CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

ETANERCEPT
(Brenzys — Merck Canada Inc.)
Indications: Rheumatoid Arthritis, Ankylosing Spondylitis

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that Brenzys (etanercept subsequent entry biologic [SEB]) be reimbursed in accordance with the Health Canada–approved indications for the treatment of rheumatoid arthritis (RA) and ankylosing spondylitis (AS), if the following clinical criterion and conditions are met:

Clinical Criterion:
- For use in patients for whom etanercept is considered to be the most appropriate treatment option.

Conditions:
- Reimburse in a manner similar to Enbrel.
- The cost of treatment with Brenzys should provide significant cost savings for jurisdictions compared with the cost of treatment with Enbrel.

Reasons for the Recommendation:
1. One phase 1 clinical trial in healthy males (SB4-G11-NHV; N = 138) and one phase 3 trial in patients with RA (SB4-G31-RA; N = 596) demonstrated that Brenzys has similar pharmacokinetics, efficacy, safety, tolerability, and immunogenicity as the reference product (Enbrel).
2. Extrapolation of the data from RA to AS is supported by the similar pathophysiology of the conditions.
3. At the submitted price ($305.00 per 50 mg/mL pre-filled syringe/auto-injector), Brenzys is less costly than Enbrel ($405.99 per 50 mg/mL pre-filled syringe/auto-injector) for use in accordance with the Health Canada–approved indications for the treatment of RA and AS.

Of Note:
1. An open-label extension phase of study SB4-G31-RA suggested that there were no efficacy, safety, or tolerability concerns in patients who either remained on Brenzys or were switched from Enbrel to Brenzys, after the double-blind phase of the study. These results, however, were not compared statistically to a group of patients who remained on Enbrel.

Background:
Brenzys is an etanercept SEB based on Enbrel as a reference product. Brenzys has been approved in Canada for the following indications:

- Treatment of moderately to severely active RA in adults. Brenzys can be initiated in combination with methotrexate (MTX) in adult patients or used alone.
- Reducing signs and symptoms of active AS.

In contrast to Enbrel, Brenzys is not approved in Canada for the treatment of juvenile idiopathic arthritis, psoriatic arthritis, or plaque psoriasis.

Summary of CDEC Considerations
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a review of manufacturer-provided information on the clinical efficacy, biosimilarity, and extrapolation of data for Brenzys; a critique of the manufacturer's pharmacoeconomic evaluation; and patient group–submitted information about outcomes and issues important to patients.

Patient Input Information:
Arthritis Consumer Experts, Canadian Arthritis Patient Alliance, The Arthritis Society, and the Canadian Spondylitis Association responded to CDR's call for patient input. CDEC heard the following:

- Therapeutic options are required for patients who live with RA and AS, and SEBs offer another biologic drug therapy that may be effective for patients who are biologic-naive or who have failed on other biologic drugs.
- Some patients see the introduction of Brenzys as having the potential advantages of improving access to the medication and reducing the burden to public plans.
- Patients expressed concern about the following:
  - The possibility that existing patient support programs will be eliminated or reduced and that new such programs will not replace them. (Many patients value the programs that pharmaceutical companies have set up to help patients with biological therapies, and these patients are unclear as to whether the manufacturers of SEBs will offer them, and whether the manufacturers of the reference products will continue offering them.)
  - Being switched to the SEB from the reference drug without their consent.
  - Monitoring of the safety and efficacy of SEBs. (Patient groups stress the need for careful and extended surveillance of all SEBs.)

Clinical Trials
The manufacturer provided efficacy data from two pivotal clinical trials.

