KOMBIGLYZE XR- Metformin FDA Drug Safety Communication

Background[1]

- On April 8th 2016, the Food and Drug Administration (FDA) issued a Drug Safety Communication announcing a revision of warnings regarding the use of metformin in patients with reduced kidney function.
- The FDA is requiring labeling changes for metformin-containing medicines to expand metformin's use in certain patients with reduced kidney function. The currently approved labeling strongly recommends against the use of metformin in patients with renal impairment.
- After a review of numerous medical studies regarding the safety of metformin use in patients with mild to moderate renal impairment, the FDA is requiring changes to the labeling of all metformincontaining medicines to indicate that these products may be used safely in patients with mild to moderate renal impairment.
- AstraZeneca will work closely with the FDA on updates to the Prescribing Information for KOMBIGLYZE XR.
- Since the manufacturer has the most complete information on its products, you may wish to contact the manufacturer of metformin, or other metformin-containing medicines, for more information regarding their products.
- For more information, please refer to the FDA Drug Safety Communication available at: http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm.

Relevant Labeling Information[2]

Please refer to the KOMBIGLYZE XR Prescribing Information for further product information including Boxed Warning and Warnings and Precautions.

Boxed Warning

WARNING: LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation.

The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure.

The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress.

Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate.

If acidosis is suspected, KOMBIGLYZE XR should be discontinued and the patient hospitalized immediately.

Contraindications
KOMBIGLYZE XR is contraindicated in patients with:
• Renal impairment (e.g., serum creatinine levels ≥1.5 mg/dL for men, ≥1.4 mg/dL for women, or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction (MI), and septicemia.

Warnings and Precautions
Assessment of Renal Function
Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic
acidosis increases with the degree of impairment of renal function. Therefore, KOMBIGLYZE XR is
contraindicated in patients with renal impairment.
Before initiation of KOMBIGLYZE XR, and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal impairment is anticipated (e.g.,
elderly), renal function should be assessed more frequently and KOMBIGLYZE XR discontinued if evidence of renal impairment is present.

Reporting of Postmarketing Adverse Events
It is AstraZeneca policy to provide adverse event information to health care professionals from the labeling information, the published literature, and clinical trial data for our marketed products. Key findings from the clinical trials, including safety information, form the basis for the labeling information.
We generally do not provide specific adverse event information from the AstraZeneca Safety database
because of the inherent limitations of spontaneous reports.
Such limitations include, but are not limited to adverse event recognition, underreporting, reporting biases, estimates of patient exposure, report quality, and lack of established causality of reported adverse
events
The safety profile of each AstraZeneca product is continuously monitored, and the labeling information is
updated whenever new safety issues are identified.

Adverse Event Reporting
In order to monitor the safety of our products we encourage clinicians to report suspected adverse events to AstraZeneca at mail to: FarmacovigilanciaChile@astrazeneca.com

Reference(s):
1 US Food and Drug Administration. FDA Drug Safety Communication: FDA revises warnings regarding use of thediabetes medicine metformin in certain patients with reduced kidney function. http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm. Accessed April 5, 2016.
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