioners that the relationship between the specified SCr cut-points in the metformin labeling (i.e., SCr \geq 1.5 mg/dL in males and SCr \geq 1.4 mg/dL in females) and the ability to eliminate metformin is unclear. It appears that the early pharmacokinetic studies cited in the Yale Petition used CrCL (e.g., timed urine collection and plasma SCr levels) as a measure of renal function to relate to metformin clinical pharmacology parameters.⁴³ However, the current metformin labeling does not provide an explanation for the specified SCr cut-points.

The Yale Petitioners say that

[t]he principal reason for carefully setting renal thresholds is that metformin is eliminated unchanged primarily by the kidneys. Thus, one of the most important risk factors for elevated metformin concentrations (which are proposed to lead to lactic acidosis) is the inability to clear the drug efficiently.⁴⁴

We agree that the kidney plays an important role in lactate handling, which can be affected by the degree of renal impairment (see discussion in section I.B of this response). The presence of renal impairment is an important factor for both altered lactate handling, as well as reduced metformin clearance.⁴⁵

We also agree that the absolute level of SCr alone has limitations as a measure of renal function and that the inverse relationship between an absolute level of SCr to an absolute level of kidney function holds only when renal function is in a steady state. Furthermore, inter-subject differences in SCr production (e.g., because of differences in muscle mass) also affect the relationship between creatinine levels and renal function.

The Yale Petitioners state that calculated estimates using the Cockcroft-Gault (CG) equation (which calculates CrCL) and the Modification of Diet in Renal Disease (MDRD) equation (which calculates eGFR)⁴⁶ have been developed to incorporate known demographic and clinical

⁴² Id.

⁴³ See Yale Petition at 2, note 8 (citing Sambol, NC, et al., 1995, Kidney Function and Age Are Both Predictors of Pharmacokinetics of Metformin, *J Clin Pharmacol*, 35:1094-1102); Yale Petition at 2, note 7 (citing Tucker, GT, et al., 1981, Metformin Kinetics in Healthy Subjects and in Patients With Diabetes Mellitus, *Br J Clin Pharmacol*, 12:235-246).

⁴⁴ Yale Petition at 2.

⁴⁵ We concur with the Yale Petitioners' description of the absorption, accumulation and elimination of metformin, including the correlation between renal clearance of metformin and creatinine clearance. Yale Petition at 2-3. We also agree with the Yale Petitioners' statement that studies and reports on renal clearance of metformin have limitations, including lack of evidence regarding lactate production and chronic treatment pharmacokinetics. Yale Petition at 2-3.

⁴⁶ The MDRD formula is available at http://www.nephron.com/MDRD_GFR.cgi.

factors affecting serum concentrations, and despite their shortcomings, provide a better estimation of renal function than creatinine alone.⁴⁷ They say that dosing considerations by FDA for other medications (such as sitagliptin or fenofibrate) are now generally based upon CrCl estimates from such calculations and not based solely on creatinine levels.⁴⁸

The Yale Petitioners say any potential labeling recommendation ought to incorporate eGFR as the renal metric because this metric more accurately reflects renal function and is easily calculated in clinical laboratories using equations that include further defining factors, such as the patient's weight, race and sex. The Yale Petitioners cite studies that indicate that a switch to an eGFR-based cut-point may be both a more practical and accurate way to limit metformin access in those with significantly impaired renal function.⁴⁹ Therefore, they recommend that the current creatinine-based contraindications to metformin therapy be replaced with GFR-based guidelines. The Yale Petitioners state that their recommendations are based on a better estimation of renal function (using GFR) and on metformin's continued record of safety with respect to lactic acidosis risk.⁵⁰

We agree that serum creatinine is an imperfect measure of renal function because several factors contribute to the determination of renal function. We also agree that the SCr values in the current metformin labeling should be replaced. Yale Petitioners correctly note that the SCr-based equations (e.g., CG and MDRD) incorporate demographic and clinical factors (such as age, sex, race, or weight) that are correlated with differences in average muscle mass to correct for variations in creatinine production among individuals.⁵¹ We agree that, in general, these estimation equations are currently regarded as more sensitive in detecting a measured GFR 60 mL/min per 1.73 m² than is serum creatinine alone and are felt to provide a better estimate of kidney function than serum creatinine values alone, particularly for detecting early stages of kidney disease.⁵² In addition, estimating equations, such as the CG and MDRD equations, are generally preferred over absolute SCr values as measures of renal function for drug development and labeling.⁵³

⁴⁷ Yale Petition at 3.

⁴⁸ Id. at 3-4.

⁴⁹ Id. at 6.

⁵⁰ Id. at 7.

⁵¹ Id. at 3.

⁵² The estimation equations are more sensitive in detecting a GFR < 60 mL/min per 1.73m² than is an absolute value of serum creatinine. If the MDRD method is used for eGFR estimation and classification, all patients with mild renal impairment and most patients with moderate renal impairment would qualify for metformin use. If prescribers are using the serum creatinine values as the cut-points, then metformin is perhaps already being used in all patients with mild renal impairment and most patients with moderate renal impairment. Therefore, we agree with the Yale Petitioners that metformin is likely used more frequently in patients with an eGFR <60 mL/min per 1.73m² than suggested in some of the studies. This conclusion is also supported by some of the literature cited by the Yale Petitioners. Yale Petition at 5.

⁵³ FDA's 1998 guidance for Industry, *Pharmacokinetics in Patients With Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing and Labeling*, advised the use of CrCl to relate to PK parameters. The 2010 draft guidance for industry, which revised the 1998 guidance, though, suggests that either the 4-variable MDRD equation or the CG equation can be used to stratify enrollment of subjects with renal impairment into PK studies but

Though an argument could be made for using an estimate of CrCL, such as the CG equation, we believe that an estimate of measured GFR, such as the MDRD or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, should be used to guide use of metformin in patients. With regard to diagnosing chronic kidney disease, eGFR is, in most cases, a more sensitive and accurate way to ascertain for the presence of underlying disease than the CG equation and most U.S. laboratories report a patient's level of renal function using an estimate of GFR (as opposed to an estimate of CrCL). We also note that there is concern about the accuracy of the CG equation since the creatinine measurement has now been standardized and there is no validated version of the CG equation for use with standardized creatinine results.⁵⁴ Hence, we agree with Yale Petitioners' proposal to use eGFR as a measurement of renal impairment to guide metformin use in patients.

We consider this information on the use of eGFR to measure renal function in patients using metformin to be *new safety information* as defined in section 505-1(b)(3) of the FD&C Act. As mentioned above in section I.D.2, section 505(o)(4) of the FD&C Act authorizes FDA to require holders of approved drug and biological product applications to make safety-related labeling changes based on "new safety information" that becomes available after approval of the drug or biological product.