SB4-G31-RA (N = 596) was a randomized, double-blind, 52-week, parallel-group, multi-centre clinical study conducted in Europe, South Korea, and Latin America, designed to evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of Brenzys (etanercept SEB) compared with Enbrel (reference product) in patients with moderate-to-severe RA despite MTX therapy. The primary end point was American College of Rheumatology 20% response criteria (ACR20) at week 24, through which therapeutic equivalence was concluded between Brenzys and Enbrel if the 95% confidence interval (CI) of the adjusted treatment difference was entirely contained within the equivalence margin of −15% to +15%. An extension, open-label phase included

participants from Poland and the Czech Republic (N = 245) who were either switched from Enbrel to Brenzys or remained on Brenzys and were followed up for a further 48 weeks to assess for safety, tolerability, immunogenicity, and efficacy.

SB4-G11-NHV (N = 138) was a controlled, randomized, single-blind, three-part, two-period, two-sequence, single-dose, crossover study to compare the pharmacokinetics, safety and tolerability, and immunogenicity of three formulations of etanercept (Brenzys, European Union–sourced Enbrel [EU-Enbrel], and United States–sourced Enbrel [US-Enbrel]), in healthy male participants. The primary end points (pharmacokinetic [PK]) were area under the concentration-time curve from time 0 to infinity (AUC_{inf}) and maximum serum concentration (C_{max}), through which PK similarity was concluded between Brenzys and Enbrel if the 90% CI of the ratios of the geometric means were entirely contained within the equivalence margin of 80% to 125%.

Outcomes

CDEC discussed the following outcomes:

- ACR20 response rate at week 24 and week 52 — defined as the proportion of patients achieving 20% improvement in tender and swollen joint counts and 20% improvement in three of the five remaining ACR core set measures: Patient pain assessment (measured by visual analogue scale [VAS]), patient global assessment (measured by VAS), physician global assessment (measured by VAS), patient self-assessed disability (measured by Health Assessment Questionnaire), and acute-phase reactant (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]).
- ACR50 and ACR70 at week 24 and week 52 — similar to the ACR20, but with improvements of 50% and 70%.
- ACR-N at week 24 and week 52 — provides a numeric index for ACR response that characterizes the percentage of improvement from baseline that a patient has experienced in analogy to ACR20, ACR50, and ACR70 responses.
- Disease Activity Score 28 (DAS28) at weeks 24 and 52 — a measure or disease activity that takes into consideration the 28-joint counts of tenderness and swelling, plus the ESR or CRP, and a general health assessment scored on a VAS. Scores < 2.6 are considered to be remission, and a score > 5.1 is considered to be high disease activity.
- European League Against Rheumatism (EULAR) response criteria at weeks 24 and 52 — classification of disease state based on the DAS28 scale.
- Modified total Sharp score (mTSS) change from baseline at week 52 — a radiographic measure of disease activity and extent of damage calculated from joint erosion score plus joint space narrowing score. The joint erosion score is a summary of erosion severity in 32 joints of the hands and 12 joints of the feet.
- Immunogenicity, serious adverse events, total adverse events, and withdrawals due to adverse events.
- Primary PK (AUC_{inf} and C_{max}) end points.

Efficacy

<u>SB4-G31-RA (Double-Blind Phase)</u>

The proportion of patients achieving an ACR20 response at week 24 was similar in the Brenzys group (73.6%) and the Enbrel group (71.7%). The difference of proportions between the groups was 1.66% (95% CI, –5.50% to 8.82%) in the full analysis set (FAS) analysis and –2.37% (95% CI, –9.54% to 4.80%) in the per-protocol (PP) set analysis. The 95% CIs for the treatment

difference were contained within the pre-determined equivalence range of ± 15% for both intention-to-treat and PP analyses. Results of ACR20 at 52 weeks show an adjusted difference rate of –0.74% (95% CI, –8.03% to 6.56%).

The proportion of patients who demonstrated ACR50 and ACR70 responses was similar between the Brenzys and Enbrel groups, with treatment differences at week 24 and week 52 in the PP set analysis reported as follows:

- ACR50
  - At week 24: [redacted]% (95% CI, [redacted]% to [redacted]%)
  - At week 52: 4.50% (95% CI, –4.67% to 13.67%)
- ACR70
  - At week 24: [redacted]% (95% CI, [redacted]% to [redacted]%)
  - At week 52: 5.90% (95% CI, –2.32% to 13.29%).

