# CEDAC FINAL RECOMMENDATION

## AZELAIC ACID
## (Finacea – Bayer Inc.)
## Indication: Rosacea

**Recommendation:**
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that azelaic acid 15% gel be listed.

**Reason for the Recommendation:**
In two randomized controlled trials (RCT) azelaic acid 15% gel had similar efficacy compared with metronidazole, as either 0.75% or 1% gel, for patients with mild-to-moderate papulopustular rosacea in terms of reduced lesion count and investigator assessed global severity.

**Of Note:**
Azelaic acid 15% gel is similar in cost to metronidazole 0.75% gel, but more costly than metronidazole 1% gel, when all three products are applied at the frequencies recommended in the product monographs.

**Background:**
Azelaic acid has a Health Canada indication for the treatment of inflammatory papules and pustules and erythema of mild-to-moderate rosacea. Azelaic acid has antikeratinizing and antibacterial properties, but its mechanism of action in rosacea is unknown. It is available as a 15% topical gel, and the Health Canada-approved dose is 0.5 g applied twice daily.

**Summary of CEDAC Considerations:**
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of randomized controlled trials of azelaic acid, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

***Clinical Trials***

The systematic review included four RCTs of adult patients with mild-to-moderate rosacea. Two trials, A03125 (N = 329) and A03126 (N = 335) were double-blind, vehicle-controlled trials. A08681 (N = 251) was a double-blind, active-controlled trial and Wolf (N = 160) was a single (investigator), blind, active-controlled trial.

Studies A03125 and A03126 were similarly conducted trials comparing azelaic acid 15% gel with vehicle gel, both applied twice daily for a duration of 12 weeks. The proportion of patients withdrawing from the trials was 14% and 12% for A03125 and A03126 respectively.

Study A08681 compared azelaic acid 15% gel with metronidazole 0.75% gel, both applied twice daily for 15 weeks; 10% of patients withdrew from the trial (11% for azelaic acid and 8% for metronidazole). Wolf compared azelaic acid 15% gel applied twice daily with metronidazole 1% gel applied once daily; the trial duration was 15 weeks, and 15% of patients withdrew from the trial (the frequency of withdrawal by treatment arm was not reported).

The three trials that were funded by the manufacturer of azelaic acid (A03125, A03126, and A08681) were designed to test the superiority of azelaic acid to comparator. The Wolf study was funded by a manufacturer of metronidazole gel, and was designed to test the non-inferiority of metronidazole gel 1% compared with azelaic acid 15% gel, employing a non-inferiority margin of -15% for the primary outcome.

***Outcomes***

The co-primary outcomes in the vehicle-controlled trials were the nominal change in inflammatory lesion count from baseline and the investigator global assessment of severity (IGAS) at the end of treatment. The primary outcome in study A08681 was the nominal change in inflammatory lesion count from baseline. The primary outcome in the Wolf study was the percent change in inflammatory lesion count from baseline; metronidazole would be considered non-inferior to azelaic acid if the between-treatment difference in the percent change in inflammatory lesion count did not exceed -15%.

Other outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: quality of life, investigator global assessment of improvement (IGAI), patient global assessment of improvement (PGAI), investigator assessment of improvement in erythema and telangiectasia, patient assessment of cosmetic acceptability, and adverse events.

***Results***

***Efficacy or Effectiveness***

- Quality of life was not evaluated in any of the four trials.
- In study A08681 azelaic acid 15% gel was statistically significantly superior to metronidazole 0.75% gel based on the difference in the reduced number of inflammatory lesions at end of treatment; mean difference (MD) = −2.9 (95% confidence interval [CI], −4.9 to −1.0). In the Wolf study, metronidazole 1% gel once daily was reported to be non-inferior to azelaic acid

15% gel twice daily (non-inferiority margin of −15%) based on the difference in the percent change in inflammatory lesion count at end of treatment; median difference = −5% (95% CI, −11.2 to 0.7) for the per-protocol population.