Based on this new safety information, we believe that the metformin labeling should be revised to reflect an eGFR-based cutoff for metformin contraindications. This eGFR measurement will provide a clear recommendation to prescribers regarding when metformin should not be used in patients with impaired renal function. The use of the eGFR should eliminate any confusion that may arise from the SCr values currently included in the approved labeling. We have notified the metformin application holders that under section 505(o)(4) of the FD&C Act, the labeling must be revised to address this new safety information using the eGFR-based calculations.

Specifically, we have notified the metformin application holders that the CONTRAINDICATIONS and PRECAUTIONS sections of the metformin labeling should be revised as follows:

- CONTRAINDICATIONS. [Metformin] is contraindicated in patients with severe renal impairment (e.g. eGFR < 30 mL/min/1.73 m²).

recommends that the PK parameters relate to both equations in the analysis. When final, this draft guidance will represent FDA's current thinking on this issue.

⁵⁴ "Current Status Of Reporting Estimated Glomerular Filtration Rate (eGFR) (2013)," posted on http://www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtlt_actionOverride=%2Fportlet%2FcontentViewer%2Fshow&_windowLabel=cntvwrPtlt&cntvwrPtlt%7BactionForm.contentReference%7D=committees%2Fchemistry%2Fchemistry_resources.html&_state=maximized&_pageLabel=cntvwr. The creatinine measurement has now been standardized and there is no validated version of the CG equation for use with standardized creatinine results. References: <http://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr/creatinine-standardization/Pages/creatinine-standardization.aspx> and <http://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/a-z/ckd-drug-dosing/Pages/CKD-drug-dosing.aspx>.

- PRECAUTIONS. *Renal Impairment* - The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney (see CLINICAL PHARMACOLOGY).
 - Before initiating [metformin] obtain an estimated glomerular filtration rate (eGFR);
 - [Metformin] is contraindicated in patients with an eGFR < 30 mL/min/1.73 m²;
 - Initiation of [metformin] is not recommended in patients with an eGFR between 30 - 45 mL/min/1.73 m²;
 - 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
 - In patients taking [metformin] whose eGFR falls below 45 mL/min/1.73 m², assess the benefit and risk of continuing therapy.

Our letters notifying the metformin application holders that we believe the labeling for metformin should be modified to include the eGFR-based cut-points were issued based on our authority to require safety labeling changes under section 505(o)(4) of the FD&C Act. Under section 505(o)(4) of the FD&C Act, the metformin application holders are now required either (1) to submit within 30 days following notification a supplement containing the proposed labeling changes or (2) to notify the Agency that they do not believe labeling changes are warranted and submit a statement detailing the reasons they believe such changes are not warranted.

If the metformin application holders do not submit proposed safety labeling changes or if we disagree with either the language proposed or the statement setting forth the reasons why no labeling change is necessary, the FD&C Act provides timelines under section 505(o)(4) for discussions between FDA and the application holders regarding the labeling changes. Within 15 days of the conclusion of these discussions, section 505(o)(4)(E) of the FD&C Act authorizes FDA to issue an order directing labeling changes as we deem appropriate to address the new safety information.

We are awaiting the responses of the metformin application holders, under these procedures, to our notification that additional warnings and other revisions to product labeling are necessary. The specific language we have recommended in the notification is subject to change depending on the language the application holders propose. We have not yet ordered specific labeling changes at this stage of the process under section 505(o)(4) of the FD&C Act. However, we have taken all the steps required under section 505(o)(4) of the FD&C Act to pursue the changes.

B. The Cornell Petition

The Cornell Petitioners request that FDA take the following five actions on the labeling for metformin:

- (1) Eliminate the boxed warning regarding lactic acidosis associated with metformin
- (2) Relax the contraindication against metformin use in renal impairment so that the contraindication does not apply to patients with a CrCL greater than [or equal to] 30 milliliters (mL)/minute (min)
- (3) Revise the PRECAUTIONS section to emphasize close monitoring of renal function rather than strict avoidance of metformin in renal dysfunction
- (4) Revise the contraindication to metformin use with iodinated contrast so that it only applies to individuals with a baseline CrCL of < 60 mL/min
- (5) Revise the PRECAUTIONS section so that the recommendation to retest renal function after iodinated contrast exposure only applies to individuals with a baseline CrCL < 60 mL/min

We address each of these requests below.

I. Removal of the Boxed Warning on Lactic Acidosis

As explained above, the current labeling for metformin includes a boxed warning for lactic acidosis. The warning states that lactic acidosis is a rare but serious metabolic complication that can occur due to metformin accumulation during treatment and that, when it occurs, is fatal in approximately 50 percent of cases.

The Cornell Petitioners request that FDA remove the boxed warning regarding lactic acidosis in metformin users. In support of this request, the Cornell Petitioners state that:

- Metformin's approval was conditional on the boxed warning against lactic acidosis because of concerns that metformin would cause lactic acidosis like phenformin, a related biguanide.
- Studies have not shown an increase in lactic acidosis with routine use of metformin.
- Significant numbers of patients with renal insufficiency take metformin despite the renal contraindication, and there is no evidence of an increased risk of lactic acidosis or other adverse outcomes in this population.

For the reasons explained below, we deny the Cornell Petitioners' request to remove metformin's boxed warning on lactic acidosis.

a. Metformin and Phenformin

The Cornell Petitioners and the Yale Petitioners assert that concerns that metformin may cause lactic acidosis arose because phenformin,⁵⁵ a related biguanide was removed from the market in 1978 because of concerns with potentially fatal lactic acidosis. Both Petitioners discuss the distinctions between phenformin and metformin and state that lactic acidosis occurred more frequently with phenformin than with metformin.⁵⁶ The Yale Petitioners state that lactic acidosis with phenformin appears to occur approximately 10 to 20 times more frequently than with metformin.⁵⁷

We agree with the Metformin Petitioners that lactic acidosis occurs more frequently with phenformin than with metformin. In reaching this determination, we focused on studies that included both metformin and phenformin, which includes 14 studies on the incidence of lactic acidosis among users of biguanides.⁵⁸ Despite some limitations in the cited studies, these studies represent the best available evidence for the comparative risk of lactic acidosis between metformin and phenformin and support Yale Petitioners' estimate of a 10 to 20 times elevated risk for lactic acidosis associated with phenformin compared with metformin.

The Cornell Petitioners also state that the differential effect of phenformin and metformin on lactic acid levels likely relates to pharmacokinetic, rather than mechanistic, differences between

⁵⁵ Cornell Petition at 5; Yale Petition at 2.

⁵⁶ Id.

⁵⁷ Yale Petition at 2.

