Formulary Drug Reviews

Daclizumab

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Each month, subscribers to *The Formulary Monograph Service* receive 5 to 6 well-documented monographs on drugs that are newly released or are in late phase 3 trials. The monographs are targeted to Pharmacy & Therapeutics Committees. Subscribers also receive monthly 1-page summary monographs on agents that are useful for agendas and pharmacy/nursing in-services. A comprehensive target drug utilization evaluation/medication use evaluation (DUE/MUE) is also provided each month. With a subscription, the monographs are available online to subscribers. Monographs can be customized to meet the needs of a facility. Through the cooperation of *The Formulary*, *Hospital Pharmacy* publishes selected reviews in this column. For more information about *The Formulary Monograph Service*, contact Wolters Kluwer customer service at 866-397-3433. The December 2016 monograph topics are ozenoxacin cream, ocrelizumab, naldemedine, eteplirsen, and abaloparatide. The Safety MUE is on buprenorphine buccal.

Generic Name:	Daclizumab
Proprietary Name:	Zinbryta (Biogen Idec, AbbVie, Inc.)
Approval Rating:	1
Therapeutic Class:	Anti-CD25 Humanized Monoclonal Antibodies
Similar Drugs:	Basiliximab
Sound- or Look-Alike Names:	Daclatasvir, Daratumumab, Dinutuximab, Eculizumab

INDICATIONS

In 1997, the US Food and Drug Administration (FDA) approved daclizumab (*Zenapax*; Roche) for prophylaxis of acute organ rejection in renal transplant patients, but the product was discontinued in 2009.^{1,2} In 2016, a new version of the drug, daclizumab high-yield process, was approved for the treatment of adult patients with relapsing forms of multiple sclerosis (MS). Daclizumab high-yield process will be discussed in this monograph.

Because of its safety profile, daclizumab should generally be reserved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of MS.^{3,4}

Daclizumab is also being studied in patients with high-inflammatory MS.⁵

CLINICAL PHARMACOLOGY

Daclizumab high-yield process is similar to daclizumab in that it has the same sequence of amino acids, but it differs in the final glycosylation modifications. Daclizumab high-yield process is associated with decreased antibody-dependent cellular cytotoxicity activity compared with daclizumab.⁶

Daclizumab is a humanized monoclonal antibody of immunoglobulin G1 (IgG1). Daclizumab is composed of 2 humanized gamma-1 heavy chains and 2 humanized kappa light chains, with a molecular weight of approximately 144 kDa.^{3,7} It binds to the Tac epitope on the alpha subunit (CD25) of the interleukin 2 (IL-2) receptor.^{3,6-9} CD25 is constitutively expressed at high levels on CD4⁺ CD25⁺ FoxP3⁺ regulatory T cells and at low levels on resting T cells. CD25 expression is upregulated in resting T cells after they become activated, which allows for a greater capacity for IL-2 to bind.^{3,7} IL-2 signaling is required for these T cells to proliferate and survive.⁷ Daclizumab masks the IL-2 binding site on the low- and high-affinity IL-2 receptor, thereby inhibiting the activation and proliferation of T cells.^{7,10} The efficacy of daclizumab may also be attributable to its

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ability to remove CD25 from the surfaces of T cells via monocyte-dependent trogocytosis (transfer of plasma membrane fragments).¹⁰ In vitro studies show that daclizumab minimally affects CD4⁺ and CD8⁺ T-cell concentrations.¹¹

Under normal physiology, regulatory T cells suppress the activity of effector T cells (eg, CD4⁺ and CD8⁺ T cells).⁷ However, in the presence of daclizumab, IL-2 is unable to stimulate regulatory T cells to induce apoptosis in effector T cells.⁷ Additionally, daclizumab reduces the proliferation and impairs the suppressive capability of CD4⁺ regulatory T cells.¹²⁻¹⁴ However, the decrease in regulatory T cells does not impact daclizumab's ability to decrease inflammation in the brain.¹²

The proliferation of CD56^{bright} natural killer (NK) cells is regulated by IL-2.^{7,11,13,15} Because daclizumab blocks IL-2 from binding to T cells, there is more opportunity for IL-2 binding on CD56^{bright} NK cells via the beta subunit (CD122) of the IL-2 receptor.^{6,7,8,9,11,14} Thus, daclizumab dramatically increases CD56^{bright} NK cell concentrations, and this expansion of CD56^{bright} NK cells is associated with reduced inflammation in the brain.^{11,13,15-17} CD56^{bright} NK cells migrate to areas with inflammatory lesions, such as the central nervous system (CNS), and kill activated T cells.⁷ Patients expressing more CD122 on CD56^{bright} NK cells at baseline had fewer new or enlarged gadolinium-enhancing lesions after 8 weeks and up to 24 weeks of daclizumab therapy.¹⁵ Additionally, a retrospective study showed that atrophy of brain tissue was decreased in patients treated with daclizumab.¹⁸

