Letter on Failure to Warn U.S. Doctors and Patients of Zoledronic Acid (Reclast) Dangers

March 10, 2011

Margaret A. Hamburg, M.D.

Commissioner

Food and Drug Administration

Department of Health and Human Services

WO 2200

10903 New Hampshire Avenue

Silver Spring, MD 20993-0002

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research

Food and Drug Administration

Department of Health and Human Services

WO51/Room 6133

10903 New Hampshire Avenue

Silver Spring, MD 20993-0002

Dear Drs. Hamburg and Woodcock,

On October 12, 2010, Novartis, presumably at the behest of the Canadian government, issued a " Dear Health Care Professional Letter" alerting Canadian physicians and other healthcare providers about the link between the osteoporosis drug Aclasta (zoledronic acid) and renal dysfunction, including acute renal failure requiring dialysis which in some cases resulted in a fatal outcome.[1] A similar " Public Communication" was issued on October 14, 2010 alerting Canadian consumers.[2] However, in the five months since then, the Food and Drug Administration (FDA) has failed to take similar action requiring Novartis to alert physicians and patients in the United States (U.S.) about the growing evidence linking Reclast (the U.S. name for zoledronic acid, identical to Canadian Aclasta) to this serious, life-threatening adverse event.

We therefore urge the FDA to immediately require that Novartis issue a similar " Dear Doctor Letter" to all physicians in the U.S.

According to the FDA-approved label, Reclast is administered as a 5 mg infusion once a year for treatment of osteoporosis in postmenopausal women and men and for the prevention of glucocorticoid-induced osteoporosis, and once every two years for prevention of osteoporosis in postmenopausal women.[3] Novartis reported in October 2010 that more than one million infusions of Aclasta (zoledronic acid) had been administered worldwide for the treatment of early to advanced bone loss.[4]

Novartis' s October 12, 2010 " Dear Health Care Professional" letter reported the following:

> The ACLASTA Product Monograph, has been revised to further emphasize precautions that should be taken into account to minimize the risk of renal adverse reactions:
>
> - ACLASTA has been associated with renal dysfunction manifested as deterioration in renal function and in rare cases, acute renal failure.
> - Renal impairment has been observed following the administration of ACLASTA, occasionally after a single administration.
> - Renal failure requiring dialysis or with a fatal outcome has occurred especially in patients with history of renal impairment or other risk factors. Risk factors include advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy or dehydration occurring after ACLASTA administration.
>
> As of April 30, 2010 Novartis has received 265 spontaneous reports of renal impairment following administration of ACLASTA, corresponding to a reporting rate of approximately 20 cases per 100,000 patient-years of exposure.
>
> The following precautions should be taken to minimize the risk of renal adverse reactions:
>
> - ACLASTA should not be used in patients with severe renal impairment (creatinine clearance <30 mL/min).
> - ACLASTA should be used with caution when concomitantly used with other drugs that could impact renal function.
> - Creatinine clearance should be calculated (e.g., Cockcroft-Gault formula) before each treatment with ACLASTA followed by periodic monitoring of serum creatinine in

patients with risk factors. Transient increase in serum creatinine may be greater in patients with underlying impaired renal function.

- Patients should be appropriately hydrated (500 mL or 2 glasses of water) prior to and following administration of ACLASTA, especially elderly patients and those receiving diuretic therapy.
- A single dose of ACLASTA should not exceed 5 mg and the duration of infusion should be no less than 15 minutes.[5]

As you are aware, the FDA estimates that, at most, 10% of prescription drug adverse reactions are reported. As a result, the numbers of cases of renal dysfunction and acute renal failure reported to Novartis for zoledronic acid can probably be multiplied by a factor of more than 10 to obtain an estimate closer to reality.

Clearly, the current warnings and precautions in the FDA-approved label for Reclast[6] about the risk of renal impairment are not sufficient for making physicians adequately aware of this serious, life-threatening renal toxicity associated with Reclast, the very reason that the Canadian government convinced the company to initiate the additional warnings. Many physicians in the U.S. fail to read the labels for drugs and thus are unaware of the renal toxic effects of Reclast and the precautions that must be taken to avoid such toxicity. Therefore, in order to adequately protect the public health, the FDA must immediately require that Novartis issue a " Dear Doctor Letter" to all physicians in the U.S. that communicates the same information provided to Canadian health care professionals on October 12, 2010. In addition, the FDA should issue an alert to patients in this country similar to the October 14, 2010 alert in Canada. We look forward to a prompt response to our request.

Sincerely,

Michael Carome, M.D.
Deputy Director
Sidney Wolfe, M.D.
Director
Public Citizen Health Research Group

http://www.citizen.org/hrg1936 - _ednref1[1] Novartis. Health Canada endorsed important safety information on ACLASTA (zoledronic acid). October 12, 2010. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/advisories-avis/prof/2010/aclasta_hpc-cps-eng.pdf. Accessed March 10 2011.

http://www.citizen.org/hrg1936 - _ednref2[2] Novartis. Public communication: Health Canada endorsed important safety information on ACLASTA (zoledronic acid). October 14, 2010. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/advisories-avis/public/2010/aclasta_pc-cp-eng.pdf. Accessed March 10, 2011.

http://www.citizen.org/hrg1936 - _ednref3[3] Drug label for Reclast (zoledronic acid). Updated January 2011. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021817s009lbl.pdf. Accessed March 10, 2011.

http://www.citizen.org/hrg1936 - _ednref4[4] Novartis Global Communications. Media release: long-term data show Novartis once-yearly Aclasta preserves bone mass and provides fracture protection in postmenopausal osteoporosis. http://hugin.info/134323/R/1452458/393262.pdf. Accessed March 10, 2011.

http://www.citizen.org/hrg1936 - _ednref5[5] Novartis. Health Canada endorsed important safety information on ACLASTA (zoledronic acid). October 12, 2010. http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/medeff/advisories-avis/prof/2010/aclasta_hpc-cps-eng.pdf. Accessed March 10 2011.

http://www.citizen.org/hrg1936 - _ednref6[6] Drug label for Reclast (zoledronic acid). Updated January 2011. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021817s009lbl.pdf. Accessed March 10, 2011.