⁵⁸ The Yale Petitioners reference a review article (Yale Petition at 2, note 2 (citing Bailey, CJ, et al., 1996, *N Engl J Med*, 334:574-579 (Bailey, 1996))), which is consistent with their statement of a 10 to 20 times increase in lactic acidosis rates with phenformin compared with metformin. This review article, however, used other review articles and not original studies to support this claim. Thus, our discussion on this point is focused on the following 14 studies cited in the Bailey article: (1) Brown JB, Pedula K, Barzilay J, et al., 1998, Lactic acidosis rates in type 2 diabetes. *Diabetes Care*, 21:1659-63; (2) Stang M, Wysowski DK, Butler-Jones D., 1999, Incidence of lactic acidosis in metformin users. *Diabetes Care*, 22:925-7; (3) Emslie-Smith AM, Boyle DI, Evans JM, et al., 2001, Contraindications to metformin therapy in patients with Type 2 diabetes--a population-based study of adherence to prescribing guidelines. *Diabet Med*,18:483-8; (4) Bodmer M, Meier C, Krahenbuhl S, et al., 2008, Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: A nested case-control analysis. *Diabetes Care*, 31:2086-91; (5) Kamber N, Davis WA, Bruce DG, et al., 2008, Metformin and lactic acidosis in an Australian community setting: the Fremantle Diabetes Study. *Med J Aust* 2008;188:446-9; (6) Salpeter SR, Greyber E, Pasternak GA, et al., 2010, Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev*, CD002967; (7) Isnard F, Lavieville M., 1977, [Lactic acidosis and biguanides: present state of the question in France]. *Journ Annu Diabetol Hotel Dieu*, 362-75; (8) Berger W, Amrein R., 1978, [Lactic acidosis associated with various types of biguanide-therapy (phenformin, buformin, metformin). Results of a survey of the years 1972--1977 in Switzerland (author's transl)]. *Schweiz Rundsch Med Prax*, 67:661-7; (9) Scale T, Harvey JN., 2011, Diabetes, metformin and lactic acidosis. *Clin Endocrinol (Oxf)*, 74:191-6; (10) van Berlo-van de Laar IR, Vermeij CG, Doorenbos CJ., 2011, Metformin associated lactic acidosis: incidence and clinical correlation with metformin serum concentration measurements. *J Clin Pharm Ther*, 36:376-82; (11) Bergman U, Boman G, Wiholm BE., 1978, Epidemiology of adverse drug reactions to phenformin and metformin. *Br Med J*, 2:464-6; (12) Korhonen T, Idanpaan-Heikkila J, Aro A., 1979, Biguanide-induced lactic acidosis in Finland. *Eur J Clin Pharmacol*, 15:407-10; (13) Wiholm BE, Myrhed M., 1993, Metformin-associated lactic acidosis in Sweden 1977-1991. *Eur J Clin Pharmacol*, 44:589-91; (14) Misbin RI, Green L, Stadel BV, et al., 1998, Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med*, 338:265-6.

the two drugs, including phenformin's longer half-life and lipophilic composition.⁵⁹ The Cornell Petitioners state that these differences are consistent with observations that phenformin raises lactic acid levels at far lower concentrations than metformin.⁶⁰

The difference between phenformin and metformin with regard to lactic acidosis is consistent with the pharmacokinetic differences between the drugs. Phenformin has a longer half-life (t_{1/2}) (12 h vs. 1.5 h) and lipophilic composition. Phenformin is metabolized in humans and metformin is excreted unchanged. Protein binding is negligible with metformin and 12-20% with phenformin. While the differences in pharmacokinetics between metformin and phenformin exist, they do not necessarily demonstrate a cause and effect relationship for a magnitude of pharmacokinetic differences and the risk of lactic acidosis between these two drugs. It may be more difficult to use phenformin clinically than metformin based on these differences in pharmacokinetics specifically due to its longer half-life than metformin. There are also attributed differences in the mechanism of action of metformin and phenformin.

The distinctions that exist between phenformin and metformin as outlined by the Cornell Petitioners help explain the difference in the apparent frequency of lactic acidosis associated with members of the biguanide drug class, and are consistent with the observation that phenformin raises lactic acid levels at lower drug concentrations than metformin.⁶¹ However, lactic acidosis is observed in patients with renal dysfunction, and because renal excretion is the major elimination pathway for biguanides, there may be conditions such as renal and/or hepatic impairment where elevated metformin levels may reach toxic levels, resulting in the development of lactic acidosis.

b. Studies on Lactic Acidosis and Metformin Use

(i) The Cornell Petition

The Cornell Petitioners state that case reports and case series suggest that in extreme overdose metformin may cause lactic acidosis, but that these cases do not offer convincing evidence that lactic acidosis is caused by "clinically used" metformin doses.⁶² The Cornell Petitioners state that these cases also demonstrate that non-overdose cases of lactic acidosis in metformin usually offer alternative explanations for the acidosis.⁶³

We agree that metformin-associated lactic acidosis observed with overdosage does not offer convincing evidence that lactic acidosis is caused by "clinically used" doses; however, the case reports and case series cited by the Cornell Petitioners do not necessarily rule out the possibility

⁵⁹ Cornell Petition at 6.

⁶⁰ Id.

⁶¹ Id.

⁶² Id. at 8. For the purposes of responding to the petition, we have assumed that "clinically used" doses are doses that conform to the dosing recommendations found in the FDA-approved labeling for metformin-containing products.

⁶³ Id.

of metformin-associated lactic acidosis at clinical doses. In assessing the Cornell Petitioners' statements, we reviewed the published literature on reviews of metformin-associated lactic acidosis and case presentations, and found that there are several case reports in the literature that support the possibility that metformin-associated lactic acidosis may occur at clinical doses.⁶⁴

(ii) The Yale Petition

The Yale Petitioners state that the causal relationship between metformin and lactic acidosis remains in question.⁶⁵ They say that lactic acidosis remains exceedingly rare in clinical trials and in cohort studies of metformin therapy and that the number of lactic acidosis cases is small compared to the widespread use of metformin.⁶⁶

We note, however, that there are no well-designed clinical trials that address the Yale Petitioners' statement "that there is no tangible evidence from prospective observational studies or clinical trials that [metformin] increases [the] incidence" of lactic acidosis.⁶⁷ The few prospective observational studies that explore this question have yielded very little data, which preclude definitive conclusions.

The Yale Petitioners also state that "available data suggest that lactate levels and risk of lactic acidosis do not differ appreciably in patients taking [metformin] versus other glucose-lowering agents."⁶⁸ However, none of the publications cited by the Yale Petitioners directly compared lactate levels in patients taking metformin versus other glucose-lowering agents.⁶⁹ Our review of published literature identified some studies that demonstrated an increase in lactate levels (1) with use of metformin (and phenformin) versus a sulfonylurea⁷⁰ or (2) when metformin was used

⁶⁴ Berner, B, Feb. 15, 2002, [Metformin-Induced Lactic Acidosis with Acute Renal Failure in Type 2 Diabetes Mellitus], Med Klin, 97:99-103; Pertek, JP, et al., May 2003, [Metformin-Associated Lactic Acidosis Precipitated by Acute Renal Failure], Ann Fr Anesth Reanim, 22(5): 457-460; Kruse, JA, 2001, Metformin-Associated Lactic Acidosis, J Emerg Med, 20(3): 267-272; Perrone, J, 2011, Occult Metformin Toxicity in Three Patients With Profound Lactic Acidosis, J Emerg Med, 40(3): 271-275.

