

Committee to Evaluate Drugs (CED)

Recommendations and Reasons

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Everolimus for renal angiomyolipoma associated with tuberous sclerosis complex

Product: everolimus (Afinitor®)

Class of Drugs: kinase (mTOR) inhibitor

Reason for Use: renal angiomyolipoma associated with tuberous sclerosis complex

Manufacturer: Novartis Pharmaceuticals Canada Inc.

Date of Review: December 11, 2013

CED Recommendation

The CED recommended everolimus (Afinitor®) be funded for the treatment of renal angiomyolipoma associated with tuberous sclerosis complex (AML-TSC). Although the clinical efficacy and cost-effectiveness of this treatment were unclear, the CED noted that a small subgroup of AML-TSC patients at risk of imminent renal failure and with no other treatment options may benefit from access to everolimus.

Executive Officer Decision*

Based on the CED's recommendation and an agreement with the manufacturer to help address concerns raised by the CED, the Executive Officer decided to fund everolimus for the treatment of AML-TSC through the Ontario Drug Benefit's (ODB) Exceptional Access Program according to specific criteria.

Funding Status*

Funded through the ODB's Exceptional Access Program (EAP) according to specific criteria.

(EAP criteria can be found at: http://www.health.gov.on.ca/en/pro/programs/drugs/eap_criteria.aspx)

* This information is current as of the posting date of the document. For the most up-to-date information on Executive Officer decision and funding status, see: www.health.gov.on.ca/en/pro/programs/drugs/status_single_source_subm.aspx.

Highlights of Recommendation:

- The EXIST-2 study showed that a significantly larger proportion of patients treated with everolimus had a substantial reduction in AML lesion size compared with patients who received placebo. There are no clinical studies to show that everolimus improves clinical important outcomes such as bleeding, renal failure, pain, and patients' quality of life.
- The side effects seen in EXIST-2 were consistent with the known safety profile of everolimus.
- At the recommended dose of 10 mg once daily, everolimus costs \$191.58 per day and \$69,927 per patient per year. The lack of evidence linking a reduction in AML volume to clinically important outcomes made it difficult to determine the cost-effectiveness of everolimus.
- The Committee acknowledged that some patients with renal angiomyolipoma associated with tuberous sclerosis complex (AML-TSC) may experience significant complications and that a small subgroup of patients at risk of imminent renal failure and with no other treatment options may benefit from access to everolimus.

Background:

Tuberous sclerosis complex (TSC) is a genetic condition usually caused by a mutation in either the TSC1 gene or the TSC2 gene, leading to the formation of benign tumours in many parts of the body, such as the skin, brain and kidneys.

Renal symptoms of TSC include the development of angiomyolipoma (AML), a benign kidney tumour. AMLs are usually bilateral and associated with renal failure due to bleeding or encroachment. Current management of AML includes monitoring or active treatment by embolization (blocking blood vessels) and removal of the kidney.

Detailed Discussions:

- For this evaluation, the CED considered:
 - Findings from the Common Drug Review (CDR) and the recommendation of the Canadian Drug Expert Committee (CDEC);
 - Information in the manufacturer's submission;
 - Input from clinical experts who treat patients with AML-TSC;
 - Submission from one patient group.
- The CED evaluated one international, multicentre, double-blind, randomized controlled study, EXIST-2, in adult patients. The study demonstrated that a statistically significantly larger proportion of everolimus-treated patients achieved the primary endpoint of objective response compared with placebo-treated patients (42% vs. 0%; $P < 0.0001$). The objective response was a combination of several criteria relating to the presence and size of AMLs.
- There was a substantial reduction in mean AML lesion volume with everolimus compared with placebo ($82 \pm 110.6 \text{ cm}^3$ vs. $9.2 \pm 38.1 \text{ cm}^3$, respectively). It was unclear how reduction in AML volume correlated with clinically important outcomes such as bleeding, renal failure, pain, and quality of life.

- The proportion of patients with severely reduced kidney function (i.e., decrease in glomerular filtration rate (GFR) below 30 mL/min) was not statistically significantly different between the everolimus group and the placebo group (3% vs. 8%).
- The adverse events (AEs) seen in EXIST-2 were consistent with the known safety profile of everolimus. The proportion of patients with serious AEs was similar between everolimus and placebo (19% vs 18% respectively). There were fewer withdrawals due to AEs with everolimus (3% everolimus vs 10% placebo).
- At the list price, everolimus costs \$191.58 per tablet. At the recommended dose of 10 mg once daily, everolimus costs \$191.58 per day and \$69,927 per patient per year. The CED expressed concerns over the high drug cost. Several limitations were identified with the manufacturer's economic analysis, and the lack of evidence linking a reduction in AML volume to clinically relevant outcomes made it difficult to determine the cost-effectiveness of everolimus.
- The optimal duration of treatment with everolimus is unknown.
- The patient submission highlighted the burden of illness. Patients highly value treatments that are non-invasive and that could treat all the manifestations of TSC.
- Overall, everolimus has been shown to reduce AML lesion volume in adult patients with AML-TSC. There are no clinical studies to show that everolimus improves clinical important outcomes such as bleeding, renal failure, pain, and patients' quality of life. The treatment cost is high and the cost-effectiveness is unknown. The CED acknowledged that AML-TSC patients with tumours that grow can experience significant complications and that a small subpopulation of patients at risk of imminent renal failure and with no other treatment options may benefit from access to everolimus.

Committee to Evaluate Drugs (CED)

The Committee to Evaluate Drugs (CED) is comprised of practicing physicians, pharmacists, health economists, and patient representatives. In conducting its review, the CED considers data contained in the drug manufacturer's submission, input provided by patient groups, findings from the national Common Drug Review and the pan-Canadian Oncology Drug Review, and other scientific information as necessary.

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