CDEC FINAL RECOMMENDATION

EVEROLIMUS
(Afinitor — Novartis Pharmaceuticals Canada)
Indication: Renal Angiomyolipoma Associated with Tuberous Sclerosis Complex

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that everolimus not be listed.

Reason for the Recommendation:
In one double-blind, randomized controlled trial (RCT), everolimus was shown to reduce the size of angiomyolipomas (AML) in 42% of treated patients. However, it has not been definitively established that a reduction in AML size is correlated with a reduction in bleeding complications, avoidance of surgery, or long-term preservation of renal function.

Of Note:
CDEC considered subpopulations of patients for whom everolimus could be recommended (e.g., those who are experiencing AML growth and who are not candidates for surgery); however, there was no evidence for making such recommendations.

Background:
This submission for everolimus is for the treatment of adult patients (≥ 18 years of age) with renal AML associated with tuberous sclerosis complex (TSC) who do not require immediate surgery. Everolimus currently has a Health Canada Notice of Compliance with Conditions (NOC/c) for the indication under review. Everolimus is available in 2.5 mg, 5 mg, and 10 mg tablets. The dose recommended in the product monograph for renal AML associated with TSC is 10 mg once daily. The product monograph states that the optimal duration of treatment with everolimus is not known.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the Common Drug Review (CDR) — a systematic review of RCTs of everolimus, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Patient Input Information

The following is a summary of key information provided by one patient group that responded to the CDR call for patient input:

- People living with TSC suffer from a variety of symptoms including seizures; kidney symptoms; skin symptoms; communication and social problems; mood-related disorders; behavioural issues; learning, intellectual, and developmental delays; and tumours of the brain, heart, lungs, eyes, kidneys, liver, face, and/or skin.
- TSC profoundly affects the whole family of someone living with the condition, and often two or more people in a family share the diagnosis. Some people with the condition decide not to have children for fear of passing the condition on to them.
- All available treatments are for symptom management and do not address the cause of TSC. Patients and family members were grateful for the available drugs and surgeries, despite their adverse effects and the temporary nature of these solutions. However, people living with TSC are looking for a treatment that will stop recurring AMLs and organ damage, and show greater and sustained benefits without serious adverse effects. Some members of the patient group have been treated with everolimus and, largely because of their positive experience with the drug, the patient group regards everolimus as the treatment they have been hoping for.

Clinical Trials

One double-blind RCT was included in the CDR systematic review. EXIST-2 randomized 118 patients in a 2:1 manner to either everolimus 10 mg daily or placebo. Patients were treated until they experienced AML progression. The mean treatment duration was 45 weeks with everolimus and 40 weeks with placebo.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Objective response — defined as the combination of the following criteria:
  - reduction in AML volume of at least 50% relative to baseline
  - no new AML lesions ≥ 1.0 cm in longest diameter identified
  - no increase in kidney volume > 20% from the lowest kidney volume previously measured for the patient
  - no AML-related bleeding of ≥ grade 2
- AML progression — defined as one or more of the following:
  - increase of at least 25% in AML volume from the lowest AML volume achieved by the patient previously in the trial to a value greater than baseline
  - appearance of a new AML ≥ 1.0 cm in longest diameter
  - increase of at least 20% in the volume of either kidney to a value greater than baseline from the lowest kidney volume obtained for the patient
  - AML-related bleeding ≥ grade 2
- Renal function — assessed using the lowest post-baseline glomerular filtration rate
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The primary outcome of EXIST-2 was objective response.

Results

Efficacy

- A statistically significantly larger proportion of everolimus-treated patients achieved an objective response compared with placebo-treated patients (42% versus 0%; *P* < 0.0001).
- Everolimus was superior to placebo for prolonging the time to AML progression (hazard ratio 0.08; 95% confidence interval, 0.02 to 0.37; *P* < 0.0001). The median time to AML progression was 11.4 months with placebo and was not reached with everolimus.
- Mean AML lesion volume (± standard deviation) was reduced with everolimus (–82 ± 110.6 cm^3) compared with placebo (9.2 ± 38.1 cm^3).
- The proportion of patients with a decrease in glomerular filtration rate below 30 mL/min was 3% in the everolimus group and 8% in the placebo group; however, this difference was not statistically significant.

