

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

DACLIZUMAB (ZINBRYTA — BIOGEN CANADA INC.)

Indication: Relapsing-Remitting Multiple Sclerosis

RECOMMENDATION:

The Canadian Drug Expert Committee (CDEC) recommends that daclizumab be reimbursed for the treatment of adult patients with active relapsing-remitting multiple sclerosis (RRMS) who have had an inadequate response to, or who are unable to tolerate, one or more therapies indicated for the treatment of multiple sclerosis, if the following conditions are met:

Conditions:

- Patient under the care of a specialist with experience in the diagnosis and management of RRMS.
- Reduction in price of at least 25%.

Since the original issuance of this document on June 20, 2017, the manufacturer has voluntarily withdrawn Zinbryta (daclizumab) from the Canadian market and Health Canada has indicated that market authorization will be discontinued (March 16, 2018).

Service Line: CADTH Drug Reimbursement Recommendation
Version: 1.0
Publication Date: June 2017
Report Length: 7 Pages

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Recommendation:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that daclizumab be reimbursed for the treatment of adult patients with active relapsing-remitting multiple sclerosis (RRMS) who have had an inadequate response to, or who are unable to tolerate, one or more therapies indicated for the treatment of multiple sclerosis, if the following conditions are met:

Conditions:

- Patient under the care of a specialist with experience in the diagnosis and management of RRMS.
- Reduction in price of at least 25%.

Reasons for the Recommendation:

1. Two randomized controlled trials (RCTs) demonstrated that daclizumab statistically significantly decreased the annualized relapse rate (ARR) in patients with RRMS compared with interferon (IFN) beta-1a 30 µg intramuscularly once weekly (Avonex) (DECIDE trial [N = 1,841; rate ratio 0.461; 95% confidence interval (CI), 0.318 to 0.668 over 96 to 144 weeks]), and compared with placebo (SELECT trial [N = 621; rate ratio 0.550; 95% CI, 0.469 to 0.645 over 52 weeks]). Statistically significantly greater proportions of patients treated with daclizumab as compared with IFN beta-1a and placebo were relapse-free at the end of both studies.
2. There is insufficient evidence to determine if daclizumab offers any meaningful clinical benefits more than other disease-modifying therapies for RRMS. Limitations associated with the two indirect comparisons (one unpublished manufacturer-provided and one published) reviewed by the CADTH Common Drug Review (CDR) precluded any definitive conclusions regarding the comparative efficacy and safety advantages of daclizumab to other disease-modifying options for RRMS.
3. The manufacturer-submitted price of daclizumab is \$2,308 per 150 mg pre-filled pen or syringe, giving an annual cost of \$27,700. Based on CDR re-analyses to account for limitations in the manufacturer's economic model, alemtuzumab dominates all therapies including daclizumab in that it is associated with lower total costs and greater quality-adjusted life-years (QALYs). The probability that daclizumab is cost-effective given an incremental cost-utility ratio (ICUR) of \$50,000 per QALY was 0%. Re-analysis limiting comparators to fingolimod, glatiramer acetate, dimethyl fumarate, and teriflunomide suggested the probability that daclizumab would be cost-effective at an ICUR of \$50,000 per QALY was 1.9%.

Of Note:

Based on the CDR re-analyses, a price reduction of 25% would be needed in order to achieve a cost per QALY of \$50,000, as compared with fingolimod, glatiramer acetate, dimethyl fumarate, and teriflunomide, irrespective of whether the interferons were included. CDEC noted that this percentage reduction may need to be greater once the pricing of subsequent entry glatiramer becomes available.

Discussion Points:

- The Health Canada indication for daclizumab states it should be used second-line or later. Most patients enrolled in SELECT and almost half of those enrolled in DECIDE were RRMS treatment-naïve. A subgroup analysis based on prior therapy implies that the magnitude of relative reduction in ARR with daclizumab versus placebo or IFN beta-1a may be somewhat larger among treatment-naïve patients as compared with patients who had received prior RRMS therapies. However, the subgroups were likely underpowered to draw any conclusions.
- DECIDE was the only study that enrolled patients from Canada and the US; results of subgroup analyses based on geographic regions, although not pre-specified for the CDR review, showed that the ARR was not statistically significantly different in the region of the US and Canada between treatment groups. The relatively small sample size in this region may to some extent explain the finding. Therefore, this likely reduces the generalizability of the results to RRMS patients in Canada.

