Common Drug Review
Pharmacoeconomic Review Report

September 2017

Drug	everolimus (Afinitor) (oral tablets)
Indication	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
Listing request	As per indication
Manufacturer	Novartis Canada

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in pediatrics who provided input on the conduct of the review and the interpretation of findings.

Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

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ABBREVIATIONS

ADHD	attention-deficit/hyperactive disorder
BSA	body surface area
NOC/c	Notice of Compliance with conditions
SEGA	subependymal giant cell astrocytoma
TSC	tuberous sclerosis complex

SUMMARY

At the time everolimus was submitted to the CADTH Common Drug Review (CDR) for review, the Health Canada indication (Notice of Compliance with conditions [NOC/c]) was for the treatment of patients three years of age or older with subependymal giant cell astrocytomas (SEGAs) associated with TSC that have demonstrated serial growth, who are not candidates for surgical resection, and for whom immediate surgical intervention is not required. The NOC/c was based on data from study 2485 only.

CDR was, however, notified by the manufacturer (through comments on the draft Clinical and Pharmacoeconomic Reviews) that a new product monograph for everolimus had been issued (date of revision: November 3, 2014) with a change to the indication whereby the age limit (≥ 3 years) was removed. According to the manufacturer, the revision was based on inclusion of the EXIST-1 data as part of the post-approval commitment following the initial NOC/c. Because these data were already included in the CDR review, the revision in the indication does not affect the reported results or the conclusions of the review.

Of note:

- The revised indication also includes Afinitor Disperz (everolimus tablets for oral suspension), which was not part of the current submission to CDR and therefore not within the scope of this review.
- Although the age limit was removed from the indication, the revised product monograph states for pediatric populations that, "Afinitor and Afinitor Disperz have not been studied in pediatric patients with SEGA < 1 year of age and are not recommended for use in this age group. There are limited efficacy and safety data in patients 1 to 3 years of age with Afinitor."{55}

Background

Everolimus (Afinitor) is being reviewed for treatment of patients three years of age or older with SEGAs 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. The recommended daily dose is 2.5 mg for patients with a body surface area (BSA) of 0.5 to 1.2 m^2, 5 mg for patients with a BSA of 1.3 to 2.1 m^2, and 7.5 mg for patients with a BSA greater than 2.2 m^2. The cost of everolimus is $191.58 for a 2.5 mg, 5 mg or 10 mg tablet.

Everolimus was previously reviewed by CADTH for the treatment of renal angiomyolipoma associated with TSC in 2013. The Canadian Drug Expert Committee (CDEC) recommended that everolimus not be listed, based on clinical reasons.[2]

Summary of the Economic Analysis Submitted by the Manufacturer

The manufacturer submitted a cost analysis comparing one-year costs associated with everolimus treatment against 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.[3]

The costs associated with everolimus treatment included the drug costs and costs associated with adverse events (including convulsion, stomatitis, pyrexia, neutropenia, bronchitis, mouth ulceration, and amenorrhea). The costs associated with SEGA surgery included the surgery costs and the costs due to the surgery complications (hydrocephalus, headache, stroke or hemiparesis, and autism). The costs associated with management of hydrocephalus included the costs due to shunt placement and the costs due to the complications (shunt revision and shunt complications or infections). Only grade 3 or 4 everolimus adverse events as per the EXIST-1 study were included in the analysis. The prevalence of the complications associated with SEGA surgery and hydrocephalus were based on published literature, while the unit costs were based on Ontario Case Costing Initiative (OCCI). In addition to the base-case analysis, the manufacturer reported cost offsets associated with facial angiofibroma and TSC-angiomyolipoma, as well as indirect costs of stroke, autism, attention-deficit/hyperactivity disorder (ADHD) and mental retardation.