Harms (Safety and Tolerability)

- Serious adverse events were reported for 19% of patients in the everolimus group and 18% of patients in the placebo group.
- There were fewer withdrawals due to adverse events with everolimus than with placebo (3% versus 10% of patients).
- All of the everolimus-treated patients and 97% of the placebo-treated patients experienced at least one adverse event. The most common adverse events that occurred more frequently with everolimus than placebo were stomatitis, acne, and hypercholesterolemia.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-consequence analysis comparing the cost and consequences of everolimus treatment 10 mg daily versus current management options (including watchful waiting, embolization, partial nephrectomy, and complete nephrectomy) in adult patients with renal AML associated with TSC who do not require immediate surgery. A cost-consequence analysis was used given the absence of quality of life data from the pivotal clinical trial (EXIST-2) and a lack of clinical data on the relevant comparators. The analysis was undertaken from the perspective of the public health system over a one-year period.

The manufacturer's analysis suggested that the incremental cost of treatment with everolimus ranges from $40,254 to $59,901 over one year compared with standard care. However, several limitations with the manufacturer's analysis led to substantial uncertainty with the economic evaluation:

- The most appropriate comparator(s) for a pharmacoeconomic analysis is uncertain. Watchful waiting (active monitoring) might be an appropriate comparator for everolimus, which would necessitate a cost-effectiveness analysis. In the absence of such an analysis, whether everolimus is cost-effective is unknown.
- The use of a one-year time horizon was inappropriate, as TSC is a chronic condition. It is likely that everolimus treatment will continue for many years, incurring substantial treatment costs; by contrast, standard treatments (embolization and surgery) represent finite costs due to a finite number of interventions. In addition, patients who do not respond to everolimus likely still require subsequent embolization or surgery. Therefore, use of a short time horizon substantially underestimated the cost of everolimus treatment.

- A lack of evidence definitively linking a reduction in tumour size in TSC patients treated with everolimus to clinically relevant outcomes such as bleeding, renal function, and quality of life precluded an analysis of cost-effectiveness.

Due to these limitations, there is considerable uncertainty regarding the incremental cost of everolimus treatment compared to standard treatment. However, there is certainty that everolimus is associated with a substantial annual cost at a price of $186 daily or $67,890 annually.

Other Discussion Points:
CDEC noted the following:

- Everolimus is not indicated for the treatment of patients less than 18 years old with renal AML associated with TSC.
- Details regarding the impact of everolimus on the frequency and intensity of pain were not assessed in the EXIST-2 trial.
- The number of patients using seizure medications in EXIST-2 may be lower than in routine Canadian clinical practice.
- Objective response, as defined in the EXIST-2 trial, is not a validated surrogate marker for the clinical outcomes of greatest interest to patients with renal AML associated with TSC, including hemorrhage, renal function, and pain. Although clinical opinion suggests that an increase in AML size results in an increased risk of complications, there is no published literature to suggest that a subsequent reduction in AML size will result in a reduction in bleeding complications, avoidance of surgery, or long-term preservation of renal function.
- There is uncertainty regarding the timing of initiating treatment with everolimus. CDEC noted that AMLs less than 4 cm in size are commonly observed with no medical interventions if they remain asymptomatic. The same approach is often applied to AMLs above 4 cm, although clinicians may become more vigilant in assessing AML growth by diagnostic imaging in this setting. AMLs above 4 cm are more likely to receive an intervention (e.g., a surgical procedure) in the case of active bleeding or suspicion of malignancy.
- There was insufficient data to indicate if treatment with everolimus should be discontinued if AML size is reduced below a particular threshold or if treatment should be continuous.
- Treatment with everolimus appeared to cause bleeding at sites other than the AML in EXIST-2.

Research Gaps:
CDEC noted that there is an absence of evidence regarding the following:

- The effect of everolimus on clinical outcomes, such as reduction in bleeding complications, avoidance of surgery, or long-term preservation of renal function.
- Information regarding the optimal duration of treatment with everolimus and the effect of intermittent treatment for patients who demonstrate a response.
- Information regarding whether or not refractory AMLs are responsive to everolimus.

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

Regrets:

July 17, 2013: None

September 18, 2013: One CDEC member could not attend the meeting.

Conflicts of Interest:

None

About This Document:

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The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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