CD56^{bright} NK cells specifically target and kill activated T cells by degranulation and by releasing granzymes, particularly granzyme K. Daclizumab therapy enhances the release of granzyme K from CD56^{bright} NK cells into activated T cells. By contrast, CD56^{bright} NK cells do not trigger resting T cells to undergo cell death via this caspase-independent pathway.¹⁹ Thus, only the survival of activated T cells is diminished in the presence of CD56^{bright} NK cells.^{6,11,19}

Daclizumab also inhibits the activation and proliferation of T cells by blocking dendritic cells from presenting IL-2 to resting T cells.^{6,7,20} Patients with MS tend to have high circulating levels of lymphoid tissue inducer cells. In the presence of daclizumab, IL-2 signals shift hematopoietic stem cells from producing lymphoid tissue inducer cells to producing more CD56^{bright} NK cells.^{6,7,8,21} However, some studies

indicate that lymphoid tissue inducer cell concentrations are not significantly reduced with exposure to daclizumab.¹⁷

PHARMACOKINETICS

The maximum serum concentration (C_{max}) of daclizumab occurred between 5 and 7 days after a single subcutaneous injection. At steady state, daclizumab mean C_{max} was 30 mcg/mL, minimum serum concentration (C_{min}) was 15 mcg/mL, and area under the curve over the dosing interval (AUC_{tau}) was approximately 640 mcg•day/mL. The absolute bioavailability of subcutaneous daclizumab 150 mg was approximately 90%.³

At steady state, C_{max} is 31.5 mcg/mL and AUC is 13.4 mg•h/mL, based on pharmacokinetic modeling of healthy volunteer data. Administration of daclizumab once every 4 weeks is expected to produce a steady-state accumulation ratio of approximately 1.9.²² Clearance of daclizumab is 10 mL/h, and the volume of distribution is 6.4 L. The bioavailability of daclizumab is 84%.^{22,23} The half-life of daclizumab is long, ranging from 21 to 25 days.²² The estimated steady-state volume of distribution is 6.34 L.³

Pharmacokinetic parameters of daclizumab are similar in patients with relapsing-remitting MS: C_{max} is 29.1 mcg/mL, AUC is 15.3 mg•h/mL, AUC accumulation ratio is approximately 2.5, clearance is 8.8 mL/h, bioavailability is 88%, and elimination half-life is about 22 days.^{24,25}

COMPARATIVE EFFICACY

Indication: Relapsing-Remitting Multiple Sclerosis

Guidelines

Guideline: Recommendations for drug therapies for relapsing-remitting multiple sclerosis

Reference: Canadian Agency for Drugs and Technologies in Health (CADTH), 2013²⁶

Comments: The recommended first-line therapy for patients with relapsing-remitting MS is glatiramer acetate or interferon beta-1b (interferon beta-1b is less expensive than interferon beta-1a). Patients failing or having a contraindication to glatiramer acetate therapy should be started on interferon beta-1b therapy, and patients failing or having a contraindication to interferon beta-1b therapy should be started on glatiramer acetate therapy. Second-line therapy options include dimethyl fumarate, fingolimod, and natalizumab. Consider cost and specific safety profiles

when choosing second-line therapy. Combination therapy is not recommended for patients with relapsing-remitting MS. Alemtuzumab and teriflunomide are mentioned in the guideline but were not approved for use in Canada, so no formal recommendations were provided. Daclizumab is not mentioned in this guideline.

Studies

Drug: Daclizumab vs Placebo

Reference: Gold R, et al, 2013 (SELECT trial)^{6,27-29}

Study Design: Randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multicenter, international study

Study Funding: Biogen Idec, AbbVie Biotherapeutics

Patients: 621 patients 18 to 55 years of age with relapsing-remitting MS. All patients had an Expanded Disability Status Scale (EDSS) score of 5 or lower and had experienced at least 1 MS relapse within 12 months of the study or 1 new gadolinium-enhancing lesion on brain MRI within 6 weeks of study. At baseline, average patient age was 35.7 years, 64.7% of patients were women, 96.5% were White, 76% had no previous exposure to MS therapy (except steroids), and 43.5% had at least 1 gadolinium-enhancing lesion. Other average baseline characteristics included time since diagnosis of 2 to 3 years (range, 1-7 years), 1.3 relapses in the past year, EDSS score of 2.7, 1.8 gadolinium-enhancing lesions, and 40 T2 hyperintense lesions. Exclusion criteria were primary progressive, secondary progressive, or progressive relapsing MS; history of malignancy; known hypersensitivity to daclizumab; or previous exposure to the following medications or procedures: daclizumab, cladribine, mitoxantrone, T-cell or T-cell receptor vaccine, monoclonal antibodies (except natalizumab or rituximab), or total lymphoid irradiation; cyclophosphamide or rituximab within 1 year of the study; cytapheresis within 6 months of the study; live vaccination, glatiramer acetate, interferon beta, or interferon alpha within 3 months of the study; or exposure to corticosteroids, 4-aminopyridine, or related drugs within 30 days of the study. Of the 621 patients, 600 comprised the primary analysis population (modified intention-to-treat [mITT]), and all 621 patients comprised the intention-to-treat (ITT) population used for sensitivity analyses.