Key Limitations

- **Uncertain clinical efficacy.** Best SEGA response, a surrogate end point, was the primary outcome of the EXIST-1 trial, in which a statistically significant difference of 35% in response rates among patients receiving everolimus compared with placebo was observed. There is, however, uncertainty around the correlation between the best SEGA response as a surrogate end point and the progression of the diseases or risk of hydrocephalus. EXIST-1 had a small sample size, making it difficult to assess clinical outcomes, such as need for neurosurgery or episodes of hydrocephalus, which are the key drivers in the estimated cost offsets in the manufacturer-submitted economic evaluation. In addition, based on data from the EXIST-1 study, everolimus did not appear to reduce the risk of seizures for patients with SEGAs, a major complication for patients with SEGAs as per patient input received through the CDR process.
- **Type of analysis.** The submitted analysis is a cost analysis and does not take into account the effectiveness of the drug and comparator interventions. As a result, the comparative cost-effectiveness of everolimus is unknown.
- **Cost for everolimus treatment for patients with body surface are greater than 2.2 m^2.** The recommended dose 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. As 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.
- **Short time horizon.** 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 suggesting 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 a total drug cost of $1.3 million per patient with BSA < 2.2 m^2 or $2.0 million per patient with a BSA greater than 2.2 m^2 (when discounting costs at 5% per annum).
- **Development of hydrocephalus or need for resective surgery post-treatment.** There is no strong clinical evidence that treatment with everolimus will prevent hydrocephalus or the need for resective surgery post-treatment. Adding the cost of shunt replacement or resective surgery to the total cost of everolimus treatment leads to a total annual cost of $110,058 or $112,373, respectively ($145,021 or $147,336 for patients with BSA greater than 2.2 m^2).

- **Minimally invasive surgeries**. There are minimally invasive techniques that are now used for SEGAs associated with TSC that substantially improve outcomes, resulting in fewer complications than standard resective surgery.[4] The manufacturer did not consider minimally invasive surgeries as a comparator in the submitted analysis.

Issues for Consideration

There is potential for use of everolimus among asymptomatic patients, which will most likely be a lifelong therapy, as evidence suggests that the tumours begin to regrow after treatment cessation, and the outcomes to identify the progression toward symptomatic SEGAs when patients are asymptomatic are unknown.[5] The clinical effectiveness, and consequently the cost-effectiveness, of everolimus in this patient population are unknown.

Results and Conclusions

Based on the type of economic 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 as to the impact of SEGA volume reduction on clinically important outcomes. The cost analysis submitted by the manufacturer does not allow for the assessment of 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.

Cost Comparison Table

Clinical experts have deemed the comparator treatments presented in Table 1 to be appropriate. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified.

TABLE 1: COST COMPARISON FOR PHARMACEUTICALS USED TO TREAT SUBEPENDYMAL GIANT CELL ASTROCYTOMA

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Daily Drug Cost ($)	Annual Drug Cost ($)
Everolimus (Afinitor)	2.5 mg 5 mg 10 mg	Tablet	$191.5800	Body surface area of 0.5 to 1.2 m^2: 2.5 mg daily 1.3 to 2.1 m^2: 5 mg daily >2.1 m^2: 10 mg daily	191.58	$69,927

Source: Manufacturer's submission.[3]