⁶⁵ Yale Petition at 4.

⁶⁶ Id.

⁶⁷ Id.

⁶⁸ Id.

⁶⁹ The Yale Petitioners cite a case study by Bodmer, et al., to support their assertion that there is no difference in lactate levels and risk of lactic acidosis with metformin and other glucose-lowering agents. Yale Petition at 4, note 13 (citing Bodmer, 2008, *supra* note 58). The study's concurrent use of metformin and sulfonylureas confounds the assessment and raises questions regarding the authors' conclusion on the risk of lactic acidosis. Although Bodmer's study is described as a case-control study, no control subjects were selected for the question of lactic acidosis, only for a comparison of hypoglycemia.

⁷⁰ McAlpine, LG, 1988, A Comparison of Treatment With Metformin and Gliclazide in Patients With Non-Insulin-Dependent Diabetes, Eur J Clin Pharmacol, 34(2):129-132; Nattrass, M, et al., Apr 1977, Comparative Effects of Phenformin, Metformin and Glibenclamide on Metabolic Rhythms in Maturity-Onset Diabetics, Diabetologia, 13(2):145-152. We note the differences were not necessarily in fasting lactate, but were noted at different time points throughout the day, particularly in the post-lunch period. We also note that the lactate levels were more elevated with phenformin than with metformin.

as an add-on to a sulfonylurea versus a sulfonylurea alone.⁷¹ Other studies, however, did not suggest an increased risk of lactic acidosis associated with metformin when compared to sulfonylureas or when compared to the risk of lactic acidosis associated with diabetes in general.⁷²

The Yale Petitioners also state that studies suggest that elevated circulating lactate levels, often attributed to metformin, may actually not be caused by metformin but instead may be caused by other factors. We agree that there are multiple factors that may play a role in the elevation of lactate levels and lactic acidosis. Studies indicate that, although metformin levels may be associated with lactate levels, the studies are neither able to establish nor rule out a causal relationship between metformin and elevated lactate levels.⁷³ Metformin levels can only partially explain variations in lactate levels, and other factors besides metformin use appear to account for a larger share of the variations. The available evidence, however, is limited to small case series that were mostly conducted among patients with lactic acidosis. Thus, by definition, these patients had elevated lactate levels and many had underlying diseases that could cause both metformin accumulation and lactic acidosis. Therefore, these studies are limited in their ability to show a causal relationship between metformin and lactate levels.

c. Lactic Acidosis and Metformin Use in Patients With Moderate Renal Insufficiency

The Cornell Petitioners state that significant numbers of patients with renal insufficiency take metformin despite the renal contraindication and that there is no evidence of an increased risk of lactic acidosis or other adverse outcomes even in this population.⁷⁴ The Cornell Petitioners also state that it is likely that there were “significant” numbers of patients with renal insufficiency in the large meta-analysis and epidemiological studies referenced in their petition.⁷⁵

It cannot be determined that these meta-analysis and epidemiological studies, which analyzed the

⁷¹ Nattrass M, et al., 1979, Metabolic Effects of Combined Sulphonylurea and Metformin Therapy in Maturity-Onset Diabetics, Horm Metab Res, 11(5):332-337.

⁷² Only one out of the four studies we reviewed included an incidence rate for metformin that exceeded that of the diabetic comparison group; however, this one study included only five cases of lactic acidosis and confidence intervals that widely overlapped. See Kamber, 2008, *supra* note 58.

⁷³ See, e.g., van Berlo-van de Laar, 2011, *supra* note 58; Lalau, JD, et al., Jun 1995, Role of Metformin Accumulation in Metformin-Associated Lactic Acidosis, Diabetes Care, 18(6):779-84; Stades, AM, et al., Feb 2004, Metformin and Lactic Acidosis: Cause or Coincidence? A Review of Case Reports, J Intern Med, 255(2):179-187; and Lalau JD, et al., Apr 1999, Lactic Acidosis in Metformin-Treated Patients: Prognostic Value of Arterial Lactate Levels and Plasma Metformin Concentrations, Drug Saf, 20(4):377-84.

⁷⁴ Cornell Petition at 2.

⁷⁵ Cornell Petition at 6 (citing Salpeter SR, Greyber E, Pasternak GA, Salpeter EE, 2010, Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev (4):CD002967; Alkhailil, C., et al., 2002, *Clinical pharmacology physiology conference: metformin and lactic acidosis (LA)*, Int Urol Nephrol, 34(3): p. 419-23; Wiholm, B. E. and M. Myrhed, 1993, *Metformin-associated lactic acidosis in Sweden 1977-1991*; Eur J Clin Pharmacol, 44(6): p. 589-91; Misbin, R.I., et al., 1998, *Lactic acidosis in patients with diabetes treated with metformin*. N Engl J Med, 338(4): p. 265-6; 47. Stang, M., O.K. Wysowski, and D. Butler-Jones, 1999, *Incidence of lactic acidosis in metformin users*, Diabetes Care, 22(6): p. 925-7).

rates of lactic acidosis in metformin users, included “significant” numbers of patients with renal insufficiency.⁷⁶ In 57 percent of the prospective studies reviewed in the meta-analysis, subjects with a SCr > 1.5 mg/dL were excluded. Of the remaining studies in the meta-analysis, it is unclear what percentage of subjects had renal insufficiency (either defined by SCr or eGFR). The authors of the meta-analysis⁷⁷ state that

it is not clear how many participants with each of these contraindications [chronic renal insufficiency, liver function abnormalities, congestive heart failure, peripheral vascular disease, pulmonary disease, age > 65] were included in the trials, so the safety of metformin in the presence of these standard conditions cannot be assessed.⁷⁸

The authors also state that

it is especially difficult to assess the risk of lactic acidosis in the presence of standard contraindications such as renal or hepatic insufficiency because it is unclear exactly how many of the participants had these conditions. For that reason, no conclusions can be made about the safety of metformin use in the presence of these conditions.⁷⁹

These statements from the cited meta-analysis are counter to the use of the word “significant” by the Cornell Petitioners. Although there may be metformin usage in subjects with renal insufficiency, as noted in the additional epidemiological studies cited by the Cornell Petitioners,⁸⁰ the conclusions of the meta-analysis cannot be extrapolated to this population.

The Cornell Petitioners also state that studies on the rates of lactic acidosis in metformin users with impaired renal function (1) support a finding of metformin’s safety in renal failure, (2) show no evidence of increased risk for lactic acidosis in metformin users with impaired renal function, and (3) show no evidence of life-threatening events associated with metformin use.⁸¹

We agree that the studies cited in the Cornell Petition suggest that metformin use is safe in patients with mildly impaired renal function, but we do not feel that these studies provide sufficient data to state with confidence that metformin is safe in all severities of impaired renal function. On the surface, the cited publications present safety of metformin use in impaired renal function, with no increased risk of lactic acidosis, and/or no evidence of increased risk for life-

⁷⁶ The Cornell Petitioners’ use of the term *significant* suggests that large numbers of subjects with renal insufficiency were included in the studies reviewed in the meta-analysis thus allowing for extrapolating the finding of an absence of increased risk for lactic acidosis to subjects with renal insufficiency. A more appropriate discussion would be, though, whether the meta-analysis findings are applicable to patients with renal insufficiency.