Intervention: Patients were randomized 1:1:1 with concealed allocation to receive subcutaneous daclizumab 300 mg (mITT, $n = 203$; ITT, $n = 209$), daclizumab 150 mg (mITT, $n = 201$; ITT, $n = 208$), or placebo (mITT, $n = 196$; ITT, $n = 204$) once every 4 weeks for 13 doses over a total of 52 weeks. After the last dose of study treatment, patients were followed for an additional 20 weeks.

Results

Primary Endpoint(s)

- Daclizumab was associated with a lower annualized relapse rate at week 52 compared to placebo: 0.23 (95% confidence interval [CI], 0.17 to 0.31; $p < .001$) with daclizumab 300 mg, 0.21 (95% CI, 0.16 to 0.29; $p < .001$) with daclizumab 150 mg, and 0.46 (95% CI, 0.37 to 0.57) with placebo. The lower relapse rates corresponded to fewer patients relapsing with daclizumab therapy than with placebo: 20% ($p < .001$) of patients treated with daclizumab 300 mg and 19% ($p < .001$) of patients treated with daclizumab 150 mg experienced a relapse by week 52 compared to 36% of patients treated with placebo. The number needed to treat (NNT) was 7 for daclizumab 300 mg and 6 for daclizumab 150 mg.

Secondary Endpoint(s)

- The average total number of new gadolinium-enhancing lesions at week 52 from baseline was decreased with daclizumab compared with placebo: 0.2 lesions with daclizumab 300 mg (odds ratio [OR], 0.12; 95% CI, 0.07 to 0.2; $p < .001$), 0.3 lesions with daclizumab 150 mg (OR, 0.15; 95% CI, 0.09 to 0.25; $p < .001$), and 1.4 lesions with placebo. The average number of new gadolinium-enhancing lesions was similarly reduced with daclizumab therapy compared with placebo when the timeframe was restricted to weeks 8 to 24. Post hoc analyses showed that fewer of the new gadolinium-enhancing lesions detected at week 24 evolved into T1 hypointense lesions by week 52 with daclizumab than with placebo.³⁰
- The average total number of new or newly enlarged T2 hyperintense lesions at week 52 was reduced with daclizumab compared with placebo: 1.7 lesions (95% CI, 1.4 to 2.2) with daclizumab 300 mg (percentage reduction of 79%; 95% CI, 71.3% to 84.2%; $p < .001$), 2.4 lesions (95% CI, 2 to 3) with daclizumab

150 mg (percentage reduction of 70%; 95% CI, 59.4% to 77.9%; $p < .001$), and 8.1 lesions (95% CI, 6.7 to 9.9) with placebo.

- There were fewer patients with confirmed disability progression at week 52 in the daclizumab 150 mg group compared to placebo; however, because daclizumab 300 mg did not show statistical improvement compared to placebo, the significant difference with daclizumab 150 mg was considered nominal.

Endpoint(s)

- Percentage differences in T1 hypointense lesion volume changes and in T2 hyperintense lesion volume changes at week 52 from baseline were significantly reduced with daclizumab compared with placebo ($p < .001$ for each comparison vs placebo).
- There were no significant differences in whole brain volume changes at week 52 from baseline with daclizumab compared with placebo.
- Quality of life was assessed using the EuroQoL visual analog scale, the EuroQoL 5 Dimensions (EQ-5D) health survey, the 12-item Short-Form Health Survey, and the Multiple Sclerosis Impact Scale (MSIS-29) psychological impact subscale. Daclizumab 300 mg did not significantly improve quality of life according to these scales, except for the EuroQoL visual analog scale. This finding was confirmed in a separate, exploratory post hoc study focused on patient-reported outcomes.³¹
- CD56^{bright} NK cells were increased with daclizumab exposure compared with placebo. However, plasma levels of B cells, CD4⁺ T cells, and CD8⁺ T cells were decreased with exposure to daclizumab compared with placebo. The ratio of CD4⁺ to CD8⁺ T cells remained constant regardless of treatment arm.
- Percentage of patients experiencing at least 1 adverse event up to 20 weeks after therapy was 75.8% (471 of 621 patients). Common adverse events observed in at least 5% of patients treated with daclizumab included relapse, nasopharyngitis, headache, upper respiratory tract infection, pharyngitis, oral herpes, and rash. Serious adverse events occurred more commonly in the daclizumab groups than with placebo, and the majority of these consisted of infection or rash. One death occurred in a patient from the daclizumab 150 mg group who was recovering from a serious rash. More patients treated with daclizumab had abnormal liver enzyme

laboratory values (greater than 5 times the upper limit of normal [ULN]) than did patients treated with placebo. Injection-site reactions occurred similarly across all treatment groups.

