CDEC FINAL RECOMMENDATION

EVEROLIMUS
(Afinitor — Novartis Pharmaceuticals [Canada] Inc.)
Indication: Subependymal Giant Cell Astrocytoma Associated With Tuberous Sclerosis Complex

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that everolimus not be listed for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) that have demonstrated serial growth, who are not candidates for surgical resection and for whom immediate surgical intervention is not required.

Reasons for the Recommendation:

1. One randomized controlled trial (RCT) (EXIST-1; N = 117) and one open-label uncontrolled trial (study 2485; N = 28) demonstrated that treatment with everolimus reduces the size of SEGA lesions; however, the clinical significance of this finding is uncertain, as reducing lesion size has not been shown to improve outcomes of importance to patients, including quality of life, seizure frequency, hydrocephalus, or the need for neurosurgery.
2. Although EXIST-1 demonstrated that everolimus was statistically superior to placebo for the proportion of patients who achieved a SEGA response (difference of proportions, 35%; 95% confidence interval [CI], 15% to 52%), there was no statistically significant difference between everolimus and placebo in the frequency of seizures (P = 0.2004). In contrast, study 2485 demonstrated a statistically significant reduction in seizure frequency (median daily difference −0.99; P = 0.022) in addition to a reduction in SEGA volume (−0.83 cm^3; 95% CI, −0.5 to −1.2); however, this study was limited by a small sample size, open-label design, and the absence of a control group. Neither study was designed to evaluate the impact of everolimus on the risk of hydrocephalus or the need for neurosurgery.
3. Although EXIST-1 was not designed to evaluate differences in harms between everolimus and placebo, CDEC noted that serious adverse events were more commonly reported in the everolimus group (19%) compared with the placebo group (8%).
4. The cost-effectiveness of everolimus as a treatment option for SEGA associated with TSC is uncertain. The pharmacoeconomic evaluation submitted by the manufacturer is limited by the absence of clinical data regarding the effect of everolimus on clinically meaningful end points.

Background:
The Health Canada approved indication for everolimus is for the treatment of patients with SEGA associated with TSC that have demonstrated serial growth, who are not candidates for surgical resection, and for whom immediate surgical intervention is not required. For SEGA associated with TSC, everolimus dose selection and dose adjustments are individualized (based on body surface area [BSA], in square metres [m^2]) and determined in conjunction with therapeutic drug monitoring. The recommended starting daily dose for all patients with SEGA is 4.5 mg/m^2.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs and pivotal studies of everolimus in the treatment of SEGA associated with TSC, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to individuals with SEGA associated with TSC, and to their caregivers.

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

- Patients with SEGA associated with TSC can experience severe headaches, epilepsy (some have multiple seizures per day), hydrocephalus, intellectual disabilities, behavioural issues, and mood disorders.
- SEGA associated with TSC negatively affects the lives of the patients, families, and caregivers, with constant uncertainty and stress due to unpredictable seizures, worries about the need for and the possible consequences of surgery, and the eventual course of their disease.
- No disease-modifying drugs are available to treat patients with SEGAs. Surgical resection of the tumours may be possible if they are in operable locations in the brain. Multiple brain surgeries are often needed, as the tumours can reappear in the same tissue and can result in permanent cognitive disabilities, damage to motor skills, changes in personality, and other behavioural issues. As a consequence, patients and caregivers express a strong preference for a non-surgical treatment. Most patients also take antiepileptic medications to control their seizures, which are not always effective and can have serious side effects.

Clinical Trials
The CDR systematic review included two studies, EXIST-1 (N = 117) and study 2485 (N = 28). EXIST-1 was a pivotal phase 3, double-blind RCT that randomized patients (2:1) to either everolimus or placebo. EXIST-1 consisted of a six-month double-blind treatment phase and an ongoing four-year open-label extension phase. Study 2485 was a pivotal, single-centre, phase 3, single-treatment group study (N = 28) with an initial six-month treatment phase and an extension phase of up to five years.

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

- SEGA response rate — defined as the proportion of patients with a best overall status of "SEGA response" as per independent central radiological review and confirmed with a