- Serious adverse events and withdrawal due to adverse events were more common among patients treated with daclizumab versus IFN beta-1a or placebo, after excluding MS relapse events. These events among daclizumab-treated patients were most frequently related to infections, skin disorders, and hepatobiliary abnormalities. The product monograph for daclizumab recommends monitoring transaminase levels and total bilirubin monthly for six months after the last dose of daclizumab. CDEC noted that the burden of regular monitoring may impact the acceptability of daclizumab for patients and clinicians.
- A number of scales or questionnaires, such as disease-specific ones and ones in generic health-related quality of life assessment tools, were used in the DECIDE and SELECT trials to explore the quality of life benefits of the study drug. Although statistical significance was achieved for between-group differences for many of these outcome measures in both studies, the clinical relevance remains uncertain because of the lack of an estimated minimal clinically important difference for many of the scales, or a lack of demonstrated validation of the scale for a RRMS population.
- Fatigue and productivity were not directly evaluated in the included RCTs, although they were identified as important clinical outcomes by the patient group.
- Direct comparisons of daclizumab with other disease-modifying therapies (with the exception of IFN beta-1a) recommended for patients with inadequate response to prior therapies for RRMS are lacking. A network meta-analysis (NMA) was submitted to CDR by the manufacturer; however, methodological issues and significant heterogeneity across the included clinical trials limit the ability to draw conclusions regarding the comparative efficacy and safety of daclizumab.

Background:

Daclizumab is a monoclonal antibody that binds the alpha-subunit of the interleukin (IL)-2 receptor, CD25, and modulates IL-2 signalling. It is indicated for the treatment of adult patients with active RRMS who have had an inadequate response to, or who are unable to tolerate, one or more therapies indicated for the treatment of multiple sclerosis. Daclizumab is available as a solution for injection as 150 mg/mL in pre-filled pen or pre-filled syringe. The recommended dose of daclizumab is 150 mg injected subcutaneously once a month.

Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a systematic review of RCTs of daclizumab and a critique of the manufacturer's pharmacoeconomic evaluation and patient group-submitted information about outcomes and issues important to patients.

Patient Input Information

The following is a summary of key information provided by one patient group that responded to the CDR call for patient input:

- Multiple sclerosis is characterized by symptoms that have a detrimental impact on patients' lives: fatigue, difficulty walking, visual impairment, cognitive difficulties, depression, bladder problems, and pain. In addition, patients can also experience issues with balance, sexual dysfunction, spasticity, tremor, weakness, difficulties with speaking and swallowing, and medication-related side effects.
- Many patients are unable to maintain full-time employment status or to attend school. Multiple sclerosis can seriously affect patients' ability to participate in physical activities, recreational life, and interpersonal relationships. Family commitments can also be interfered with.
- Current disease-modifying therapies for multiple sclerosis reduce the ARR, slow disability progression, and reduce the number of new or enhanced lesions. Because of the various clinical effectiveness and safety profiles and routes of administration of the current drug therapies, patients expect more treatment options so that they can find one that best suits them.

Clinical Trials

The systematic review included two double-blind, RCTs of adult patients with active RRMS. DECIDE (N = 1,841) was a phase III active-controlled RCT that assessed the superiority of daclizumab to interferon beta-1a. Patients were randomized to receive daclizumab 150 mg subcutaneously once every four weeks or interferon beta-1a 30 µg intramuscularly once a week over a period of 96 to 144 weeks. SELECT (N = 621) was a dose ranging, phase II placebo-controlled trial that evaluated the efficacy and safety of

