CEDAC FINAL RECOMMENDATION

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 cyclosporine ophthalmic emulsion not be listed.

Reasons for the Recommendation:
1. There are no double-blind randomized controlled trials (RCTs) comparing cyclosporine ophthalmic emulsion with appropriate comparators specifically in patients with moderate to moderately severe dry eye disease (level 2 to 3 severity by Dry Eye Workshop [DEWS] guidelines).

2. The outcomes reported in the post hoc subgroup meta-analysis conducted by the manufacturer were considered to be of uncertain clinical importance.

Background:
Cyclosporine ophthalmic emulsion has a Health Canada indication for the treatment of moderate to moderately severe (level 2 to 3 severity by DEWS guidelines) aqueous-deficient dry eye disease, characterized by moderate to moderately severe: ocular staining, reduction in tear production and fluctuating visual symptoms, such as blurred vision.

Cyclosporine ophthalmic emulsion is a topical solution with immunomodulatory and anti-inflammatory properties. It 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:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of cyclosporine ophthalmic emulsion, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials

The CDR identified no published or unpublished RCTs that met the inclusion criteria specified in the systematic review protocol with respect to the study population; i.e., a RCT of patients with moderate to moderately severe dry eye disease (level 2 to 3 severity by DEWS guidelines). Rather, the CDR reviewed and replicated a number of post hoc subgroup meta-analyses conducted by the manufacturer, which included up to five RCTs. The primary subgroup meta-analysis, which was the basis for the Health Canada approval of cyclosporine ophthalmic suspension, included three RCTs.

The focus of the CDR review was the primary subgroup meta-analysis and the data from the three individual RCTs included in the meta-analysis. Further meta-analyses that included two additional RCTs were conducted by the manufacturer as sensitivity analyses.

The three RCTs included in the primary subgroup meta-analysis (studies 192371-002, -003, and -501, total N = 1,316) were similarly conducted trials that randomized patients to cyclosporine 0.05%, cyclosporine 0.1%, or vehicle, all administered twice daily for six months; concomitant administration of artificial tears was allowed in all trials. None of the trials enrolled patients with mild (level 1) dry eye disease. Patients with severe (level 4) disease were included in the original trials, but excluded from the subsequent subgroup meta-analysis.

The primary subgroup meta-analysis included only patients with level 2 to 3 dry eye disease, who received either cyclosporine 0.05% or vehicle; N = 316. Safety was assessed for all randomized patients in the three trials who received at least one dose of cyclosporine 0.05% or vehicle; N = 878.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: blurred vision, ocular surface staining, Schirmer's test score, and a measure of symptoms and function (the Ocular Surface Disease Index [OSDI]). None of the three trials reported quality of life data.

The co-primary outcomes for the primary subgroup meta-analysis were:

- the proportion of total staining responders (total staining score of 0 at six months)
- the proportion of blurred vision responders (score of 0 at six months).

Staining provides an estimate of damage to the ocular surface. The total staining score ranges from 0 to 15, with higher numbers indicative of worse damage. Blurred vision was graded on a scale of 0 to 4, with higher numbers indicating greater severity. The Schirmer's test is an assessment of tear secretion, wherein 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. A responder in the Schirmer's test was defined as an increase from baseline of ≥ 10 mm after five minutes. The OSDI includes three domains (ocular symptoms, vision-related function, and environmental triggers) and is scored from 0 to 100, or alternatively from 0 to 1, with higher scores indicating greater disability. The minimally clinically important difference for the OSDI depends upon disease severity, 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).

With the exception of the OSDI, no published information regarding minimally clinically important differences was identified by the CDR for any of the above outcomes; nor was there any evidence for the validity or reliability of the blurred vision scale.