second scan performed approximately eight to 12 weeks later. SEGA response was defined as follows:
  - A reduction in SEGA volume of ≥ 50% relative to baseline, where SEGA volume was the sum of the volumes of all target SEGA lesions identified at baseline
  - No unequivocal worsening of non-target SEGA lesions, no new SEGA lesions (≥ 1 cm in longest diameter), and no new or worsening hydrocephalus (defined by central radiological assessment of ventricular configuration changes, ventricular cap signs [periventricular edema], and qualitative assessment of cerebrospinal fluid [CSF] flow dynamics).
- Time to SEGA progression — defined as the time from the date of randomization to the date of the first documented SEGA progression. SEGA progression was defined as one or more of the following:
  - Increase from nadir of ≥ 25% in SEGA volume to a value greater than the baseline SEGA volume (where SEGA volume was the sum of the volumes of all target SEGA lesions identified at baseline, and where nadir was the lowest SEGA volume obtained for the patient previously in the trial [including baseline]), or
  - Unequivocal worsening of non-target SEGA lesions, or
  - Appearance of a new SEGA lesion ≥ 1.0 cm in longest diameter, or
  - New or worsening hydrocephalus, defined by central radiological assessment of ventricular configuration changes, ventricular cap signs (periventricular edema), and qualitative assessment of CSF flow dynamics.
- Seizure frequency — evaluated using the absolute change from baseline in the number of seizures per 24 hours.
- Seizure Severity Questionnaire (SSQ) — an instrument with 11 questions in four sections that gather information about the events before, during, and after typical seizures, and includes an overall assessment of the seizures in the recent past. Higher scores indicate worsening of seizures.
- Quality of Life in Childhood Epilepsy Questionnaire (QOLCE) — a 76-item questionnaire with 16 subscales (quality of life, physical restrictions, general health, energy/fatigue, behaviour, attention/concentration, stigma, memory, social activities, social interactions, language, other cognitive processes, anxiety, control/helplessness, and self-esteem) and five functional life domains (physical function, social function, cognition, behaviour, and emotional well-being).

The primary outcome of EXIST-1 was the proportion of patients with a confirmed tumour response (reduction of ≥ 50% in total target SEGA volume), in the absence of worsening of non-target SEGA, new lesions of at least 1 cm in diameter, and new or worsening hydrocephalus. The primary outcome of study 2485 was change from baseline in volume of the primary SEGA lesion after six months of treatment with everolimus.

Efficacy

Placebo-Controlled Trial (EXIST-1)

- 35% of everolimus patients and no placebo patients had achieved a response at 24 weeks, for a difference in response rates of 35% (95% CI, 15% to 52%), $P < 0.0001$.
- The least squares mean difference for change from baseline in total SEGA volume between everolimus and placebo was statistically significant (–0.88 cm^3; 95% CI, –1.24 to –0.52, $P < 0.0001$).

- There was no statistically significant difference in the mean (standard deviation [SD]) change from baseline in seizure frequency, as both everolimus (–1.24 [6.12]) and placebo (–0.24 [5.70]) groups demonstrated a reduction from baseline in seizure frequency at 24 weeks (*P* = 0.2004).
- Changes in mean (SD) SSQ global score were similar between everolimus (3.1 [1.1]) and placebo (3.0 [1.1]) at 24 weeks.
- SEGA progression at 24 weeks was reported for 15% of patients in the placebo group and 0% of patients in the everolimus group (in accordance with the hierarchical testing procedure, statistical testing was not conducted for this end point).

Uncontrolled Trial (Study 2485)

- There was a statistically significant reduction from baseline to 24 weeks in median seizure frequency per 24 hours of 0.99 (*P* = 0.022).
- There was a statistically significant improvement from baseline to 24 weeks in QOLCE, with a least squares mean change of 3.47 (95% CI, 0.19 to 6.74).
- Everolimus demonstrated a statistically significant reduction from baseline in SEGA volume after 24 weeks (median reduction 0.83 cm^3; 95% CI, 0.5 to 1.2).

Harms (Safety and Tolerability)

- At least one serious adverse event was reported for 19% of patients in the everolimus group and 8% of patients in the placebo group in EXIST-1. The most commonly reported serious adverse events were convulsion (4% everolimus versus 5% placebo) and pyrexia (4% everolimus versus 0% placebo). In study 2485, 32% of patients experienced at least one serious adverse event with abscessed limb, cellulitis, and convulsion being the most commonly reported (7% of patients for each event).
- At least one adverse event was reported for 96% of patients in the everolimus group and 90% of patients in the placebo group in EXIST-1. Commonly reported and notable adverse events included the following (everolimus versus placebo): mouth ulceration (32% versus 5%), stomatitis (31% versus 21%), infections (72% versus 67%), increased cholesterol (87% versus 49%), and decreased neutrophil count (8% versus 0%). All patients in study 2485 experienced at least one adverse event, with the most commonly reported adverse events being upper respiratory tract infection (93%) and stomatitis (89%).
- There were no withdrawals due to adverse events reported in EXIST-1 or study 2485.