subcutaneous daclizumab 150 mg and 300 mg once every four weeks compared with placebo over 52 weeks. In both trials, patients were either treatment-naïve or had received prior disease-modifying therapies for multiple sclerosis.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Relapse — defined as new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination. Relapses were measured by ARR.
- Disease progression — defined as at least a 1.0-point increase on the Expanded Disability Status Scale (EDSS) from a baseline EDSS ≥ 1.0 sustained for 12 weeks to 24 weeks, or a ≥ 1.5 -point increase on the EDSS from a baseline EDSS of 0 sustained for 12 weeks to 24 weeks. The EDSS is an ordinal scale (0 to 10) that assesses eight functional systems: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral total, and cerebral mentation. Higher EDSS scores indicate more severe disability.
- Health-related quality of life — assessed using the disease-specific questionnaires (the Multiple Sclerosis Impact Scale-29 [MSIS-29] and the Multiple Sclerosis Functional Composite [MSFC]) and generic questionnaires (the 12-item Short Form Health Survey [SF-12] and the EuroQol 5-Dimensions [EQ-5D]).
 - MSIS-29: This questionnaire is used to examine the physical and psychological impact of multiple sclerosis and consists of 20 physical items and 9 psychological items. The Physical Impact Score and Psychological Impact Score are generated. Higher impact scores indicate greater impact of the disease on daily function and negative change indicates improvement.
 - MSFC: This questionnaire is used to assess multiple sclerosis disability from three dimensions: arm/hand function (with the nine-hole peg test), leg function/ambulation (with timed-25-foot walk), and cognitive function (with the Paced Auditory Serial Addition Test). An overall MSFC score (z-score) is calculated based on the scores of the three component measures. A positive change in the composite z-score indicates improvement.
- Serious adverse events, total adverse events, and withdrawal due to adverse events.

The change in ARR between baseline and study end points was the primary outcome measure in both trials.

Efficacy

DECIDE, compared with interferon beta-1a:

- The adjusted ARR was statistically significantly lower in the daclizumab group versus the IFN beta-1a group; rate ratio 0.55 (95% CI, 0.47 to 0.65). The difference between the two treatment groups was considered clinically meaningful.
- Over 96 to 144 weeks, the proportion of patients with confirmed disability progression sustained for 12 weeks was 16% lower for the daclizumab group compared with the IFN beta-1a group (between-group difference was not statistically significant; hazard ratio 0.84 [95% CI, 0.66 to 1.07]); the proportion of patients with confirmed disability progression sustained for 24 weeks was 27% lower (difference was statistically significant; hazard ratio 0.73 [95% CI, 0.55 to 0.98]) for the daclizumab group.
- The mean changes from baseline in EDSS score were -0.02 at Week 96 (standard deviation [SD], 0.70) to -0.03 at Week 144 (SD 0.86) in the daclizumab group and -0.01 (SD 0.78) to -0.03 (SD 0.92) in the IFN beta-1a group. The between-group difference was not statistically significant at Week 96, and a between-group comparison at Week 144 was not reported.
- The mean change from baseline in the MSIS-29 Physical Impact Score was statistically significantly lower in the daclizumab group versus the IFN beta-1a group (between-group difference -2.09 points; 95% CI, -3.32 to -0.86 , $P = 0.0008$). The difference was not considered clinically important.
- The mean change from baseline in MSFC z-score was statistically significantly lower in the daclizumab group (0.09) compared with the IFN beta-1a (0.05), $P = 0.0007$; however, the clinical relevance of the between-group difference was uncertain.

SELECT, compared with placebo:

- The adjusted ARR was statistically significantly lower in the daclizumab group versus placebo; rate ratio 0.46 (95% confidence interval [CI], 0.32 to 0.67). The difference between the two treatment groups was considered clinically meaningful.
- Over 52 weeks, the proportion of patients with confirmed disability progression sustained for 12 weeks was 57% lower for the daclizumab group compared with the placebo group (hazard ratio 0.43 [95% CI, 0.21 to 0.88]); the proportion of patients with

confirmed disability progression sustained for 24 weeks was 76% lower (difference was statistically significant; hazard ratio 0.24 [95% CI, 0.09 to 0.63]) for the daclizumab group.

- The mean changes from baseline in EDSS score were -0.08 at Week 52 (SD 0.52) in the daclizumab group and 0.09 (SD 0.71) in the placebo group. The between-group difference was not reported, although a P value of 0.0102 for the between-group comparison was reported.
- The mean change from baseline in the MSIS-29 Physical Impact Score was statistically significantly lower in the daclizumab group versus placebo group (between-group difference -4.27 ; 95% CI, -6.76 to -1.78 , $P = 0.0008$). The difference was not considered clinically important.