Results

Efficacy or Effectiveness

Results are for the pooled data from the primary meta-analysis of the level 2 to 3 subgroup, from three RCTs:

- The proportion of patients achieving a total staining score of 0 was statistically significantly greater for cyclosporine compared with vehicle (12.0% versus 3.1%) at six months, but not at earlier visits (one, three, and four months). The change from baseline in the total staining score at six months was not statistically significantly different between cyclosporine and vehicle; mean difference (MD) (95% confidence interval [CI]): –0.40 (–0.95 to 0.15).
- The proportion of patients who achieved an increase of ≥ 10 mm in the Schirmer's test was statistically significantly greater for cyclosporine compared with vehicle (17.1% versus 6.2%) at six months. The change from baseline in the Schirmer's score at six months was statistically significantly greater for cyclosporine compared with placebo; MD (95% CI): 2.67 (1.08 to 4.26). Results for both the above measures of the Schirmer's test appeared inconsistent between the three included trials, and the Committee questioned the clinical importance of these differences.
- The proportion of patients with a blurred vision score of 0 was statistically significantly greater for cyclosporine compared with vehicle (49.6% versus 37.7%) at six months, but not at earlier visits (one, three, and four months). Results between the three included trials appeared inconsistent.
- Changes from baseline in the OSDI (scored 0 to 1) were not statistically significantly different between cyclosporine and vehicle; MD (95% CI): 0.01 (–0.03 to 0.05).
- Quality of life was not reported in the three RCTs.

Harms (Safety and Tolerability)

Harms data described below are for all randomized patients (i.e., not limited to the level 2 to 3 subpopulation) who received at least one dose of study treatment:

- Burning eye was the most commonly reported adverse event, occurring more frequently in subjects treated with cyclosporine 0.05% (range: 15.2% to 17.5%) compared with vehicle (range: 5.8% to 8.8%).
- Serious adverse events were numerically more frequent in the vehicle groups compared with cyclosporine 0.05% in two of three trials. The frequency of serious adverse events ranged from 5.6% to 5.9% in the cyclosporine 0.05% groups, compared with 1.9% to 8.1% in the vehicle groups.
- Withdrawals due to adverse events were numerically more frequent in the cyclosporine 0.05% groups compared with vehicle in two of three trials. The frequency of withdrawal due to adverse events ranged from 6.3% to 7.7% in the cyclosporine 0.05% groups, compared with 4.4% to 11.3% for vehicle.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing cyclosporine emulsion with preservative-free fresh tear, which closely matches the oil-based emulsion used in the comparator arms of the clinical trials. The model health states were defined using the DEWS severity classification scheme. Clinical inputs were based on the pooled post hoc subgroup analysis of patients enrolled in three Phase 3 clinical trials (-002, -003, and -501) who met the DEWS level 2 and 3 classification scheme. Quality of life data and resource use were obtained from the literature. The manufacturer reported that treatment with cyclosporine emulsion is associated with an incremental cost per quality-adjusted life-year (QALY) of $80,571 when compared with its vehicle.

A number of limitations were identified with the manufacturer's submission. The manufacturer included the cost of artificial tear substitutes, which the majority of participating drug plans do not cover; the incremental cost per QALY increases to $159,924 when removing the cost. The manufacturer assumed that improvements in DEWS classification would result in improvements in quality of life, although this was not captured in the clinical trials. The results of the economic analysis were sensitive to the utility values selected, with the incremental cost per QALY increasing to more than $135,000 when using alternative estimates obtained from the same source.

The daily cost of topical cyclosporine ophthalmic emulsion ($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 cyclosporine ophthalmic suspension to be more convenient than artificial tears, which are commonly instilled many times per day. They mentioned adverse consequences of ophthalmic corticosteroids as a concern.

Other Discussion Points:

- The Committee discussed a number of methodological issues regarding the primary post hoc subgroup analysis (e.g., selection bias based on use of a post-study classification scheme, loss of benefit of randomization, and heterogeneity in response) that reduced confidence in the reported results.
- The Committee noted that the generalizability and application of study results to clinical practice are unclear.

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:
CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

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

The Final 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 view of Health Canada or any provincial, territorial, or federal government or the manufacturer.