⁷⁷ See Cornell Petition at 2 and 6, note 4 (citing Salpeter, 2010, *supra* note 75).

⁷⁸ Salpeter, 2010, *supra* note 75.

⁷⁹ *Id.*

⁸⁰ Cornell Petition at 6-7.

⁸¹ Cornell Petition at 7-8, notes 7-10 (citing Rachmani R, et al., Oct. 2002, Metformin in Patients With Type 2 Diabetes Mellitus: Reconsideration of Traditional Contraindications, *Eur J Intern Med* ;13(7):428 (Rachmani, 2002); Kamber, 2008, *supra* note 58; Ekstrom, N, et al., 2012, Effectiveness and Safety of Metformin in 51 675 Patients with Type 2 Diabetes and Different Levels of Renal Function: A Cohort Study from the Swedish National Diabetes Register, *BMJ Open*, 2(4); and Roussel, 2010, *supra* note 33).

threatening events. However, these studies have limitations, such as the small number of patients, which results in an inability to assess statistical significance. Many of the studies were observational studies with limitations -- involving insufficient follow-up, intermittent use of metformin, potential for residual confounding, limits on the ability to identify accurately the differences in rates of lactic acidosis, and an unknown degree of renal impairment -- that preclude definitive conclusions.

In sum, the currently approved labeling for metformin includes a boxed warning that advises against the use of metformin in patients with renal insufficiency. Patients with renal impairment are considered a patient population in which metformin use may be inappropriate, especially where the risk of lactic acidosis increases with the degree of renal dysfunction. As discussed above, however, the existing data on metformin do not support the elimination of the boxed warning for lactic acidosis because metformin is capable of producing lactic acidosis in humans and because the associated mortality rate is very high (approximately 50 percent) when it occurs. Thus, the boxed warning on the risk of lactic acidosis with metformin use is needed to inform prescribers of this risk and to make them aware of a variety of risk factors, including renal impairment, to allow for risk mitigation. The Cornell Petitioners do not provide sufficient evidence of an absence of a risk of lactic acidosis with metformin use to support removal from the boxed warning. We therefore deny the Cornell Petitioners' request.

2. *Revisions to the CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS Sections Regarding Renal Impairment*

Metformin's currently approved labeling states that it is contraindicated in patients with "renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females] or abnormal creatinine clearance)"

The Cornell Petitioners request that we revise the metformin labeling on the use of metformin in patients with renal impairment as follows:⁸²

- Revise the first listed contraindication for metformin to read:

Advanced renal dysfunction as suggested by a creatinine clearance < 30 mL/min, or a risk of rapid worsening renal function, or the prospect of rapid deterioration of renal function from cause such as cardiovascular collapse (shock), exacerbation of heart failure, or exposure to nephrotoxic agents."

- Revise the PRECAUTIONS section on monitoring renal function to read:

⁸² The Cornell Petitioners state that editorials and articles calling for relaxation of the renal contraindications to metformin are now very common in medical journals and that some major guidelines cohere with these opinions in being more liberal than the current metformin labeling. Cornell Petition at 10. Although recommendations from these articles are not unified, and different authors have put forward different thresholds (based on SCr, eGFR, or CrCl), different formulae for estimating renal function, and different recommendations on how to adjust therapy based on renal function, we concur that an academic consensus is forming regarding support for modification of the current SCr-based restrictions on metformin use.

Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and the theoretical risk of lactic acidosis is thought to increase with the degree of impairment of renal function. Thus, patients with any impairment of renal function should be monitored regularly and, in these patients [metformin] generally should not be titrated to the maximum dose (see WARNINGS and DOSAGE AND ADMINISTRATION). Before initiation of [metformin] therapy and at least annually thereafter, renal function should be assessed. In patients in whom development or worsening of renal dysfunction is anticipated, renal function should be assessed more frequently and [metformin] discontinued if evidence of fluctuating or rapidly worsening renal impairment is present.⁸³

In support of their request, the Cornell Petitioners say that the current contraindications against metformin use above a creatinine threshold of 1.4 mg/dL for women and 1.5 mg/dL in men actively discourages the use of metformin in the large population of diabetics with mild to moderate renal disease and “is a significant detriment to clinical care and public health.”⁸⁴ The Cornell Petitioners state that data “strongly suggest[]” that diabetics with moderate renal insufficiency, who may be at higher risk for further diabetic complications, “would benefit considerably by access to metformin.”⁸⁵

The safety and efficacy data on patients with moderate renal insufficiency is too limited to find that diabetics with moderate renal insufficiency would benefit considerably from access to metformin. Published articles that discuss the use of metformin in renal insufficiency have focused on its safety, not on improved outcomes. We are unaware of any large, prospective, randomized studies that demonstrate a clear benefit with metformin use in moderate renal insufficiency. The randomized withdrawal study that Cornell Petitioners cite showed neither increased risk nor increased benefit from continuing metformin despite having one or more contraindications.⁸⁶

Moreover, discouraging the use of metformin in this patient population is not a significant detriment to clinical care or to public health because metformin is one of many other anti-diabetic agents that can be used to improve glycemic control. First, excluding metformin from

⁸³ Cornell Petition at 1.

⁸⁴ Id. at 5.

⁸⁵ Id.

⁸⁶ Cornell Petition at 2 and 7, note 7 (citing Rachmani, 2002, *supra* note 81). In this study, 393 subjects were randomized to either continue or to discontinue metformin. All had a SCr between 1.47 and 2.49 mg/dL. The subjects randomized to discontinue metformin experienced a greater weight gain than those subjects continuing metformin. Also, the subjects who discontinued metformin experienced a rise in hemoglobin A1c compared to those subjects continuing metformin (0.5 percent versus 0.2 percent), but the article contains no discussion of whether the metformin was replaced with another anti-diabetic agent or how treatments were adjusted. Interestingly, the incidence of microvascular and macrovascular outcomes was no different between these two groups, but we note that the study was not of sufficient size to evaluate these outcomes. Also, a similar number of subjects in each group had the new development of diabetic retinopathy and there was a similar incidence of death and of cardiovascular events between both groups, which, based on the lack of controlled clinical trial data, do not support the Petitioners’ statement that the moderate renal insufficiency population would benefit considerably by having access to metformin.

use does not result in a complete loss of useful therapies to improve glycemic control. Second, it is unclear whether use of specific anti-diabetic agents results in improved outcomes compared to other agents. As long as glycemic control can be maintained, there is no detriment to clinical care and public health.

