Canadian Expert Drug Advisory Committee
Final Recommendation – Plain Language Version

CYCLOSPORINE OPHTHALMIC EMULSION 0.05%
(Restasis – Allergan Inc.)
Indication: Moderate to Moderately Severe Dry Eye Disease

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that Restasis, which is also called cyclosporine ophthalmic emulsion, not be listed by Canada's publicly funded drug plans for the treatment of moderate to moderately severe dry eye disease.

Reasons for the Recommendation:
1. There are no good-quality medical studies that compare Restasis with other appropriate treatments in patients with moderate to moderately severe dry eye disease (level 2-3 severity by Dry Eye WorkShop [DEWS] guidelines).
2. It was unclear if the results reported by the manufacturer for a specially selected group of patients from several trials represented important improvements.

Background:
Restasis acts as a topical immunomodulator with anti-inflammatory effects. Restasis is approved by Health Canada for the treatment of moderate to moderately severe (level 2-3 severity by DEWS guidelines) aqueous deficient dry eye disease. The symptoms themselves are moderate to moderately severe and include ocular (eye) staining, lowering of tear production and changing visual symptoms, such as blurred vision. Restasis is used to treat certain patients whose eyes are not producing enough tears to keep the eye moist and comfortable.

Restasis is available as a 0.05% sterile preservative-free emulsion in 0.4 mL single-use vials. The Health Canada-approved dose is one drop instilled twice a day in each eye, approximately 12 hours apart.

Summary of CEDAC Considerations:
To make their decision, the Committee considered the following information prepared by the Common Drug Review (CDR): a review of the medical studies of Restasis and a review of economic information prepared by the manufacturer of Restasis. Also, CEDAC considered information that patient groups submitted about outcomes and issues important to patients who have the condition for which the drug is indicated or who might use the drug.

Clinical Trials

The CDR did not find any published or unpublished good-quality studies that met the criteria specified in the CDR review protocol regarding the types of patients studied; that is, a study of patients with moderate to moderately severe dry eye disease (level 2-3 severity by DEWS guidelines). Rather, the CDR reviewed and redid a number of the manufacturer's analyses in which results for patients that were specially selected from up to five medical studies were pooled. The main pooling of results, which was the basis for the Health Canada approval of Restasis, was for a specially selected group of patients participating in one of three studies.

The focus of the CDR review was the main pooling of results (from three of the five studies), as well as the results from the three individual studies. Further pooling of results that included patients specially selected from two additional studies was conducted by the manufacturer to see if adding results from more studies changed their conclusions.

The three studies used in the main pooling of results (studies 192371-002, -003, and -501, with 1,316 patients) were similarly conducted studies where patients were given eye drops containing Restasis 0.05%, Restasis 0.1%, or vehicle (a liquid containing no active medication). All eye drops were to be used twice daily for six months. Patients were also allowed to use artificial tears in all of the studies. None of the studies included patients with mild (level 1) dry eye disease. Patients with severe (level 4) disease were included in the original studies, but not included in the group of patients whose results were pooled.

The main pooling of results included only patients in the aforementioned three studies that had level 2-3 dry eye disease, and who received either Restasis 0.05% or vehicle; that is, 316 patients. Safety was assessed for all patients (878 patients) in the three studies who received at least one dose of cyclosporine 0.05% or vehicle.

Outcomes

Outcomes of interest were defined in advance in the CDR review protocol. Of these, the Committee discussed the following: blurred vision, staining of the eye surface, Schirmer's test score, and a measure of symptoms and function. The Ocular Surface Disease Index (OSDI) was used to measure symptoms and function. None of the three studies reported quality of life data.

The two main purposes of the manufacturer's pooled analysis were to determine:

- the percentage of patients who had a total staining score of zero at six months
- the percentage of patients who had a blurred vision score of zero at six months.

Staining provides an estimate of damage to the eye surface. The total staining score ranges from 0 to 15, with higher numbers meaning worse damage. Blurred vision was graded on a scale of 0 to 4, with higher numbers meaning more severe blurred vision. The Schirmer's test is an assessment of tear formation in which a small piece of filter paper is placed inside the lower eyelid for five minutes, after which the length of wetting is measured in millimetres (mm). A responder in the Schirmer's test was defined as a patient having an increase of at least 10 mm after five minutes, compared with the result at the beginning of the study. The OSDI includes three areas of concern (eye symptoms, vision-related function, and environmental triggers) and is scored from 0 to 100, or alternatively from 0 to 1, with higher scores being worse. The smallest change in the OSDI which is important for patients depends upon the severity of their

disease, and is suggested to range from 4.5 to 7.3 for mild or moderate disease, and from 7.3 to 13.4 for severe disease (on a 0-to-100 scale).

Except for the OSDI, no published information regarding the smallest change, which is important for patients, was identified by CDR for any of the aforementioned outcomes; nor was there any evidence of the accuracy or consistency of the blurred vision scale.

Results

Efficacy or Effectiveness

The description of effectiveness, which follows, is from the main pooling of results; that is, results from patients with level 2 to 3 dry eye disease participating in one of three studies.