Cost and Cost-Effectiveness

The manufacturer submitted a cost analysis for patients with SEGA associated with TSC, comparing one-year costs associated with everolimus treatment with the costs associated with SEGA resective repeat surgery; medical management of hydrocephalus as a complication from primary surgery; and medical management of hydrocephalus as a result of a wait-and-watch strategy. The costs associated with everolimus treatment included the drug costs and costs of treating grade 3 or 4 adverse events. The costs associated with SEGA surgery included costs of surgery and any surgical complications (e.g., hydrocephalus, headache, stroke or hemiparesis, and autism). The costs associated with the management of hydrocephalus included shunt placement and any complication costs (e.g., shunt revision, or shunt complications or infections). The prevalence of the complications associated with SEGA surgery and hydrocephalus was based on published literature, while the unit costs were based on the Ontario Case Costing Initiative.

CDR noted the following key limitations with the manufacturer's pharmacoeconomic submission:

- Best SEGA response is a surrogate end point and there is uncertainty regarding the correlation between the best SEGA response and the progression of the disease or risk of hydrocephalus. The EXIST-1 study had a small sample size, making it difficult to assess clinical outcomes such as the need for neurosurgery or episodes of hydrocephalus — the key drivers in the estimated cost offsets in the manufacturer's pharmacoeconomic evaluation. In addition, based on data from EXIST-1, everolimus did not appear to reduce the risk of seizures for patients with SEGA, a major complication for patients with SEGA identified in the patient input received through the CDR process.
- The cost analysis does not take into account the effectiveness of everolimus and comparator interventions; as a result, the comparative cost-effectiveness of everolimus is unknown.
- The recommended dose of everolimus for patients with a BSA greater than 2.2 m^2 is 7.5 mg daily. The cost of treatment for these patients has not been considered in the submitted analysis. Because everolimus is available in tablet strengths of 2.5 mg, 5 mg, and 10 mg, these patients will require 1.5 tablets of the 5 mg dose, increasing the daily cost to $287.37, or $104,890 annually.
- There is no clinical evidence that treatment with everolimus will prevent the development of hydrocephalus or reduce the need for resective surgery.
- The submitted analysis was conducted over a one-year time horizon, which is too short to fully assess the impact of everolimus treatment, considering the long-term evidence that suggests tumour regrowth after drug discontinuation. Because patients with TSC can have a normal life expectancy, as long as they have appropriate follow-up, a treatment duration of up to 50 years is possible, which would lead to total drug costs of $1.3 million per patient with BSA less than 2.2 m^2, or $2.0 million per patient with BSA greater than 2.2 m^2 (when discounting costs at 5% per annum).
- There are minimally invasive surgical techniques now used for SEGA associated with TSC that substantially improve outcomes, resulting in fewer complications than the standard resective surgery. The manufacturer did not consider the minimally invasive surgeries as a comparator in the submitted analysis.

Based on the type of pharmacoeconomic evaluation submitted by the manufacturer, the cost-effectiveness of everolimus versus comparator interventions is unknown. The assessment of the cost-effectiveness of everolimus is complicated by the lack of clinical information on how treatment with everolimus affects the need for surgery, the development of hydrocephalus, and the risk of seizures. Further, uncertainty exists regarding the impact of SEGA volume reduction on clinically important outcomes. The cost analysis submitted by the manufacturer does not allow for the assessment of this uncertainty.

The annual cost of everolimus treatment varies by BSA: $69,927 for patients with a BSA less than 2.2 m^2 and $104,890 for patients with a BSA more than 2.2 m^2.

Other Discussion Points:
CDEC noted the following:

- A component of the indication and the manufacturer's suggested listing criteria is patients with SEGA associated with TSC "who are not candidates for surgical resection". CDEC considered this subpopulation, but these patient populations were not identifiable in EXIST-1 and study 2485.
- Everolimus tablets for oral suspension were not included in the manufacturer's submission and were not within the scope of the CDR review.
- Episodes of hydrocephalus were a component of the primary end point of EXIST-1 (i.e., SEGA response); however, no episodes of hydrocephalus were reported in either group.
- The open-label design and the absence of a control group limit the conclusions that can be drawn regarding the efficacy or safety of everolimus from study 2485.

Research Gaps:
CDEC noted that there is insufficient evidence regarding the following:

- The clinical benefit of everolimus for improving quality of life, reducing the risk of hydrocephalus, and reducing the need for neurosurgery requires evaluation.
- The long-term safety profile of everolimus in patients with SEGA associated with TSC requires further evaluation.

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, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, and Dr. Adil Virani

Regrets:

February 18, 2015: Two CDEC members were unable to attend the meeting
April 8, 2015: None

Conflicts of Interest:

February 18, 2015: None
April 8, 2015: None

About This Document:
CDEC provides formulary listing 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 not requested the removal of confidential information.

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