- Compared with vehicle gel, azelaic acid 15% gel resulted in a statistically significantly greater reduction in the number of inflammatory lesions at end of treatment in studies A03125 and A03126; MD = −3.6, (95% CI: −5.3 to −2.0) and MD = −2.7 (95% CI: −4.9 to −0.6) respectively.
- The proportion of patients achieving a treatment response (defined as an IGAS score of clear or minimal) at study end was statistically significantly greater for azelaic acid compared with vehicle in A03125, and just missed statistical significance in A03126. In A08681 and the Wolf study the proportion of patients achieving an IGAS score of clear or minimal at study end was not statistically significantly different between azelaic acid and metronidazole.
- In A08681, global improvement, as measured by the IGAI was statistically in favour of azelaic acid compared with metronidazole 0.75% gel. In A03125 and A03126, global improvement as measured by the IGAI and the PGAI was statistically significantly in favour of azelaic acid compared with vehicle gel. The Wolf study did not include the measures IGAI or PGAI.
- Investigator assessed improvement in erythema was statistically significantly greater for azelaic acid compared with vehicle gel (in both A03125 and A03126) and compared with metronidazole 0.75% (in A08681).
- Investigator assessed telangiectasia was not statistically significantly different between azelaic acid and metronidazole 0.75% (in A08681) or between azelaic acid and vehicle gel (in A03125 and A03126).

***Harms (Safety and Tolerability)***

- Serious adverse events were infrequent in all four trials.
- The proportion of patients experiencing cutaneous adverse events was higher among those treated with azelaic acid compared with vehicle gel (A03125 and A03126) and compared with metronidazole 0.75% (A08681). Cutaneous adverse events that were more common with azelaic acid than with comparators included, burning or pain, paresthesia, and pruritis. The majority of cutaneous adverse events observed with azelaic acid in A03125, A03126, and A08681 were considered mild or moderate.
- In the Wolf study, the proportion of patients reporting moderate or severe stinging or burning was 5% greater for azelaic acid compared with metronidazole.

***Cost and Cost-Effectiveness***

The manufacturer submitted a cost comparison of azelaic acid with metronidazole gel (MetroGel) 0.75%, based on claims of similar clinical efficacy as demonstrated in the results of study A08681. Based on product monographs, both the above topical preparations are applied twice daily, and the manufacturer assumed patients would use 1 g daily of either gel. When considering the per gram costs, azelaic acid ($0.60) is similar in price to metronidazole gel 0.75% ($0.66).

Azelaic acid at 0.5 g twice daily ($0.60) is more costly than metronidazole 1% gel at 0.5 g daily (dosed as per product monograph) ($0.30).

**Patient Input Information:**

- Patient input was received from one patient group.
- Patients indicated that controlling symptomatology is key to improving quality of life. An acceptable adverse event profile was also considered important.
- Patients pointed out that there are few indicated treatments for rosacea.

**Other Discussion Points:**

- The Committee considered that the primary outcomes of the studies were appropriate given that lesion count is a relatively objective measure, and that the number of lesions has been shown to be correlated with patient assessment of disease severity.
- The Committee noted that there were no good quality data comparing azelaic acid with other non-metronidazole products employed for rosacea, such as benzoyl peroxide.
- The greater frequency of cutaneous adverse effects observed with azelaic acid compared with metronidazole gel was not considered a great disadvantage as patients easily perceive these adverse effects and may switch to an alternative therapy.
- Based on the reviewed trials, it is unknown if patients that fail to improve on metronidazole gel will respond to azelaic acid.
- The relapsing-remitting nature of the condition was noted in the context of the difficulty of defining treatment failure.
- There was uncertainty surrounding the likely frequency of application of the different products in clinical practice. The Committee expressed concern that at the recommended frequency of application, azelaic acid (twice daily) may be more costly compared with metronidazole 1% gel (once daily). However, it was noted that patients will choose for themselves the frequency and duration of use of these products as their condition flares and remits.

**CEDAC Members Participating:**

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, and Dr. Yvonne Shevchuk.

**Regrets:**

None

**Conflicts of Interest:**

None

**About this Document:**

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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.

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