Although we do not believe sufficient evidence exists to conclude metformin would provide benefit beyond that afforded by glucose control in patients with moderate renal insufficiency, we do believe that the risk is not sufficient to warrant contraindicating metformin for patients with moderate renal insufficiency. As explained above, using the CG or MDRD formulas, the current SCr values in the metformin labeling correspond to the category of patients with moderate renal function. Thus, if health care providers are interpreting these values as a recommended cut-point for restricting metformin use, metformin may already be used in patients with mild to moderate renal impairment.

Based on this information, and as discussed in section II.A of this response, we grant in part the Cornell Petitioners' request to modify the CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS sections of the labeling to indicate that metformin is safe for use in some patients with moderate renal impairment. However, as discussed in section II.A.3 above, we agree with the Yale Petitioners' proposal to use eGFRs to estimate renal function, and thus, we deny the Cornell Petitioners' request that CrCl be the metric to gauge renal function.⁸⁷ As explained in section II.A, we are requiring the metformin application holders to revise the metformin labeling to modify the CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS sections of the labeling so that the eGFR is used as a measurement of renal impairment because this metric more accurately reflects renal function and is easily calculated in clinical laboratories using equations that include further defining factors such as the patient's weight and sex. These labeling revisions will indicate that metformin is safe for use in some patients with moderate renal insufficiency while retaining a contraindication against metformin use in patients with severe renal insufficiency.

3. *Revisions to the Labeling Related to Iodinated Contrast Exposure
Contraindications and Precautions*

Metformin currently is contraindicated in individuals who are undergoing radiological studies involving administration of iodinated contrast materials because use of such products may result in the individual's acute alteration of renal function and has been associated with lactic acidosis in patients receiving metformin. The current metformin labeling states that when patients are undergoing radiological studies involving administration of iodinated contrast materials, metformin should be temporarily discontinued at the time of or prior to the radiological procedure, withheld for 48 hours subsequent to the procedure, and reinstated only after the patient's renal function has been reevaluated and found to be normal.⁸⁸

The Cornell Petitioners request that we revise the CONTRAINDICATIONS and PRECAUTIONS sections of the metformin labeling related to metformin use with iodinated

⁸⁷ Vander's Renal Physiology, Chapter 3 in Access Medicine.

⁸⁸ See, e.g., Glucophage labeling, supra note 6, at 20 and Fortamet labeling, supra note 7, at 11.

contrast exposure. Specifically, the Cornell Petitioners request that we:

- Revise the last block of text in the Contraindication section to read “[metformin] . . . should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials who have a creatinine clearance < 60 ml/min, because use of such products may result in acute alteration of renal function.
- Revise the Precautions section on “Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contracts materials)” to read “[metformin] should be temporarily discontinued in patients with a creatinine clearance < 60 mL/min who are undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal functions (see CONTRAINDICATIONS). Therefore, in patients in whom any such study is planned and who have a creatinine clearance < 60 mL/min, [metformin] should be temporarily discontinued at the time of or prior to the procedure and withheld for 48 hours subsequent to the procedure. Creatinine clearance should be re-evaluated prior to restarting metformin.⁸⁹

As explained below, we grant in part the Cornell Petitioners’ request to revise the labeling related to metformin use in patients with iodinated contrast exposure.

a. The Incidence of Contrast-Induced Nephropathy⁹⁰ and Lactic Acidosis in Patients With Normal Renal Function

In support of their request, the Cornell Petitioners state that the incidence of CIN in diabetic patients with normal renal function who undergo a procedure involving contrast media is no different than the incidence of CIN in the non-diabetic population.⁹¹ The Cornell Petitioners also say that there is no evidence of an elevated risk of CIN or lactic acidosis in patients with a normal baseline renal function who receive contrast media while taking metformin.⁹²

We disagree with the Cornell Petitioners’ statement that the incidence of CIN in diabetic patients with normal renal function who undergo a procedure involving contrast media is no different than the incidence of CIN in the non-diabetic population. The Cornell Petitioners cite only one study to support their claim, which was a review article from 2006 written by one of the

⁸⁹ Cornell Petition at 2.

⁹⁰ *Contrast-induced nephropathy* (CIN) is a widely used term referring to a patient’s reduction in renal function induced by the administration of contrast media. CIN occurs within three days following iodinated contrast media administration, and the decrement in renal function is typically defined by either of two metrics: (1) an increase of SCr by 0.5 mg/dL or (2) a more than 25percent increase in creatinine from baseline. The first metric is more sensitive for detecting CIN in patients with advanced renal impairment, whereas the second metric is more sensitive for detecting CIN in patients with better baseline kidney function.

⁹¹ Cornell Petition at 9.

⁹² Id.

petitioners (Dr. Michael Rudnick, University of Pennsylvania).⁹³ In that article, the authors quoted two earlier studies: their own review paper from 1994 and their own clinical trial from 1995, which was among the studies we reviewed. However, the Cornell Petitioners do not address other studies that examined diabetes as a risk factor for CIN in patients without baseline CKD, which included one randomized clinical trial⁹⁴ and six observational studies⁹⁵ with results that do not support the Cornell Petitioners' statement. Some of these six studies included multivariate analyses of the role of diabetes in CIN stratified by baseline CKD.

Review studies and guidelines written by the European Society of Urogenital Radiology (ESUR)⁹⁶ and by the Contrast-Induced Nephropathy Consensus Working Panel,⁹⁷ looked at the role of diabetes as a risk factor for CIN in patients without baseline CKD and concluded that it is unclear whether the risk for CIN is significantly increased in patients with diabetes who do not have renal impairment. They also considered the role of diabetes as a risk multiplier where diabetes amplifies the risk for CIN only in patients with reduced renal function. These conclusions seem at odds with the evidence reviewed by FDA that suggests an increased risk for CIN in diabetic patients without baseline CKD.

The Cornell Petitioners also say that the recommendations by the American College of Radiology (ACR) on metformin use and SCr testing associated with iodinated contrast examinations are contrary to FDA's recommendations.⁹⁸ We agree that ACR's recommendations and FDA's currently approved labeling for metformin differ on this issue. For example, ACR recommends that, in patients with normal renal function and no known comorbidities, there is neither a need to discontinue metformin prior to administering intravenous iodinated contrast media nor a need to check creatinine levels following the test or

⁹³ See Cornell Petition at 9, note 58 (citing Rudnick, MR, et al., 2006, Contrast-Induced Nephropathy: How it Develops, How to Prevent it, Cleve Clin J Med, 73(1):75-80 and 83-87).

⁹⁴ See Rudnick, MR, et al., 1995, Nephrotoxicity of Ionic and Nonionic Contrast Media in 1196 Patients: A Randomized Trial. The Iohexol Cooperative Study, Kidney Int, 47:254-61.

