DRAFT APPEAL LETTER - ZINBRYTA (DACLIZUMAB)

Dear ______________:

This is *(select from below)*

- an appeal for re-consideration of your denial for coverage
- a request for an exception to your formulary exclusion

of my prescription for Zinbryta (Daclizumab) for my patient (*___insert patients’ name_______*) who has a diagnosis of relapsing remitting multiple sclerosis. Zinbryta is FDA approved for the treatment of relapsing forms of MS, is administered through subcutaneous injections every four weeks, and is only available to patients enrolled in a Risk Evaluation and Mitigation Strategy (REMS) program to ensure early detection of side effects and safety concerns. Both my patient and I believe Zinbryta offers the greatest likelihood of clinical benefit at this time, and that *(she/he)* is an appropriate candidate for this treatment.

**Justify your recommendation of Daclizumab for this patient at this time with details based on one or more of the following:**

- Inadequate results of at least two prior treatments, including dates of initiation and termination, patient reported and clinical outcomes, test results, other
- Known contraindications that preclude the use of another approved disease modifying treatment
- Patient’s inability to tolerate treatment regimen and/or side effects of treatment alternatives, including comments on adherence, side effects, psycho-social factors or other

Further, I can attest that my patient understands and accepts the potential risks associated with this treatment. We have discussed them, the requirements of the REMS program and need for monitoring including frequent liver enzyme checks and possibly others. *She/He* will be enrolled in the REMS program.

Daclizumab is a laboratory-created monoclonal antibody that targets a docking site (receptor) for a key immune signaling chemical called interleukin-2 (IL-2). IL-2 is required to activate the immune T cells that are involved in MS attacks. By blocking the receptor, daclizumab inhibits certain inflammatory functions of T cells. Daclizumab also increases important immune cells that help regulate the immune system. These cells are able to enter the brain and spinal cord and modulate MS inflammation.

Zinbryta was tested in a Phase 3 study involving 1,841 people with relapsing-remitting MS, which showed that Zinbryta reduced the rate of relapses by 45% and also reduced disease activity observed on MRI scans over the course of 144 weeks (nearly 3 years) compared to Avonex® (interferon beta-1a, Biogen). Known as the DECIDE trial, participants in this study were randomly assigned to receive either
150 mg Zinbryta injected under the skin every 4 weeks, or Avonex injected once weekly, for up to 144 weeks. Participants also received placebo versions of Avonex or Zinbryta as a control measure. The study was led by Ludwig Kappos, MD (University Hospital, Basel, Switzerland), and the results were published in the New England Journal of Medicine (2015; 373:1418-142).

Zinbryta was also tested in a Phase 2 study involving more than 400 people with relapsing-remitting MS. Over one year, one-third of the participants received a lower dose of Zinbryta (150mg), one-third received a higher dose (300 mg), and one-third received inactive placebo. Results suggested that the lower dose of Zinbryta reduced the relapse rate by 54% compared to the placebo. The results of this study were published in The Lancet (Volume 381, No. 9884, p2167–2175, 22 June 2013).

For a comprehensive overview of the available evidence on the MS Disease Modifying Therapies and their implications for treatment, I urge you to review ‘These of Disease Modifying Therapies in Multiple Sclerosis: Principles and Current Evidence’ by the MS Coalition.

Thank you for your consideration, and please feel free to contact me for additional information about this patient and treatment recommendation.

Sincerely,

XXXX, MD

Recommended enclosures: most recent lab, MRI or other tests and clinical notes
Abstracts -- Zinbryta


**Daclizumab HYP versus Interferon Beta-1a in Relapsing Multiple Sclerosis.**


**BACKGROUND:**
Daclizumab high-yield process (HYP) is a humanized monoclonal antibody that binds to CD25 (alpha subunit of the interleukin-2 receptor) and modulates interleukin-2 signaling. Abnormalities in interleukin-2 signaling have been implicated in the pathogenesis of multiple sclerosis and other autoimmune disorders.

**METHODS:**
We conducted a randomized, double-blind, active-controlled, phase 3 study involving 1841 patients with relapsing-remitting multiple sclerosis to compare daclizumab HYP, administered subcutaneously at a dose of 150 mg every 4 weeks, with interferon beta-1a, administered intramuscularly at a dose of 30 μg once weekly, for up to 144 weeks. The primary end point was the annualized relapse rate.