- Six patients presented with transient neutralizing anti-daclizumab antibodies; only 1 patient showed evidence of neutralizing anti-daclizumab antibodies at 52 weeks.

Comments: Exposure to daclizumab once every 4 weeks decreased the rate of relapse in patients with relapsing-remitting MS. More patients in the daclizumab groups were free of MS activity (ie, no relapse, no confirmed disability progression, no new or enlarged T2 hyperintense lesions, and no new gadolinium-enhancing lesions by week 52) than were patients in the placebo group.²⁸ Completion rates were similar across all treatment groups: 91.9% with daclizumab 300 mg, 90.9% with daclizumab 150 mg, and 91.2% with placebo. All endpoints were analyzed using the mITT population, and a sensitivity analysis used the ITT population. The mITT population excluded 21 patients from 1 study site that failed to provide patients with correct doses of study drugs due to a systematic error. This study used a sequential statistical analysis: if daclizumab 300 mg was statistically different from placebo, the same analysis was conducted for daclizumab 150 mg. Thus, although quality-of-life endpoints were significantly improved with daclizumab 150 mg, they were not considered significant because these endpoints were not significantly improved with daclizumab 300 mg. If other MS drugs were used as rescue therapy, relapse and follow-up data were censored for the primary mITT analysis population. A subgroup analysis showed that daclizumab reduced the rate of relapse and number of new T2 hyperintense lesions in patients with highly active relapsing-remitting MS, as well as for patients with less active relapsing-remitting MS.²⁷ Patients who completed this study were invited to enroll in a 12-month extension study (SELECTION).⁸

Limitations: At baseline, patients in the daclizumab 300 mg group had a lower average number of T2 hyperintense and gadolinium-enhancing lesions compared to those in the daclizumab 150 mg group and the placebo group. This study was not conducted in the United States; patients were recruited from the Czech Republic, Germany, Hungary, India, Poland, Russia, Turkey, Ukraine, and the United Kingdom.

Reference: Giovannoni G, et al, 2014 (SELECTION trial)^{8,32}

Study Design: Randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multicenter, international extension study (extension of the 52-week study)

Study Funding: Biogen Idec, AbbVie Biotherapeutics

Patients: 517 of the 621 patients with relapsing-remitting MS who completed the 52-week parent study (SELECT) were enrolled in this 52-week extension study. At baseline, average patient age was 35.8 years, 63.1% of patients were female, 96.5% were White, and 35% had at least 1 gadolinium-enhancing lesion. Other average baseline characteristics included time since diagnosis of 4 years, 1.3 relapses in the past year, 1.6 gadolinium-enhancing lesions, 38.9 T2 hyperintense lesions, and EDSS score of 2.7. All 517 patients comprised the ITT population used to analyze safety data and 424 patients comprised the mITT population used to analyze efficacy data and immunogenicity data. Patients were excluded if they had discontinued therapy during the parent study (unless the discontinued drug was placebo), if they were receiving other treatment for MS (except interferon beta therapy), or if they were unwilling to use contraception during the study and for 4 months after their last dose of study drug.

Intervention: Patients treated with daclizumab in the parent study were randomized 1:1 with concealed allocation to continue on the daclizumab dose to which they were randomized in SELECT ("continuation group," $n = 173$) for another 52 weeks (ie, until week 104), or to first receive placebo for 20 weeks and then continue on the daclizumab dose to which they were randomized in SELECT ("washout/reinitiation group," $n = 174$) for the remaining 32 weeks (ie, until week 104). Patients treated with placebo in the parent study were randomized 1:1 with concealed allocation to receive daclizumab 300 mg ($n = 84$) or daclizumab 150 mg ($n = 86$) once every 4 weeks for 52 weeks ("initiation group," $n = 170$). The last dose of the parent study (SELECT) was given at week 48, and the first dose of the extension study (SELECTION) was given at week 52.