⁹⁵ See: (1) Chong, E, et al., 2009, Diabetic Patients With Normal Baseline Renal Function Are at Increased Risk of Developing Contrast-Induced Nephropathy Post-Percutaneous Coronary Intervention, Singapore Med J, 50:250-254; (2) Lindsay, J, et al., 2003, Percutaneous Coronary Intervention-Associated Nephropathy Foreshadows Increased Risk of Late Adverse Events in Patients With Normal Baseline Serum Creatinine, Catheter Cardiovasc Interv, 59:338-43; (3) Lautin, EM, et al., 1991, Radiocontrast-Associated Renal Dysfunction: Incidence and Risk Factors, AJR Am J Roentgenol, 157:49-58; (4) Dangas, G, et al., 2005, Contrast-Induced Nephropathy After Percutaneous Coronary Interventions in Relation to Chronic Kidney Disease and Hemodynamic Variables, Am J Cardiol, 95:13-9; (5) Rihal, CS, et al., 2002, Incidence and Prognostic Importance of Acute Renal Failure After Percutaneous Coronary Intervention, Circulation, 105:2259-64; and (6) Chong, E, et al., 2010, Risk Factors and Clinical Outcomes for Contrast-Induced Nephropathy After Percutaneous Coronary Intervention in Patients With Normal Serum Creatinine, Ann Acad Med Singapore, 39:374-80.

⁹⁶ Cornell Petition at 9, note 66 (citing Stacul F, et al., 2011, Contrast Induced Nephropathy: Updated ESUR Contrast Media Safety Committee Guidelines, Eur Radiol, 21(12):2527-41 (Stacul, 2011)).

⁹⁷ McCullough, PA, et al., 2006, Risk Prediction of Contrast-Induced Nephropathy, Am J Cardiol;98:27K-36K; McCullough, PA, et al., 2006, Contrast-Induced Nephropathy (CIN) Consensus Working Panel: Executive summary, Rev Cardiovasc Med, 7:177-97.

⁹⁸ Cornell Petition at 9.

procedure before instructing the patient to resume metformin after 48 hours.⁹⁹ The current metformin labeling states that metformin should be temporarily discontinued at the time of or prior to a procedure involving contrast media, withheld for 48 hours subsequent to the procedure, and reinstated only after the patient's renal function has been reevaluated and found to be normal. The differences in ACR's recommendations and the FDA-approved metformin labeling stem from FDA's understanding of metformin's kinetics when FDA approved metformin in 1994¹⁰⁰ and when FDA approved the labeling updates in 1998.¹⁰¹

The Cornell Petitioners note that the ACR's

position is still more conservative than [some] international recommendations, including those of the Royal Australian and New Zealand College of Radiologists (RANZCR), [the] Royal College of Radiologists (RCR), [the] Canadian Association of Radiologists (CAR), and [the] ESUR, which state that metformin need not be discontinued at all in patients with normal renal function.¹⁰²

The Cornell Petitioners state that this "gap between the current metformin labeling and the recommendations of professional societies is due primarily to a lack of evidence to support the recommendations in the labeling."¹⁰³ They say that the "only available data are case reports and analyses of case series analyses, and these reports show no evidence of elevated risk of CIN or lactic acidosis in patients with *normal* baseline renal function who receive contrast media while also taking metformin."¹⁰⁴

Based upon the information we examined, we agree that there is no evidence of elevated risk of CIN or lactic acidosis in patients with normal baseline renal function who receive iodinated contrast media while also taking metformin. The most relevant studies on this issue have been analyzed by Goergen,¹⁰⁵ and have not provided evidence for an increased risk of metformin-

⁹⁹ American College of Radiology, 2015, ACR Manual on Contrast Media, Version 10.1, available at <http://www.acr.org/quality-safety/resources/~media/37D84428BF1D4E1B9A3A2918DA9E27A3.pdf>.

¹⁰⁰ The original package insert stated that metformin should be stopped for 48 hours before and 48 hours after contrast administration and that metformin should be restarted only after SCr had been measured and found to be normal.

¹⁰¹ In 1998, the package insert was approved by the FDA stating that metformin should be withheld only for 48 hours following iodinated contrast media administration.

¹⁰² Cornell Petition at 9.

¹⁰³ Id.

¹⁰⁴ Id.

¹⁰⁵ The "lack of evidence" mentioned in the Cornell Petition (Cornell Petition at 9) is highlighted in a publication by Goergen, which was cited in the Cornell Petition (see Cornell Petition at 9-10, note 62). In that article, Goergen states that "[s]ubstantial inconsistencies exist between the recommendations of the five international guidelines [that is, the guidelines by the ACR, the RANZCR, the RCR, the CAR, and the ESUR] about contrast medium administration in patients who are taking metformin. These are, in part, caused by the low level of evidence underpinning guideline recommendations." Goergen, SK, 2010, Systematic Review of Current Guidelines, and Their Evidence Base, on Risk of Lactic Acidosis After Administration of Contrast Medium for Patients Receiving Metformin, *Radiology*, 254(1):261-269.

associated lactic acidosis or CIN in patients on metformin without baseline CKD.

Two possible cases without contraindications to metformin or other risk factors for metformin associated lactic acidosis were found.¹⁰⁶ However, for these two cases we were either unable to retrieve the data or the level of detail provided¹⁰⁷ was insufficient to rule out confounding factors that could have contributed to metformin-associated lactic acidosis. In publications by McCartney and Nawaz, we are aware of 19 cases of metformin-associated lactic acidosis in patients with baseline CKD who were administered iodinated contrast media.¹⁰⁸

We also searched the FDA Adverse Event Reporting System for more metformin-associated lactic acidosis cases. The nine relevant cases we found consist of reports from the publications listed above and from patients with renal compromise or other contraindications to metformin. In addition, a pharmacologic study provides additional limited data suggesting metformin does not accumulate following iodinated contrast media administration.¹⁰⁹

In sum, the limited pharmacologic study cited above and the relative rarity of published metformin-associated lactic acidosis reports in patients without CKD compared with more numerous cases reported in the literature about patients with CKD following iodinated contrast media administration provides some support regarding the minimal risk of metformin-associated lactic acidosis in patients without CKD undergoing intravenous iodinated contrast media administration.

However, the guidelines referenced in the Goergen article did not agree on certain recommendations, such as the need to stop taking metformin after iodinated contrast media administration, the risk of metformin-associated lactic acidosis in patients with normal renal function before iodinated contrast media administration, and the necessity of retesting renal function in patients with normal baseline function before restarting metformin. We note that the Goergen article was published in 2010 and that these guidelines continue to undergo revision. The guidelines cited in the Goergen article may not reflect the current guidelines.

¹⁰⁶ Westberg G., 1995, Withdraw metformin prior to contrast radiography. A warning in the Fass was forgotten, two patients died, Lakartidningen, 92:2520; Barbare JC, Gripon P, Ricome JL, et al., 1981, Metformin induced lactic acidosis. Two new cases (author's transl)]. Sem Hop, 57:586-7. Another case reported on a 47-year old male in India with normal renal function who had an emergency cerebral angiogram. Prabhahar, H, 2007, Metformin-Associated Lactic Acidosis Following Contrast Media-Induced Nephrotoxicity, European Journal of Anaesthesiology, 25:165-167.

