Biogen

August 2018

ZINBRYTA® (daclizumab)
RE: Update Concerning Monitoring for Encephalitis After Discontinuation of Treatment

Dear Colleague,

Biogen's commitment to patient safety is our top priority. We continue to carefully monitor and report safety events as part of our on-going pharmacovigilance activities including products that have been withdrawn from the market. As such, this letter is to inform you of the following:

- **Cases of immune-mediated encephalitis, including anti- N-methyl-D- aspartate (NMDA) receptor encephalitis, have been reported in patients during treatment and also several months after discontinuation of ZINBRYTA.**
- **As of July 10, 2018, two cases of immune-mediated encephalitis, specifically anti-NMDA receptor encephalitis, occurred 14 weeks and 16 weeks after discontinuation of treatment with ZINBRYTA. These two patients presented with headache, fever, vomiting, confusion, tremor, visual disturbances and seizures.**
- **The timeframe in which development of anti-NMDA receptor encephalitis may occur after discontinuation of ZINBRYTA is unknown.**
- **All patients who have discontinued ZINBRYTA and their caregivers should be reminded to contact the patient's physician immediately if any of the common prodromal symptoms or early common behavioural, neurological, cognitive or movement-related symptoms occur.**
- **In cases where encephalitis is suspected in patients who have discontinued treatment with ZINBRYTA, the NMDA receptor antibody test in cerebrospinal fluid (CSF) and serum should be considered as early as possible to assist diagnosis.**
- **Health-care professionals should consider consulting with an expert should they suspect encephalitis in a patient who has discontinued treatment with ZINBRYTA.**

In March 2018, Biogen informed physicians that cases of immune mediated encephalitis and meningoencephalitis had been reported in patients treated with ZINBRYTA. In parallel, Biogen, in collaboration with our partner AbbVie, voluntarily withdrew the marketing application for ZINBRYTA in the United States on April 30, 2018. Physicians were advised to monitor patients at least monthly following discontinuation of the product and more frequently as clinically indicated, for up to six months after the last dose.

Biogen has recently completed a clinical assessment of encephalitis cases reported in patients treated with ZINBRYTA and concluded that immune-mediated encephalitis, including anti-NMDA receptor encephalitis, are adverse drug reactions that can be related to treatment with ZINBRYTA.

Importantly, cases of immune-mediated encephalitis and specifically anti-NMDA receptor encephalitis have been reported during treatment with ZINBRYTA as well as several months

after discontinuation of treatment with ZINBRYTA. Cases reported during treatment with ZINBRYTA included life-threatening and fatal outcomes. As of July 10, 2018, 7 cases of encephalitis have been reported after discontinuation of daclizumab and two of these cases have been confirmed. The two confirmed cases are anti-NMDA receptor encephalitis. Anti-NMDA receptor encephalitis can be diagnosed with a specific antibody test in cerebrospinal fluid and serum in the appropriate clinical setting.

If cases of encephalitis are suspected in patients who have discontinued ZINBRYTA physicians are advised to consider:

- Performing NMDA receptor antibody tests in cerebrospinal fluid and serum
- Consult with an expert

Healthcare providers and patients are encouraged to report suspected adverse events in patients who have taken ZINBRYTA to Biogen at 1-800-456-2255. You are also encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Should you have questions regarding ZINBRYTA, please reach out to your MSL or Biogen Medical Information at 1-866-633-4636.

Sincerely,

Alfred Sandrock, M.D., Ph.D.
EVP, Chief Medical Officer