Results

Primary Endpoint(s)

- Percentages of patients experiencing at least 1 adverse event were similar across all treatment groups (range, 66% to 81%). Common adverse

events observed in at least 10% of patients in any treatment group included relapse, nasopharyngitis, and upper respiratory tract infection. Serious adverse events included infection (eg, bronchitis) and rash (eg, eczema). One death occurred in the washout/reinitiation group (300 mg). The cause of death was attributed to autoimmune hepatitis, but it is unclear if daclizumab contributed. Liver enzyme laboratory values greater than 5 times the ULN and injection-site reactions occurred at similarly low rates across all treatment groups (range, 0% to 5%).

- Few patients (up to 2%) tested positive for neutralizing anti-daclizumab antibodies in all treatment groups.

Secondary Endpoint(s)

- In the continuation group, there were no significant differences in annualized relapse rate, number of new gadolinium-enhancing lesions, or number of patients with confirmed disability progression between year 1 (SELECT parent study) and year 2 (SELECTION extension study). However, the number of new or newly enlarged T2 hyperintense lesions and the volume of new T1 hypointense lesions were reduced in year 2 compared with year 1.
- In the washout/reinitiation group, annualized relapse rates during the 20 weeks of placebo and during the 32 weeks of daclizumab treatment were similar to the annualized relapse rate of the placebo group from year 1 (SELECT parent study). During the 32 weeks of daclizumab therapy, the number of new gadolinium-enhancing lesions was similar to the numbers observed in the other treatment groups at week 104. During the 20 weeks of placebo, CD56^{bright} NK cell counts decreased to baseline values of the parent study. At week 104, there was no significant difference in CD56^{bright} NK cell counts between patients in the washout/reinitiation group and those in the continuation group.
- In the initiation group, significant improvements were observed in year 2 (daclizumab therapy) compared to year 1 (placebo therapy) for all efficacy endpoints, except for total volume of T1 hypointense lesions and change in whole brain volume.

Comments: Continued exposure to daclizumab once every 4 weeks for 2 years was well tolerated. The most common adverse event was relapse, followed by nasopharyngitis and upper respiratory tract infection. The annualized relapse rate does

not appear to diminish over 2 years of continuous therapy; year 2 data were not significantly different from year 1 data. This extension study was completed by more than 80% of patients in all treatment groups (range, 80.5% to 89.3%). Safety endpoints were analyzed using the ITT population, and efficacy endpoints and immunogenicity were analyzed using the mITT population.⁶ Patients who completed this extension study were invited to enroll in another 6-year extension study (SELECTED) that is currently ongoing.³³ Interim results (at 3 to 4 years) from SELECTED ($N = 410$) indicate that the incidence of adverse events does not increase and the types of adverse events that occur do not change with long-term exposure to daclizumab.³⁴ Additionally, the annualized relapse rate and the number of new or newly enlarged T2 hyperintense lesions were similar to those in the SELECT and SELECTION studies.³⁵

Limitations: This study was not conducted in the United States; patients were recruited from the Czech Republic, Germany, Hungary, India, Poland, Russia, Turkey, Ukraine, and the United Kingdom.

Drug: Daclizumab vs Interferon Beta-1a

Reference: Kappos L, et al, 2015 (DECIDE trial)^{3,9,36}

Study Design: Randomized, double-blind, active-controlled, double-dummy, parallel-group, multicenter, international study

Study Funding: Biogen Idec, AbbVie Biotherapeutics

Patients: 1,841 patients 18 to 55 years of age with relapsing-remitting MS. Patients had an EDSS score of 5 or lower, were willing to use contraception during the study and for 4 months after their last dose of study treatment, and had experienced at least 1 MS relapse or 1 new gadolinium-enhancing lesion on MRI within 12 months of the study. At baseline, average patient age was 36.3 years, 68% of patients were female, 89.7% were White, 41.1% were previously exposed to MS therapy and 33.6% were previously exposed to interferon beta therapy, and 44.9% had at least 1 gadolinium-enhancing lesion. Other average baseline characteristics included time since diagnosis of 4.1 years, time since first symptoms of 6.9 years, 1.5 relapses in the past year, EDSS score of 2.5, MSIS-29 physical impact score of 21.7, 2.2 gadolinium-enhancing lesions, and 50.5 T2 hyperintense lesions. Exclusion criteria

were primary progressive, secondary progressive, or progressive relapsing MS; known hypersensitivity to daclizumab or interferon beta-1a; known intolerance or history of noncompliance to interferon beta therapy; history of malignancy; or previous exposure to the following medications or procedures: daclizumab, cladribine, mitoxantrone, T-cell or T-cell receptor vaccine, monoclonal antibodies (except natalizumab or rituximab), or total lymphoid irradiation; cyclophosphamide or rituximab within 1 year of the study; cytapheeresis within 6 months of the study; live vaccination, glatiramer acetate, interferon beta, or interferon alpha within 3 months of the study; or corticosteroids or glatiramer acetate within 30 days of the study. A washout period was not required for patients currently receiving interferon beta therapy, but interferon beta therapy had to be discontinued before randomization.