The proportion of patients who demonstrated ACR-N response was similar across the two groups at week 24 and week 52. The adjusted difference rate in the FAS analysis at week 24 was [redacted]% (95% CI, [redacted]% to [redacted]%), and at week 52 was [redacted]% (95% CI, [redacted]% to [redacted]%).

DAS28 (FAS) results were also similar between the Brenzys and EU-Enbrel group. The 95% CIs of the treatment differences (least squares means) at both weeks 24 and 52 were contained within the equivalence margin of ± 0.6.

The proportion of patients who had good, moderate, and no response according to EULAR classification was generally similar between the Brenzys and EU-Enbrel treatment groups at week 24 and week 52.

mTSS results at 52 weeks were similar between the Brenzys group (mean 43.70, standard deviation [SD] 67.081) and Enbrel group (mean 39.62; SD 53.414).

SB4-G11-NHV

For the primary PK end points of AUC_{inf} and C_{max}, the 90% CIs of the ratios of the geometric means both fell within the acceptance equivalence range of 80% to 125% for Parts A and B of the study.

Harms (Safety and Tolerability)

SB4-G31-RA (Double-Blind Phase)

The proportion of patients who reported at least one serious adverse event was 6.0% in the Brenzys group and 5.1% in the Enbrel group. The proportion of patients who withdrew due to adverse events was [redacted]% in the Brenzys group and [redacted]% in the Enbrel group.

SB4-G31-RA (Extension Phase)

The proportion of patients who reported at least one serious adverse event was 4.8% in patients who remained on Brenzys following the double-blind phase, and 1.7% in patients who switched to Brenzys from Enbrel in the extension phase.

The proportion of patients who withdrew due to adverse events was [redacted]% in patients who remained on Brenzys following the double-blind phase, and [redacted]% in patients who switched to Brenzys from Enbrel in the extension phase.

Extrapolation
Health Canada granted the extrapolation of data from the manufacturer's study in RA (SB4-G31-RA) to the indication of AS. Health Canada stated that the indication for AS was granted on the basis of similarity in product quality, mechanism of action, disease pathophysiology, safety, dosage regimen, and clinical experience with the reference product (Enbrel).

Cost and Cost-Effectiveness
The manufacturer submitted a cost comparison between Brenzys and the reference product, Enbrel, for the indications reviewed. As validated by CDR, the manufacturer-submitted price of Brenzys ($305.00 per 50 mg/mL vial) is 25% less than that of Enbrel when using the Ontario Drug Benefit Formulary price of Enbrel ($405.99 per 50 mg/mL vial).

CDR identified the following issues for consideration:
- The clinical expert indicated that patients may start treatment with Brenzys, or switch from Enbrel to Brenzys, but noted that additional clinical evidence would be helpful to support switching.
- Enbrel is also available for the following indications: Moderate-to-severe active polyarticular juvenile idiopathic arthritis, adult patients with psoriatic arthritis, and adult patients with chronic moderate-to-severe plaque psoriasis. While Brenzys is not currently indicated for these conditions, there is the potential for the off-label use of Brenzys. Brenzys was approved by the European Medicines Agency and by the Therapeutic Goods Administration in Australia for RA, AS, psoriatic arthritis, and plaque arthritis.
- The reimbursement criteria for Enbrel differ across publicly funded drug plans in Canada. The expected savings from Brenzys compared with Enbrel are based on the assumption that the reimbursement criteria for Enbrel would be applied to Brenzys.

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 Wijeysundera.

September 21, 2016 Meeting
Regrets: Three CDEC members did not attend.

Conflicts of Interest:
None

About This Document:
CDEC provides formulary reimbursement recommendations or advice to CDR-participating drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information. CADTH has redacted the requested confidential information in accordance with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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