APPENDIX 1: REVIEWER WORKSHEETS

Summary of Manufacturer's Submission

Drug Product	**Everolimus (Afinitor)**
Treatment	2.5 mg to 10 mg daily, depending on body surface area
Comparators	• Repeat resective surgery • Hydrocephalus (complication from primary surgery) • Hydrocephalus (as a result of wait-and-watch)
Study Question	"The objective of the study is to assess the cost implications of reimbursing everolimus based on the indication as approved by Health Canada."
Type of Economic Evaluation	Cost analysis
Target Population	Patients ≥ 3 years with subependymal giant cell astrocytoma associated with tuberous sclerosis complex that have demonstrated serial growth, who are not candidates for surgical resection, and for whom immediate surgical intervention is not required (as per Health Canada indication).
Perspective	Canadian public health system
Outcome Considered	Costs only
Key Data Sources	
Cost	Ontario Case Costing Initiative (OCCI), supplemented with published literature when unavailable.
Events	• Prevalence of surgery complications and hydrocephalus as a post-surgery complication — published retrospective cohort study by Sun et al.[6] (2011), based on three US national health claims databases. • Shunt revision rates — published patient-reported survey study by Gupta et al.[7] (2007).
Harms	Grade 3 or 4 adverse events as per EXIST-1 clinical study
Time Horizon	1 year
Results for Base Case	Total cost of everolimus (including cost of adverse events): $72,421 Incremental cost of everolimus versus • repeat respective surgery $32,469 • hydrocephalus (complication from primary surgery) $52,649 • hydrocephalus (as result of wait-and-watch) $34,785

Manufacturer's Results

The manufacturer reported that the total costs associated with everolimus treatment over a time frame of one year is $72, 421. The costs associated with subependymal giant cell astrocytoma (SEGA) surgery, hydrocephalus due to surgery complications, and hydrocephalus due to wait-and-watch were reported to be $39,952, $19,772 and $37,637 respectively (Table 2).

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

	Drug Costs/ Surgery Costs	Adverse Events Costs/ Complications Costs	Total Costs	Incremental Costs of Everolimus
Everolimus	$69,927	$2,494	**$72,421**	
SEGA surgery	$25,908	$14,044	**$39,952**	$32,469
Hydrocephalus due to surgery[a]	$18,270	$1,502	**$19,772**	$52,649
Hydrocephalus due to wait-and-watch	$34,777	$2,860	**$37,637**	$34,785

SEGA = subependymal giant cell astrocytoma.
[a] The difference in cost of management of hydrocephalus due to surgery and due to wait-and-watch is as a result of the prevalence rate of hydrocephalus due to surgery of 52.5% applied in the analysis ($19,772 = 0.525 x $37,637).
Source: Manufacturer's Pharmacoeconomic Submission.[3]

Additional Analysis

The manufacturer also submitted the costs offsets associated with angiofibroma, estimated to be $2,301 for facial angiofibroma, $8,414 for the total costs with embolization (first-line), $13,278 for partial nephrectomy (second-line), and $28,556 for complete nephrectomy.

In addition, a cost analysis including indirect costs associated with SEGA resective surgery was submitted. The indirect costs were added due to risks of stroke and autism associated with respective surgery, resulting in $5,820 annual additional indirect costs. With this analysis, the incremental cost associated with everolimus treatment versus surgery was estimated to be $26,650.

Secondary benefits in terms of cost offsets due to mental retardation and attention-deficit/hyperactivity disorders (ADHD) were included. The cost offsets were estimated to be $24,545 of direct costs and $110,632 of indirect costs for an early educational intervention program as a management of mental retardation, and a range of $728 to $1,944 as a direct cost for medications for ADHD.

CADTH Common Drug Review Results

Longer time horizon

Typically, SEGAs are very slow-growing tumours and there is potential for longer than one year of drug treatment. Moreover, the long-term evidence suggests tumour regrowth after drug discontinuation, which could mean lifetime treatment duration. As there is potential for longer than one year of drug treatment, CDR considered longer treatment durations (Table 3). Both costs that are discounted at 5% per annum and costs that are not discounted are reported.

TABLE 3: EVEROLIMUS DRUG COSTS OVER LONGER TIME HORIZON

Time horizon	Everolimus drug costs for patients with BSA less than 2.2 m^2		Everolimus drug costs for patients with BSA more than 2.2 m^2	
	Not discounted	Discounted	Not discounted	Discounted
1 year	$69,927	$69,927	$104,890	$104,890
5 years	$349,633	$317,883	$524,450	$476,825
10 years	$699,267	$566,953	$1,048,900	$850,430
20 years	$1,398,534	$915,013	$2,097,800	$1,372,500
30 years	$2,097,801	$1,128,700	$3,146,700	$1,693,000
40 years	$2,797,068	$1,259,900	$4,195,600	$1,889,800
50 years	$3,496,335	$1,340,400	$5,244,500	$2,010,600

BSA = body surface area.