Intervention: Patients were randomized 1:1 in permuted blocks with concealed allocation to receive subcutaneous daclizumab 150 mg once every 4 weeks plus intramuscular placebo once every week ($n = 919$) or subcutaneous placebo once every 4 weeks plus intramuscular interferon beta-1a 30 mcg once every week ($n = 922$) for at least 96 weeks and for up to 144 weeks. Patients were stratified based on study site and history of interferon beta therapy. After the last dose of study treatment, patients were followed for an additional 180 days (about 25 weeks) for safety data collection.

Results

Primary Endpoint(s)

- Daclizumab produced a lower annualized relapse rate at week 144 compared to interferon beta-1a: 0.22 (95% CI, 0.19 to 0.24; $p < .001$) with daclizumab and 0.39 (95% CI, 0.35 to 0.44) with interferon beta-1a, corresponding to a percentage reduction of 45% (95% CI, 36% to 53%).

Secondary Endpoint(s)

- The average total number of new or newly enlarged T2 hyperintense lesions at week 96 was reduced with daclizumab compared with interferon beta-1a: 4.3 lesions (95% CI, 3.9 to 4.8; $p < .001$) with daclizumab and 9.4 lesions (95% CI, 8.5 to 10.5) with interferon beta-1a, corresponding to a percentage reduction of 54% (95% CI, 47% to 61%).

- There was no significant difference between the daclizumab group and the interferon beta-1a group in the percentage of patients with confirmed disability progression at week 144. Because daclizumab did not produce statistical improvement compared to interferon beta-1a, no statistical analyses were conducted for the remaining secondary endpoints (ie, proportion of patients without relapse by week 144, proportion of patients with an MSIS-29 physical impact score of 7.5 or higher by week 96).

Endpoint(s)

- A total of 20 tertiary endpoints were explored; however, because the study used a hierarchical statistical analysis and the second secondary endpoint was not statistically significant, nominal results of these tertiary endpoints were not reported.
- Percentage of patients experiencing at least 1 adverse event up to 180 days after therapy was 91% for both treatment groups. Common adverse events observed in at least 10% of patients in either treatment group included nasopharyngitis, headache, upper respiratory tract infection, pyrexia, injection-site pain, urinary tract infection, and influenza-like illness. There was 1 death in the daclizumab group and 4 deaths in the interferon beta-1a group; however, no death was considered related to the study drug. More serious adverse events (eg, infection, rash) occurred in the daclizumab group than in the interferon beta-1a group, and a greater number of patients in the daclizumab group discontinued the study drug due to adverse events than in the interferon beta-1a group. A separate publication that focused solely on the cutaneous adverse events confirmed that there were more cutaneous events and discontinuations due to cutaneous events in the daclizumab group compared to the interferon beta-1a group.³⁷

Comments: Daclizumab once every 4 weeks produced lower annualized relapse rates in patients with relapsing-remitting MS than therapy with interferon beta-1a. More patients in the daclizumab group had fewer new or newly enlarged T2 hyperintense lesions at week 96. Completion rates were similar between the 2 treatment groups: 75% with daclizumab and 79% with interferon beta-1a. All endpoints were analyzed using the ITT population. To maintain blinding, double-dummy placebo injections were given; patients

in the daclizumab group received intramuscular placebo injections once every week to mimic interferon beta-1a therapy, and patients in the interferon beta-1a group received subcutaneous placebo injections once every 4 weeks to mimic daclizumab therapy. Because interferon beta-1a therapy is associated with flu-like symptoms, patients were instructed to prophylactically treat for such symptoms during the first 24 weeks of the study to further maintain blinding. The study used a sequential statistical analysis with the following order of endpoints: annualized relapse rate, number of new or newly enlarged T2 hyperintense lesions, proportion of patients with confirmed progression of disability, proportion of patients without relapse, and proportion of patients with MSIS-29 physical impact score of 7.5 or higher. Daclizumab was superior to interferon beta-1a in terms of annualized relapse rate and number of new or newly enlarged T2 hyperintense lesions but was not associated with a lower risk of confirmed disability progression. As a result, no statistical analysis was conducted for the remaining endpoints. A sensitivity analysis conducted for the primary endpoint supported the significant findings of the primary ITT analysis population. This study was conducted in the United States and 27 other countries. Patients who completed this study were invited to enroll in an extension study, which is currently ongoing.³⁸

Limitations: No active comparator group was used in the study. The flu-like adverse effects of interferon therapy may have compromised blinding in some patients.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

Daclizumab is contraindicated in patients with preexisting hepatic disease or hepatic impairment, including alanine transaminase (ALT) or aspartate transaminase (AST) at least 2 times the ULN; a history of autoimmune hepatitis or other autoimmune condition involving the liver; or a history of hypersensitivity to daclizumab or any other components of the formulation.³