- The percentage of patients with a total staining score of 0 was greater for Restasis compared with vehicle at six months (12.0% versus 3.1%), but not at earlier visits (one, three, and four months). The average change in the total staining score, from study start to six months, was about the same for Restasis and vehicle.
- The percentage of patients with an increase of at least 10 mm in the Schirmer's test was greater for Restasis compared with vehicle at six months (17.1% versus 6.2%). The average change in the Schirmer's score from study start to six months was greater for Restasis compared with vehicle. Results for both the aforementioned measures of the Schirmer's test were not the same across all three studies. Further, the Committee questioned whether the differences between Restasis and vehicle for the Schirmer's test results were important.
- The percentage of patients with a blurred vision score of 0 was greater for Restasis compared with vehicle at six months (49.6% versus 37.7%), but not at earlier visits (one, three, and four months). Results were not the same across all three studies.
- Changes from study start in the OSDI were about the same for Restasis and vehicle.
- Quality of life was not reported in the three studies.

Harms (Safety and Tolerability)

The description of harms, which follows, is for all patients in the studies who received at least one dose of study treatment; that is, not just the patients with level 2 to 3 dry eye disease.

- Burning eye was the most commonly reported side effect and occurred more often in Restasis 0.05% patients (range: 15.2% to 17.5%) compared with vehicle (range: 5.8% to 8.8%) in the three studies.
- More patients in the vehicle group had a serious side effect, compared with patients in the Restasis 0.05% group, in two of the three studies. The percentage of patients who had a serious side effect ranged from 5.6% to 5.9% in the Restasis 0.05% groups, compared with 1.9% to 8.1% in the vehicle groups.
- More patients in the Restasis 0.05% group stopped taking part in the study due to side effects compared with patients in the vehicle group, in two of three studies. The percentage of patients who stopped taking part in the study due to side effects ranged from 6.3% to 7.7% in the Restasis 0.05% groups compared with 4.4% to 11.3% for vehicle.

Cost and Cost-Effectiveness

The manufacturer submitted economic information to compare the health benefit of Restasis with a preservative-free fresh tear that is very similar to the vehicle used in the medical studies.

The manufacturer used the DEWS severity classification scheme and results from the pooled analysis of the three studies in their economic assessment. Quality of life data and resource use were obtained from the literature. A number of possible problems were identified with the manufacturer's submission, and the results of the economic analysis depended on which data were used. The manufacturer included the cost of artificial tear substitutes, which are not covered by the majority of participating drug plans. Removing the cost of artificial tear substitutes from consideration worsens the estimated cost-effectiveness of Restasis. Also, the manufacturer assumed that improvements in patients' DEWS classification would result in improvements in quality of life, although the clinical studies did not provide this information.

The daily cost of Restasis ($6.33) is significantly higher than the daily cost for other treatments used for dry eye disease: artificial tears ($0.18 to $0.39), topical corticosteroids ($0.28 to $1.24), and topical non-steroidal anti-inflammatory drugs ($0.51 to $2.51).

Patient Input Information:

The following is a summary of information provided by two patient groups that responded to the CDR Call for Patient Input:

- Patients noted that dry eye disease results in substantial discomfort. They described bothersome eye symptoms as gritty, sore, burning, painful, and sun- and wind-sensitive.
- Patients provided examples of how their quality of life was affected by their reduced ability to read, watch television, drive, and participate in outside activities because of their dry eye disease.
- Patients considered twice-daily application of Restasis to be more convenient compared with artificial tears, which are commonly instilled many times per day. They mentioned side effects of ophthalmic corticosteroids as a concern.

Other Discussion Points:

- The Committee discussed a number of problems with the pooled analysis, including that it was planned after the studies were complete, which decreased the confidence in the reported results.
- The Committee noted it is not certain that the results (as measured in the pooled analysis) will be the same when the medication is used more widely. Also, it is not certain how these results can be applied to clinical practice.

CEDAC Members:
Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. James Silvius.

June 15, 2011 Meeting

Regrets:
Two CEDAC members did not attend.

Conflicts of Interest:
One CEDAC member did not participate due to considerations of conflict of interest.

About this Document:
The information contained within this plain language version of the Canadian Expert Drug Advisory Committee (CEDAC) Recommendation about this drug is based on the information found within the corresponding technical version of the CEDAC Recommendation.

In making its recommendation, CEDAC considered the best clinical and pharmacoeconomic evidence available, up to that time. Health care professionals and those requiring more detailed information are advised to refer to the technical version available in the CDR Drug Database on the CADTH website (www.cadth.ca).

Background on CEDAC
CEDAC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). The committee is made up of drug evaluation experts and public members. CEDAC provides recommendations about whether or not drugs should be listed for coverage through the participating publicly funded drug plans; however, the individual drug plans make their own decision about whether or not to cover a drug.

In making its recommendations, CEDAC decides if the drug under review ought to be covered by the participating public drug plans based on an evidence-informed review of the medication's effectiveness and safety, and based on an assessment of its cost-effectiveness in comparison with other available treatments. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

The CEDAC Recommendation neither takes the place of a medical professional providing care to a particular patient, nor is it intended to replace professional advice. CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada, the federal government, any provincial or territorial government, or any pharmaceutical manufacturer.

The manufacturer has reviewed this document and has not requested the deletion of any confidential information.