Yale University

Section of Endocrinology

School of Medicine
Fitkin 110
P.O. Box 208020
New Haven, CT 06520

Campus Address:
FMP 110
Tel: (203) 737-4853
Fax: (203) 737-2999

Email: kasia.lipska@yale.edu

May 2nd, 2016

Division of Dockets Management,
Food and Drug Administration,
Department of Health and Human Services, rm. 1-23,
5630 Fishers Lane, rm. 1061,
Rockville, MD 20852

Petition for Reconsideration

The undersigned submits this petition for reconsideration of the decision of the Commissioner of Food and Drugs in Docket No. **FDA-2013-P-0298**.

A. Decision involved

The Commissioner issued several revisions to the labeling of metformin:

- 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 eGFR <30 mL/min/1.73m2;
    3. Initiation of metformin is not recommended in patients with an eGFR between 30-45 mL/min/1.73m2;
    4. Obtain an eGFR at least annually in all patients taking metformin. In patients at risk for development of renal impairment (e.g., elderly), renal function should be assessed more frequently; and

5. In patients taking metformin whose eGFR falls below 45 mL/min/1.73m2, assess the benefit and risk of continuing therapy.

B. Action requested

We request that the PRECAUTIONS section specifically recommend use of a lower dose of metformin (up to half maximum dose, i.e., up to 500 mg of metformin twice daily) and monitoring of renal function frequently (every 3 months) in patients with an eGFR between 30-45 mL/min/1.73m2 – as originally recommended in the Citizen's Petition. We feel that the omission of the dose adjustment in renal impairment raises safety concerns.

C. Statement of grounds

Knowledge of kidney function is important for dosage of all medications that are excreted by the kidneys. In general, Food and Drug Administration (FDA) approved drug labeling guides provide adjustments of drug dosages for patients with impaired kidney function. Drugs that are excreted by the kidneys usually require such an adjustment.

Since metformin is eliminated predominantly by the kidneys and since both lactate and metformin levels accumulate with severe renal impairment, dose adjustment is required in the case of metformin. The Commissioner agrees that eGFR should be used to guide use of metformin. Further, the Commissioner agrees that metformin use in patients with eGFR <30 mL/min/1.73m^2 should be contraindicated. We would like to suggest that in patients with lesser degrees of renal impairment (an eGFR between 30-45 mL/min/1.73m^2), dose adjustment is necessary. In these patients, creatinine clearance is compromised to some degree. This suggests that both metformin and lactate are eliminated less efficiently. Continuing full dose of metformin with this degree of renal dysfunction may therefore increase metformin accumulation and the risk of lactic acidosis.

In the U.K., the National Institute for Health and Clinical Excellence (NICE) guidelines generally allow use of metformin down to an eGFR of 30 ml/min, but with dose reduction advised at 45 ml/min.

Likewise, we recommended similar dose reduction at this eGFR cut off given the concerns over less efficient clearance of both metformin and lactate.

We acknowledge that evidence with regards to dosing of metformin is limited. There is no clear definition of its therapeutic concentration available to date. Until more data are available, we suggest that a cautious approach of reduced dosing of metformin is likely to be the safest. This approach is congruent with dose adjustment for most other drugs excreted by the kidneys.

Kasia J Lipska, MD MHS
Assistant Professor of Medicine
Yale School of Medicine
Department of Internal Medicine
Section of Endocrinology and Metabolism
PO Box 208020
New Haven, CT 06520-8020
Telephone: 203-737-4853

Silvio E Inzucchi, MD
Professor of Medicine
Director, Yale Diabetes Center
Yale School of Medicine
Department of Internal Medicine
Section of Endocrinology and Metabolism
PO Box 208020
New Haven, CT 06520-8020
Telephone: 203-737-1932