Warnings and Precautions

Daclizumab carries a boxed warning regarding hepatic injury, including autoimmune hepatitis and other immune-mediated disorders (eg, skin reactions,

lymphadenopathy, noninfectious colitis); these conditions may require treatment with systemic corticosteroids or immunosuppressive medications.³

Cases of life-threatening severe liver injury, including liver failure and autoimmune hepatitis, have occurred with daclizumab therapy; pretreatment and ongoing liver function test monitoring is required. If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction (eg, unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice and/or dark urine), promptly measure serum transaminases and total bilirubin and, if clinically appropriate, interrupt or discontinue treatment with daclizumab. If the patient develops autoimmune hepatitis, treatment with systemic corticosteroids and other immunosuppressant drugs may be needed, with some patients requiring long-term immunosuppression. Caution is recommended in patients who require treatment with other potentially hepatotoxic drugs, herbal products, or dietary supplements.³

Daclizumab is associated with infections (eg, bronchitis, upper respiratory tract infections, urinary tract infections, viral infections) and skin reactions (eg, rash, dermatitis, eczema, psoriatic conditions).^{3,6,8,9,37,39} Daclizumab should be avoided in patients with a severe active infection until the infection is fully controlled.³

Acute hypersensitivity reactions (eg, anaphylaxis, angioedema, urticaria) may occur after the first dose or at any time during treatment.³

Cases of depression-related events and suicidal ideation or suicide attempt have been reported. If the patient develops severe depression and/or suicidal

ideation, discontinuation of daclizumab therapy should be considered.³

Inadequate data are available regarding the safety of daclizumab during pregnancy in humans. Use in pregnant monkeys resulted in embryo-fetal death and reduced fetal growth at maternal exposures greater than 30 times those expected clinically.³

No data are available on the presence of daclizumab in human milk or its effects on the breast-feeding infant or milk production. Daclizumab is excreted in the milk of daclizumab-treated monkeys.³

Safety and effectiveness of daclizumab in patients younger than 17 years have not been established. Use of daclizumab is not recommended in pediatric patients because of the risks of hepatic injury and immune-mediated disorders.³

The efficacy and safety of daclizumab have not been sufficiently studied in patients 65 years and older.³

ADVERSE REACTIONS

In clinical trials, the most common adverse events (see **Table 1** and **Table 2**) observed in patients treated with daclizumab included nasopharyngitis, pharyngitis, headache, upper respiratory tract infection, pyrexia, oral herpes, rash, urinary tract infection, influenza-like illness, and elevated liver enzymes.^{3,6,8,9,39} The majority of serious adverse events consisted of infection or rash.^{6,8,9}

Few clinical trial patients (12% or less) presented with anti-daclizumab antibodies and neutralizing antibodies. Of patients with circulating neutralizing antibodies, some had corresponding decreases in daclizumab plasma levels.^{6,8,22}

Table 1. Adverse reactions in adults with relapsing forms of multiple sclerosis with an incidence $\geq 2\%$ more for daclizumab 150 mg subcutaneously every 4 weeks than for interferon beta-1a 30 mcg intramuscularly once weekly³

Adverse reaction	Daclizumab 150 mg (n = 919)	Interferon beta-1a 30 mcg (n = 922)
Nasopharyngitis	25%	21%
Upper respiratory tract infection	17%	14%
Rash	11%	4%
Influenza	9%	6%
Dermatitis	9%	2%
Oropharyngeal pain	8%	4%
Bronchitis	7%	5%
Eczema	5%	2%
Lymphadenopathy	5%	< 1%

Table 2. Adverse reactions in adults with relapsing forms of multiple sclerosis with an incidence $\geq 2\%$ more for daclizumab 150 mg subcutaneously every 4 weeks than for placebo³

Adverse reaction	Daclizumab (n = 208)	Placebo (n = 204)
Upper respiratory tract infection	9%	7%
Depression	7%	2%
Rash	7%	3%
Pharyngitis	6%	4%
Increased ALT	5%	2%

Note: ALT = alanine transaminase.