Harms (Safety and Tolerability)

- The overall adverse event rates were similar between daclizumab (91%) and IFN beta-1a (91%) in DECIDE, and between daclizumab (73%) and placebo (79%) in SELECT. In general, a higher frequency of patients treated with daclizumab experienced infection-related adverse events, while a higher proportion of patients treated with IFN beta-1a reported influenza-like illness. Common adverse events with daclizumab included nasopharyngitis (14% to 25%), headache (10% to 17%), upper respiratory tract infection (9% to 16%), and pyrexia (3% to 11%).
- The frequency of serious adverse events was higher in the daclizumab group than in the IFN beta-1a group or placebo group at study end, after excluding RRMS relapse events (DECIDE: 15% daclizumab versus 10% IFN beta-1a; SELECT: 7% daclizumab versus 6% placebo).
- More patients in the daclizumab group withdrew from treatment due to an adverse event compared with IFN beta-1a or placebo (DECIDE: 15% daclizumab versus 12% IFN beta-1a; SELECT: 3% daclizumab versus < 1% placebo).
- In both studies, treatment with daclizumab 150 mg was associated with higher frequency of hepatobiliary abnormalities, skin reactions, depression, serious infection, and lymphadenopathy, compared with IFN beta-1a or placebo.
- In DECIDE, one death in the daclizumab group and four deaths in the interferon beta-1a group were reported, and none of them was considered to be treatment-related, while in SELECT, one death was reported in the daclizumab group, and it was considered to be treatment-related.

Cost and Cost-Effectiveness

Daclizumab is available at the manufacturer's submitted price of \$2,308 per 150 mg/1 mL pre-filled syringe or pen solution for subcutaneous injection. At the recommended dose of 150 mg monthly, daclizumab costs \$27,700 per year.

The manufacturer submitted a cost-utility analysis comparing daclizumab to fingolimod for the treatment of adult patients with RRMS. Further comparisons were made with IFN beta-1 formulations (Avonex, Betaferon, Extavia, Rebif), biologics [alemtuzumab and natalizumab] and other injectable and oral disease-modifying therapies (glatiramer acetate, dimethyl fumarate, and teriflunomide). The analysis was based on a Markov state-transition model with a 25-year time horizon and was undertaken from the public health care payer perspective. The effects of treatment on disease progression and relapse rates were derived from a manufacturer-commissioned NMA. The manufacturer reported that compared with fingolimod, daclizumab was dominant (i.e., more effective and less costly).

CDR identified the following key limitations with the manufacturer's economic submission:

- The failure to present the results in a sequential manner, considering all relevant comparators in the base case. Presenting results solely compared with fingolimod provides a misleading assessment of daclizumab's cost-effectiveness in the treatment of RRMS.
- The submitted model lacked transparency and was challenging to validate.
- Certain assumptions relating to monitoring and administration costs did not appear appropriate for the Canadian setting, but are unlikely to significantly affect the results.

Using the manufacturer's base-case analysis, while daclizumab dominates fingolimod (daclizumab is more effective and less costly), it is dominated by alemtuzumab (daclizumab is more costly and less effective) and is associated with an incremental cost greater than \$50,000 per QALY when compared with all interferon formulations, glatiramer, dimethyl fumarate, and teriflunomide.

Further CDR re-analyses were conducted considering all moderately or modestly effective therapies (i.e., excluding alemtuzumab and natalizumab). Daclizumab was not cost-effective unless a decision-maker was willing to pay at least \$174,026 per QALY gained when compared with glatiramer, teriflunomide, and interferons.

When considering all comparators, a price reduction of 83% would be required for daclizumab to achieve an ICUR of \$50,000 per QALY. When excluding the highly effective therapies (natalizumab and alemtuzumab), a price reduction of 25% would be required for daclizumab to achieve an ICUR of \$50,000 per QALY, regardless of whether the interferons were included as relevant comparators. Of note, the required price reductions may be more substantial with the inclusion of subsequent entry non-biologic glatiramer recently approved by Health Canada.

CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeyesundera.

May 17, 2017 Meeting

Regrets:

One CDEC member did not attend.

Conflicts of Interest:

None