Cost for everolimus treatment for patients with body surface area greater than 2.2 m^2

The recommended dose for patients with BSA greater than 2.2 m^2 is 7.5 mg daily. As everolimus is available in tablets with strength of 2.5 mg, 5 mg, and 10 mg, these patients will require 1.5 tablets of the 5 mg dose. Therefore the daily drug cost will increase to $287 daily or $104,890 annually (Table 3).

Development of hydrocephalus

There is no strong evidence that patients treated with everolimus would not develop hydrocephalus. The EXIST-1 trial was not powered to assess need for neurosurgery or episodes of hydrocephalus. There is concern that the 30% reduction in tumour growth in study 2485 might not be clinically meaningful and that evidence in support of the efficacy of everolimus over placebo in the EXIST-1 trial relies heavily on a composite outcome that is itself heavily reliant on the surrogate marker of objective response, and therefore patients might still develop hydrocephalus and will still need shunt placement. In this case, including the cost of shunt replacement in the total cost of everolimus treatment would result in a total annual cost of $110,058 (or $145,021 for patients with a BSA greater than 2.2 m^2).

Need for resective surgery

There is no strong evidence that patients who are not immediate candidates for surgery and were treated with everolimus would not need a surgery in the later stage of the disease management. In that case, including the cost of resective surgery in the total cost of everolimus treatment would result with a total annual cost of $112,373 (or $147,336 for patients with a BSA greater than 2.2 m^2).

Key Limitations

Identified limitation	Description	Implication
Type of analysis	The submitted analysis is a cost analysis and does not take into account the effectiveness of the drug and its comparators.	Due to the lack of clinical evidence, this type of analysis might be the most appropriate at the time. However, the question of the cost-effectiveness of everolimus versus its comparators remains unanswered.
Short time horizon	Typically, SEGAs are very slow-growing tumours and there is potential for longer than one year of drug treatment. Moreover, the long-term evidence suggests tumour regrowth after drug discontinuation, which would mean lifetime treatment duration.	Full impact of treatment and costs are not fully evaluated in the manufacturer's economic submission.
Cost for everolimus	Cost for everolimus treatment for patients with BSA greater than 2.2 m^2 has not been captured. The recommended dose for patients with a BSA greater than 2.2 m^2 is 7.5 mg daily. As everolimus is available in tablets with strength of 2.5 mg, 5 mg, and 10 mg, these patients will need 1.5 tablets of the 5 mg dose, and therefore the daily cost will be $287.37 or a yearly drug cost of $104,890.	This would increase the reported cost of treatment.
Development of hydrocephalus	There is no strong evidence that patients treated with everolimus would not develop hydrocephalus.	Including the cost of shunt replacement in the total cost of everolimus treatment would result in a total annual cost of $110,058 (or $145,021 for patients with a BSA greater than 2.2 m^2).
Need for resective surgery	There is no strong evidence that patients who are not immediate candidates for surgery and were treated with everolimus would not need a surgery in the later stage of the disease management.	Including the cost of resective surgery in the total cost of everolimus treatment would result in a total annual cost of $112,373 (or $147,336 for patients with a BSA greater than 2.2 m^2).
Minimally invasive surgeries	There are minimally invasive techniques that are now used for SEGAs 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.	This may underestimate the incremental cost of everolimus.
Assumptions of everolimus treatment	Patients on everolimus treatment have no risk of repeat SEGA surgery and its associated complications.	Uncertain. There is no clinical evidence to support this assumption.
Assumptions of everolimus treatment	Patients on everolimus treatment have no risk of developing hydrocephalus and its associated complications.	Uncertain. There is no clinical evidence to support this assumption.

BSA = body surface area; SEGA = subependymal giant cell astrocytoma.

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