Adverse events associated with intravenous daclizumab exposure include infection, liver enzyme elevations, fatigue, paresthesia, GI upset, rash, fever, generalized weakness, and palindromic rheumatism.⁴⁰⁻⁴⁵ Cases of CNS vasculitis, erythematous macular rash, lymphadenopathy, and breast nodules were reported after initiating off-label intravenous daclizumab therapy in patients with MS.^{42,43,46,47}

DRUG INTERACTIONS

Daclizumab does not affect the activity of cytochrome P450 (CYP-450) 3A, 2C9, 2C19, 1A2, and 2D6 enzymes or their ability to metabolize drug substrates such as midazolam, warfarin, omeprazole, caffeine, and dextromethorphan.⁴⁸

Caution should be used when using hepatotoxic drugs, herbal products, or dietary supplements concurrently with daclizumab.³

RECOMMENDED MONITORING

Monitor MS relapse rates while the patient is receiving daclizumab.^{6,8,9}

Prior to initiation of therapy, the following tests should be completed³:

- Obtain serum transaminase (ALT and AST) and total bilirubin levels. If ALT or AST is at least 2 times the ULN or if the patient has preexisting hepatic disease or hepatic impairment, daclizumab should not be used.
- Evaluate patients at high risk for tuberculosis infection. If the patient tests positive for tuberculosis, treat the tuberculosis infection prior to initiating therapy with daclizumab. If the patient has tuberculosis or other severe active infection, therapy with daclizumab should be avoided.
- Screen patients for hepatitis B and C. Daclizumab is contraindicated in patients with preexisting hepatic disease.
- All necessary live vaccines should be administered prior to initiating daclizumab therapy. Otherwise, live vaccinations should be avoided during daclizumab therapy and for up to 4 months after discontinuation of treatment.

After initiation of therapy, the following tests should be conducted³:

- Monthly transaminase levels and total bilirubin levels should be measured prior to the next scheduled dose of daclizumab. Continue to monitor these tests for up to 6 months after the last dose of daclizumab. If liver function tests are abnormal, the recommended actions in Table 3 should be taken.

DOSING

Doses used in clinical studies for treatment of relapsing-remitting MS were daclizumab 150 mg and 300 mg subcutaneously injected once every 4 weeks.^{6,8,9} The approved dose is daclizumab 150 mg subcutaneously once monthly. Daclizumab should be injected into the thigh, abdomen, and back of the upper arm.³

Table 3. Daclizumab treatment modification for liver test abnormalities (elevated transaminases and/or total bilirubin)³

Lab value(s)	Recommendations
ALT or AST > 5 times the ULN OR	• Interrupt daclizumab therapy and investigate for other etiologies of abnormal lab value(s).
Total bilirubin > 2 times the ULN OR	• If no other etiologies are identified, discontinue daclizumab.
ALT or AST ≥ 3 times but < 5 times the ULN and total bilirubin is > 1.5 times but < 2 times the ULN	• If other etiologies are identified, reassess the overall risk-benefit profile of daclizumab for the patient and consider whether to resume daclizumab when both AST or ALT are < 2 times the ULN and total bilirubin is $\leq$ the ULN.

Note: ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal.

Daclizumab solution should be removed from the refrigerator at least 30 minutes prior to subcutaneous administration and be allowed to warm to room temperature.³ The product should not be heated using an external heat source (eg, hot water) or returned to the refrigerator after it has been warmed to room temperature.³

PRODUCT AVAILABILITY

The New Drug Application for daclizumab was accepted for review by the FDA on April 29, 2015.⁴⁹ It was approved on May 27, 2016.^{3,4}

Daclizumab is available as a 150 mg/mL sterile, preservative-free solution in a prefilled single-dose syringe. The syringe should be used only once and then placed in a sharps disposal container.³

Store daclizumab in a refrigerator between 2°C and 8°C (36°F and 46°F) in the original carton to protect it from light. The product should not be frozen or exposed to temperatures above 30°C (86°F); discard if frozen. If refrigeration is unavailable, daclizumab may be stored protected from light at up to 30°C (86°F) for a period of up to 30 days. Do not put daclizumab-containing syringes back in the refrigerator after allowing them to warm to room temperature. Discard after 30 days without refrigeration.³

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Daclizumab is only available through a restricted distribution program called the ZINBRYTA REMS Program.^{3,4}

The requirements of the ZINBRYTA REMS Program include the following³:

- Prescribers must become certified with the program by enrolling and completing training.
- Patients must enroll in the program and comply with ongoing monitoring requirements.
- Pharmacies must be certified with the program and must only dispense to patients authorized to receive daclizumab.

CONCLUSION

Daclizumab is a novel drug approved for the treatment of adult patients with relapsing forms of MS. Because of its safety profile, daclizumab should be reserved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of MS. Daclizumab is a humanized monoclonal antibody that specifically binds to the CD25 subunit of IL-2 receptors located on CD25⁺ T cells, thereby preventing

the activation and proliferation of T cells. Daclizumab activity increases circulating concentrations of CD56^{bright} NK cells, which target and kill activated T cells. It has a long half-life that allows for dosing every 4 weeks. The efficacy of daclizumab, in terms of reduced relapse rates compared with placebo or interferon beta-1a therapy, was observed at 1 year and maintained up to 3 years. Signs and symptoms of infection or rash, as well as liver function enzyme tests, should be regularly monitored.

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