**RESULTS:**
The annualized relapse rate was lower with daclizumab HYP than with interferon beta-1a (0.22 vs. 0.39; 45% lower rate with daclizumab HYP; P<0.001). The number of new or newly enlarged hyperintense lesions on T2-weighted magnetic resonance imaging (MRI) over a period of 96 weeks was lower with daclizumab HYP than with interferon beta-1a (4.3 vs. 9.4; 54% lower number of lesions with daclizumab HYP; P<0.001). At week 144, the estimated incidence of disability progression confirmed at 12 weeks was 16% with daclizumab HYP and 20% with interferon beta-1a (P=0.16). Serious adverse events, excluding relapse of multiple sclerosis, were reported in 15% of the patients in the daclizumab HYP group and in 10% of those in the interferon beta-1a group. Infections were more common in the daclizumab HYP group than in the interferon beta-1a group (in 65% vs. 57% of the patients, including serious infection in 4% vs. 2%), as were cutaneous events such as rash or eczema (in 37% vs. 19%, including serious events in 2% vs. <1%) and elevations in liver aminotransferase levels that were more than 5 times the upper limit of the normal range (in 6% vs. 3%).

**CONCLUSIONS:**
Among patients with relapsing-remitting multiple sclerosis, daclizumab HYP showed efficacy superior to that of interferon beta-1a with regard to the annualized relapse rate and lesions, as assessed by means of MRI, but was not associated with a significantly lower risk of disability progression confirmed at 12 weeks. The rates of infection, rash, and abnormalities on liver-function testing were higher with daclizumab HYP than with interferon beta-1a. (Funded by Biogen and AbbVie Biotherapeutics; DECIIDE ClinicalTrials.gov number, NCT01064401.)

PMID:
Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial.


BACKGROUND:
Daclizumab, a humanised monoclonal antibody, modulates interleukin-2 signalling by blocking the α subunit (CD25) of the interleukin-2 receptor. We assessed whether daclizumab high-yield process (HYP) would be effective when given as monotherapy for a 1 year treatment period in patients with relapsing-remitting multiple sclerosis.

METHODS:
We did a randomised, double-blind, placebo-controlled trial at 76 centres in the Czech Republic, Germany, Hungary, India, Poland, Russia, Ukraine, Turkey, and the UK between Feb 15, 2008, and May 14, 2010. Patients aged 18–55 years with relapsing-remitting multiple sclerosis were randomly assigned (1:1:1), via a central interactive voice response system, to subcutaneous injections of daclizumab HYP 150 mg or 300 mg, or placebo, every 4 weeks for 52 weeks. Patients and study personnel were masked to treatment assignment, except for the site pharmacist who prepared the study drug for injection, but had no interaction with the patient. The primary endpoint was annualised relapse rate. Analysis was by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT00390221.

FINDINGS:
204 patients were assigned to receive placebo, 208 to daclizumab HYP 150 mg, and 209 to daclizumab HYP 300 mg, of whom 188 (92%), 192 (92%), and 197 (94%), respectively, completed follow-up to week 52. The annualised relapse rate was lower for patients given daclizumab HYP 150 mg (0.21, 95% CI 0.16–0.29; 54% reduction, 95% CI 33–68%; p<0.0001) or 300 mg (0.23, 0.17–0.31, 50% reduction, 28–65%; p=0.00015) than for those given placebo (0.46, 0.37–0.57). More patients were relapse free in the daclizumab HYP 150 mg (81%) and 300 mg (80%) groups than in the placebo group (64%; p<0.0001 in the 150 mg group and p=0.0003 in the 300 mg group). 12 (6%) patients in the placebo group, 15 (7%) of those in the daclizumab 150 mg group, and 19 (9%)
in the 300 mg group had serious adverse events excluding multiple sclerosis relapse. One patient given daclizumab HYP 150 mg who was recovering from a serious rash died because of local complication of a psoas abscess.

**INTERPRETATION:**
Subcutaneous daclizumab HYP administered every 4 weeks led to clinically important effects on multiple sclerosis disease activity during 1 year of treatment. Our findings support the potential for daclizumab HYP to offer an additional treatment option for relapsing-remitting disease.

**FUNDING:**
Biogen Idec and AbbVie Biotherapeutics Inc.

Copyright © 2013 Elsevier Ltd. All rights reserved.

**Comment in**
- [Anti-interleukin-2 receptor alpha for multiple sclerosis?](Lancet. 2013)