CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(FINAL)

Etanercept (Erelzi — Sandoz Canada Inc.)
Indications: Rheumatoid Arthritis, Ankylosing Spondylitis, Polyarticular Juvenile Idiopathic Arthritis

RECOMMENDATION:

The CADTH Canadian Drug Expert Committee (CDEC) recommends that Erelzi (etanercept biosimilar) be reimbursed in accordance with the Health Canada–approved indications for the treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA), and ankylosing spondylitis (AS), if the following criterion and conditions are met:

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 Erelzi should provide significant cost savings for jurisdictions compared with the cost of treatment with existing etanercept products.

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Reasons for the Recommendation:

1. One phase I clinical trial in healthy male volunteers (study GP15-104; N = 54) and one phase III trial in patients with moderate-to-severe chronic plaque-type psoriasis (EGALITY study; N = 531) demonstrated that Erelzi's pharmacokinetics, efficacy, safety, and immunogenicity are similar to those of the reference product (Enbrel).
2. Extrapolation of the data from plaque-type psoriasis to RA, JIA, and AS is supported by the identical mode of action for all the indications.
3. At the submitted price ($304.49 per 50 mg/mL pre-filled syringe/auto-injector), Erelzi 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, JIA, and AS. Erelzi is similar in price to Brenzys, the first etanercept biosimilar approved by Health Canada ($305.00 per 50 mg/mL pre-filled syringe/auto-injector).

Of Note:

Results from the 18-week treatment crossover period and the 22-week extension phase of EGALITY suggest that switching from Enbrel to Erelzi and vice versa can be performed safely without any loss of efficacy.

Background:

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

- Treatment of moderately to severely active RA in adults. Treatment is effective in reducing the signs and symptoms of RA, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function. Erelzi can be initiated in combination with methotrexate (MTX) in adult patients or used alone.
- Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients aged four to 17 years who have had an inadequate response to one or more disease-modifying antirheumatic drugs.
- Reducing signs and symptoms of active AS.

In contrast to Enbrel, Erelzi is not approved in Canada for the treatment of psoriatic arthritis or plaque psoriasis. The manufacturer did not seek market authorization for psoriatic arthritis or plaque psoriasis.

Erelzi is the second etanercept biosimilar approved by Health Canada. Brenzys was the first approved etanercept biosimilar; it received a CDEC recommendation (October 25, 2016) to reimburse in accordance with the Health Canada–approved indications for the treatment of RA and AS, if the following criterion and conditions are met:

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.

Summary of CDEC Considerations:

The Committee 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 Erelzi; 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, JIA, and AS, in part because once-effective treatments (including biologics) often lose their effectiveness.
- Many patients are still unfamiliar with or confused about biosimilars. Some think biosimilars may be more effective than the reference products, some expect them to be as effective, and others think they may be less effective and less safe.
- Some patients see the introduction of Erelzi 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 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 about whether the manufacturers of biosimilars will offer them and whether the manufacturers of the reference products will continue offering them.
  - The prospect of being switched to the biosimilar from the reference drug without their consent: All the groups oppose such switching.
  - Monitoring of the safety and efficacy of biosimilars: Patient groups stress the need for careful and extended surveillance of all biosimilars.

Clinical Trials

The manufacturer provided efficacy data from two pivotal clinical trials.

EGALITY (N = 531) was a phase III, randomized, 52-week, double-blind, multi-centre clinical study conducted in countries in Eastern and Central Europe, South Africa, and the UK designed to evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of Erelzi (etanercept biosimilar) compared with Enbrel (reference product) in patients with moderate-to-severe chronic plaque-type psoriasis. The primary end point was 75% improvement from baseline on the Psoriasis Area and Severity Index (PASI 75) at week

12, through which therapeutic equivalence between Erelzi and Enbrel was concluded if the 95% confidence interval (CI) of the adjusted treatment difference was entirely contained within the equivalence margin of −18% to 18%. The EGALITY study consisted of four periods: screening, treatment period (TP) 1 (weeks 0 to 12), TP 2 (weeks 13 to 30), and an extension phase (weeks 31 to 52). In TP 1, patients were randomized 1:1 to self-administer 50 mg Erelzi or 50 mg Enbrel twice weekly, subcutaneously. Patients who had achieved at least a PASI 50 response at week 12 were to proceed to TP2 and were re-randomized either to continue the same treatment or to alternate treatment with GP2015 (Erelzi) or Enbrel for periods of six consecutive weeks, i.e., switching to the alternating treatment after week 12 and switching back to the original treatment after week 18, followed by a third switch of treatment regimen after week 24. After the end of TP2, patients continued to be treated for an additional 22 weeks during the extension period. They received the treatment they had last received during TP2.