¹⁰⁷ See referenced review articles, McCartney MM, Gilbert FJ, Murchison LE, et al., 1999, Metformin and contrast media--a dangerous combination? Clin Radiol, 54:29-33 (McCartney 1999); Stades AM, Heikens JT, Erkelens DW, et al., 2004, Metformin and lactic acidosis: cause or coincidence? A review of case reports. J Intern Med, 255:179-87.

¹⁰⁸ See Nawaz S, Cleveland T, Gaines PA, et al., 1998, Clinical risk associated with contrast angiography in metformin treated patients: a clinical review. Clin Radiol, 53:342-4; and McCartney 1999, supra note 107; see also Cornell Petition at 9 and 10, notes 68 and 69 (citing McCartney and Nawaz S, respectively).

¹⁰⁹ Radwan, MA, et al., 2011, Monitoring Metformin in Cardiac Patients Exposed to Contrast Media Using Ultra-High-Performance Liquid Chromatography Tandem Mass-Spectroscopy, Ther Drug Monit, 33(6):742-749. This study, although reassuring, does not provide information on metformin accumulation concomitantly with the development of CIN or in patients with other important conditions such as liver dysfunction or congestive heart failure.

b. Specific Cut-Points for Renal Function in Patients Who Will Receive Contrast Media

The Cornell Petitioners state that in patients with normal renal function, the incidence of CIN is less than 1 to 2 percent.¹¹⁰ They say that the most severe cases of CIN are seen in diabetic patients with advanced renal impairment because diabetes exacerbates the effect of impaired renal function on CIN.¹¹¹ The Cornell Petitioners recommend that FDA (1) advise providers to measure SCr in patients who will receive contrast media and to withhold metformin at the time of contrast media use only in patients with a CrCL < 60 mL/min and (2) recommend retesting of renal function only in patients with a CrCL < 60 mL/min at baseline.¹¹²

We do not agree with the Cornell Petitioners that metformin should only be withheld in patients with a baseline CrCl < 60 mL/min. We believe that only withholding metformin from patients with a CrCl < 60 mL/min might not be adequate because it neither considers comorbidities that may exist among diabetic patients nor the possibility that intra-arterial iodinated contrast media administration may carry a higher risk of CIN than that associated with intravenous iodinated contrast media. Though baseline renal dysfunction is a major predictor of CIN, other factors (e.g., the patient's level of hydration, the patient's diuretic use, the type of contrast media used, or the volume of contrast media used) also contribute to CIN. Notably, diabetes mellitus itself is considered to be a risk factor for the development of CIN.¹¹³ None of these factors alone is perfectly predictive.

We also do not agree that a retesting of renal function should occur only in patients with a baseline CrCl < 60 mL/min. As discussed above, baseline renal dysfunction is only one of several risk factors for the development of CIN, and the absence of one factor does not confer complete protection from developing CIN. Given both the concern of adverse events with metformin use in patients with renal dysfunction and the possibility of reduced renal function following contrast media administration, patients' resumption of metformin without reevaluating their renal function could be perilous for them.

Moreover, although the Cornell Petitioners' request that FDA recommend retesting of renal function only in patients with a CrCL < 60 mL/min at baseline may be applicable to diabetic patients on metformin who are otherwise healthy, this measurement cannot be accepted as the only criteria to retest renal function. Patients with a CrCl < 60 mL/min should be tested for renal function because the incidence of CIN increases with diminished renal function. And, as mentioned above, other conditions such as liver dysfunction or heart failure should be considered as reasons to retest renal function post iodinated contrast media administration.

The Cornell Petitioners also state that there is no evidence to support either a retesting of renal function or a temporary discontinuation of metformin in patients with normal baseline renal

¹¹⁰ Cornell Petition at 9.

¹¹¹ Id.

¹¹² Id. at 10.

¹¹³ Stacul, 2001, *supra* note 96.

function.¹¹⁴ The Cornell Petitioners say that such retesting or discontinuation causes disruptions in clinical workflow and would entail the risk that patients fail to recommence metformin, which would worsen the patient's blood glucose control and risk of diabetic complications.¹¹⁵

We agree that there is a lack of evidence to support either retesting of renal function or temporary discontinuation of metformin in patients with normal baseline renal function. Thus, we recognize that the metformin labeling could be revised to better explain how providers should consider temporary discontinuation of metformin with retesting of renal function for only certain patients, specifically patients who have comorbidities that increase the risk for CIN, such as congestive heart failure, receipt of concomitant nephrotoxic drugs and liver dysfunction.

We also agree that temporary discontinuation of metformin creates a temporary disruption in clinical care/workflow. However, this result would be true of withholding treatment for any chronic condition and is not unique to metformin or to diabetes. We also agree that this temporary discontinuation entails some risk of failing to recommence metformin therapy. However, many factors impact medication adherence. Additionally, failing to recommence metformin seems unlikely given that patients with diabetes mellitus should have regular follow-ups, especially after exposure to contrast media. At these follow-up visits, failure to recommence metformin or worsened glycemic control should be easily detected by the health care provider.¹¹⁶

Based on the information we reviewed and as explained in section II.A of this response, we believe that an eGFR-based measurement of renal function, as well as other clinical factors such as significant concomitant diseases (like liver or heart disease), should be considered when determining whether to suspend treatment with metformin at the time of iodinated contrast imaging.

We consider this information to be *new safety information*, as defined in section 505-1(b)(3) of the FD&C Act. Accordingly, the letters we have issued to the metformin application holders under section 505(o)(4) of the FD&C Act requiring eGFR-based revisions to the metformin labeling also include revisions to address this new safety information. Specifically, we have notified the metformin application holders that the PRECAUTIONS section of the metformin labeling regarding radiological studies involving the use of intravascular iodinated contrast materials should be revised to state:

- PRECAUTIONS. *Radiological studies with contrast* - Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an

¹¹⁴ Cornell Petition at 10.

¹¹⁵ Id.

¹¹⁶ We agree that there would be worsening of blood glucose control with the discontinuation of metformin, but we do not agree that this increases the risk of diabetic complications. As discussed above, it is unlikely that failure to recommence metformin would go unnoticed, so the worsened blood glucose control would be temporary. Nearly all diabetes-related complications are due to chronic poor glycemic control, which should not be the case once therapy is resumed. Return of prior glycemic control would return the risk of developing long-term diabetes-related complications to the patient's previous risk.

acute decrease in renal function and the occurrence of lactic acidosis. Stop [metformin] 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 m²); in patients with a history of hepatic impairment, alcoholism, or heart failure; and in patients that will be administered intra-arterial iodinated contrasts. Reevaluate the patient's eGFR 48 hours after the imaging procedure, and restart [metformin] if renal function is stable.

As explained above, these letters were issued based on our authority with respect to safety labeling changes under section 505(o)(4) of the Act and will follow the process described in section II.A.3 of this response.

III. CONCLUSION

For the reasons explained above, the Metformin Petitions are granted in part and denied in part.

Sincerely,

A handwritten signature in blue ink, appearing to read "Janet Woodcock" followed by "FDA".

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research