### Emerging Drug List

**ETANERCEPT**

<table>
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<tr>
<th><strong>Generic (Trade Name):</strong></th>
<th>Etanercept (Enbrel®)</th>
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<tr>
<td><strong>Manufacturer:</strong></td>
<td>Amgen Canada Inc.</td>
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<td><strong>Indication:</strong></td>
<td>To reduce the signs and symptoms in patients with active ankylosing spondylitis (AS).¹</td>
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<td><strong>Current Regulatory Status:</strong></td>
<td>Etanercept is marketed in Canada by Amgen, although it was previously marketed by Wyeth-Ayerst. It is used in adults with active rheumatoid arthritis² and has been approved to treat psoriatic arthritis.³ In July 2003, the US Food and Drug Administration (FDA) approved etanercept for use in AS.¹ Wyeth-Ayerst has announced that the Committee for Proprietary Medicinal Products voted to recommend etanercept’s approval for use in severe AS. This decision has been forwarded to the European Commission.⁴ Etanercept for use in AS is under review by Health Canada with approval pending (Anita Hammer, Amgen Canada Inc., Mississauga, ON: personal communication, 2003 Nov 12).</td>
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<td><strong>Description:</strong></td>
<td>Etanercept is a recombinant human tumour necrosis factor (TNF) alpha receptor p75-Fc fusion protein. TNF alpha is thought to be involved in the pathogenesis of AS.⁵ Etanercept’s mechanism of action could be competitive inhibition of TNF binding to cell surface receptors, rendering TNF biologically inactive.² The drug is administered subcutaneously, with a bioavailability of 76% after the administration of a 25 mg dose. On average, peak serum concentration is reached 48 hours after administration, with an elimination half-life of 72 hours. Enbrel® is supplied in Canada as lyophilized powder in single-use vials that contain 25 mg of etanercept, with the necessary tools for parenteral self-administration (i.e., syringe, bacteriostatic water, alcohol swabs).²</td>
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<td><strong>Current Treatment:</strong></td>
<td>AS, which is the most common form of spondyloarthritis, occurs more often in men. Patients tend to exhibit stiffness and back pain, typically starting in the late teens and early 20s. Sacroiliitis can be noted radiographically; and in some cases, acute anterior uveitis may be documented. Symptom management generally includes tailored regular exercise, possibly with specific therapies (i.e., hydrotherapy, physical therapy) and the use of non-steroidal anti-inflammatory drugs (NSAIDs). Sulfasalazine may be used as a second-line agent. Other disease-modifying modalities have been studied, although the data are minimal and generally not as impressive as the data for other rheumatic disorders. Steroids, when injected into affected areas, have produced some success. Immunosuppressive and immunoregulatory drugs such as chlorambucil, cyclosporine and azathioprine have been tried for refractory disease, although their use in practice is rare. Other adjunctive therapies such as analgesics or muscle relaxants have also been used.⁶,⁷ Recent investigations have looked at infliximab, thalidomide and pamidronate.⁵,⁸</td>
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<td><strong>Cost:</strong></td>
<td>According to the PPS® Pharma Publication dated January 2004, the Canadian price for Enbrel® is $660 for a package of four vials.⁹</td>
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Evidence: In a multicentre randomized placebo-controlled trial,\textsuperscript{10} patients aged 18 to 70 years with active AS were randomized to receive either etanercept 25 mg subcutaneously twice weekly (n=138) or placebo (n=139) for 24 weeks. The primary efficacy endpoint, assessed at week 12, was a 20% improvement in the assessments of AS response criteria (ASAS 20), while a 50% to 70% improvement in the ASAS response criteria was a secondary outcome (assessed at weeks 12 and 24). Among etanercept recipients, 91% completed the full 24 weeks of therapy. Compared with placebo, a greater proportion of etanercept recipients achieved the primary endpoint (60\% versus 27\%, p<0.0001). At 24 weeks, the ASAS 20 response remained favourable in the etanercept group (58\% versus 23\%, p<0.0001). Etanercept was also statistically superior to placebo for the secondary endpoints of ASAS 50 and ASAS 70 (p<0.0001 at 12 and 24 weeks). Statistically superior improvement in individual efficacy measurements (e.g., spinal mobility, peripheral tender joints, acute phase reactant serum levels) was generally attained, although there was no statistical difference in the number of swollen joints.

A similar multicentre randomized placebo-controlled trial conducted in Europe produced similar proportions of etanercept and placebo ASAS 20 responders (60\% versus 23\%, p<0.0008) after 12 weeks.\textsuperscript{10}

A third single-centre placebo-controlled trial randomized patients (n=40) with active AS to placebo or etanercept 25 mg administered subcutaneously twice weekly for 16 weeks, followed by a six-month open-label extension phase. Using the ASAS 20 criteria, a post hoc analysis of the intent-to-treat population showed that 80\% and 30\% of patients who received etanercept and placebo respectively met this endpoint at four months (p=0.004). The improvement in secondary outcomes was favourable, reaching statistical significance for most. There were a few exceptions, notably the score for peripheral joint tenderness and a modified Schober’s index. Treatment response seemed to be maintained during the open-label extension.\textsuperscript{11}

The reported results of a small (n=30) trial comparing six weeks of etanercept to placebo showed a similar response. After six weeks, etanercept was administered for 12 weeks to placebo recipients and for six additional weeks to etanercept recipients. Results from the 24-week observational phase are also reported.\textsuperscript{12} Case reports; trials examining the effects of etanercept on the entheseal pathophysiology and immune response mediators; and preliminary work in the pediatric population have been published.\textsuperscript{13-16}

Adverse Effects: In the largest randomized trial, 10 serious adverse events occurred in nine (7\%) etanercept recipients and five serious adverse events occurred in five (4\%) placebo recipients. Approximately three-quarters of the patients enrolled in both arms reported at least one adverse event. Etanercept recipients experienced a higher incidence of injection site reac-
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tions, accidental injury and infections (particularly upper respiratory), when compared with those in the placebo arm. Withdrawals from therapy for safety reasons were more frequent in the etanercept group (seven versus one patient). The most common cause of withdrawal was a condition that resembled inflammatory bowel disease. Antibodies against etanercept were noted in 2.2% of the group treated with the drug, although none were considered to have neutralizing activity.10

A growing amount of literature explores new technologies that are aimed at altering TNF alpha activity in patients with AS. The clinical data suggest that etanercept can produce a favourable response in patients with AS and reduce symptoms. The Canadian Rheumatology Association has published a consensus document suggesting that these agents be used in patients with spondyloarthropathies who are refractory to traditional therapy with NSAIDs or sulfasalazine.

Several issues may be of concern to drug-plan managers and decision makers. These include the price of the drug and its potential for long-term use.

Data from head to head comparative trials of etanercept with other TNF alpha inhibitors, information about the safety implications from long-term usage and data about the overall effect of etanercept on disease progression will minimize uncertainty about the effectiveness and cost-effectiveness of this drug.17

References:


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This series highlights medical technologies that are not yet in widespread use in Canada and that may have a significant impact on health care. The contents are based on information from early experience with the technology; however, further evidence may become available in the future. These summaries are not intended to replace professional medical advice. They are compiled as an information service for those involved in planning and providing health care in Canada. These summaries have not been externally peer reviewed.

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