Study GP15-104 (N = 54) was a single-centre, randomized, double-blind, two-way crossover study to compare the pharmacokinetics, safety, and immunogenicity of Erelzi and Enbrel in healthy male patients. Participants were randomized to receive a single 50 mg subcutaneous injection of Erelzi or European-sourced Enbrel. Participants had a washout period of 35 days before crossing over. After the washout period, patients were crossed over and received a single 50 mg subcutaneous injection of the opposite treatment. The primary end points (pharmacokinetic) were to determine the bioequivalence of Erelzi and Enbrel in terms of maximum observed serum concentration (C_{max}), area under the serum concentration time curve (AUC) measured from the time of dosage to the last measurable concentration ($AUC_{0–tlast}$), and AUC measured from the time of dosage extrapolated to infinity ($AUC_{0–inf}$), through which pharmacokinetic bioequivalence between Erelzi and Enbrel was concluded if the 90% CIs for the geometric mean ratios were entirely contained within the range of 80% to 125%.

Outcomes

CDEC discussed the following outcomes:

- Proportion of patients with a PASI 75 response
- Proportion of patients achieving a PASI 50 response
- Health-related quality of life and functional outcomes (e.g., the Dermatology Life Quality Index)
- Immunogenicity, serious adverse events, total adverse events, and withdrawals due to adverse events
- Primary pharmacokinetic end points (C_{max}, $AUC_{0–tlast}$, and $AUC_{0–inf}$,).

Efficacy

EGALITY Study (Treatment Period 1)

The proportion of patients achieving PASI 75 at week 12 was similar in the Erelzi group (73.4%) and the Enbrel group (75.7%). The difference in proportions between the groups was −2.3% (95% CI, −9.85% to 5.30%) in the per-protocol set analysis and −1.2% (95% CI, −8.77% to 6.45%) in the full analysis set analysis. The 95% CIs for the treatment difference were contained within the pre-determined equivalence margin of ± 18% for both the full analysis set and the per-protocol set analyses.

[redacted]

Study GP15-104

For the primary pharmacokinetic end points of C_{max}, $AUC_{0–tlast}$, and $AUC_{0–inf}$, the 90% CIs of the ratios of the geometric means fell within the acceptance equivalence range of 80% to 125%.

Harms (Safety and Tolerability)

EGALITY Study (up to Week 52 of Treatment)

The number of patients with at least one adverse event was 98 (59.8%) in the Erelzi-only treatment group, while it was 98 (57.3%) in the Enbrel-only treatment group, and it was 61 (61.0%) and 57 (59.4%) in the switched Erelzi and the switched Enbrel treatment groups, respectively.

The frequency of serious adverse events and study discontinuation due to adverse events was generally similar between the two switched treatment groups and the two continued treatment groups.

The frequency of adverse events of special interest was higher for the continued and switched Erelzi treatment groups (11.0%) than for the continued and switched Enbrel treatment groups (4.7% and 5.2%, respectively). The most commonly reported adverse events of special interest in the continued Erelzi treatment group were herpes simplex, tinea infection, and neutropenia, with two incidences (1.2%) each.

Extrapolation

Health Canada granted the extrapolation of data from the manufacturer's study in plaque-type psoriasis (EGALITY) to the indications of RA, AS, and polyarticular JIA. Health Canada stated that the indications for RA, AS, and polyarticular JIA were granted on the basis of the totality of scientific data supporting biosimilarity between Erelzi and Enbrel and on the identical mode of action for all indications of Enbrel.

Cost and Cost-Effectiveness

The manufacturer submitted a cost comparison between etanercept biosimilar (Erelzi) and the reference product (Enbrel) for the Health Canada–approved indications. As validated by CDR, the manufacturer-submitted price of Erelzi ($304.49 per 50 mg/mL pre-filled syringe) is 25% less ($101.50 less per 50 mg/mL pre-filled syringe) than the list price of the reference product (Enbrel) on the Ontario Drug Benefit formulary ($405.99 per 50 mg/mL pre-filled syringe). CDR previously reviewed another etanercept biosimilar product (Brenzys); the price of Erelzi is similar to the Brenzys price submitted to CADTH ($305 per 50 mg/mL pre-filled syringe).

CDR identified the following issues for consideration:

- The manufacturer's cost comparison did not consider another available etanercept biosimilar (Brenzys) as a relevant comparator.
- Enbrel is also available for the following indications: treatment of adult patients with psoriatic arthritis and adult patients with chronic moderate-to-severe plaque psoriasis. While Erelzi is not currently indicated for these conditions, there is potential for its off-label use.
- The listing criteria for Enbrel differ across CDR-participating drug plans in Canada. The expected savings from Erelzi compared with Enbrel are based on the assumption that the listing criteria for Erelzi would be applied to Enbrel.

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.

June 21, 2017 Meeting

Regrets:

Two CDEC members did not attend the meeting.

Conflicts of Interest:

None