



CDEC FINAL RECOMMENDATION

DIENOGEST

(Visanne – Bayer Inc.)

Indication: Management of Pelvic Pain Associated With Endometriosis

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that dienogest be listed for the management of pelvic pain associated with endometriosis in patients for whom one or more less costly hormonal options are either ineffective or cannot be used.

Reasons for the Recommendation:

1. In two randomized controlled trials (RCTs) included in the systematic review, dienogest was superior to placebo (study A32473), and non-inferior to leuprolide (study AU19), in reducing pelvic pain in patients with endometriosis.
2. At the submitted price, the daily drug cost of dienogest (\$1.96) is less than all alternatives with a Health Canada indication for the treatment or hormonal management of endometriosis (\$2.09 to \$13.86), with the exception of generic injectable medroxyprogesterone (\$1.29). Dienogest is more costly than combined hormonal contraceptives (\$0.33 to \$0.64 daily).

Of Note:

The Committee noted that the Health Canada indication for dienogest was specific to the management of pelvic pain associated with endometriosis.

Background:

Dienogest has a Health Canada indication for the management of pelvic pain associated with endometriosis. Dienogest is a progestin. It is available as 2 mg oral tablets, and the dose approved by Health Canada is 2 mg once a day.

Summary of CDEC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of dienogest, a critique of the manufacturer's pharmaco-economic evaluation, and patient group-submitted information about outcomes and issues important to patients.

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Clinical Trials

The systematic review included three RCTs of patients with pelvic pain associated with endometriosis.

- Study AU19 (N = 252) was a 24-week open-label non-inferiority RCT that randomized patients to dienogest 2 mg daily or leuprolide acetate 3.75 mg intramuscular depot injection every four weeks.
- Study A32473 (N = 198) was a 12-week double-blind RCT that randomized patients to dienogest 2 mg daily or placebo.
- The Harada study (N = 271) was a 24-week double-blind RCT that randomized patients to dienogest 1 mg twice daily or buserelin 300 mcg intranasally three times a day. The formulation and dosing of dienogest in this trial differed from that approved by Health Canada.

Concomitant use of analgesics was allowed in all trials. However, only study A32473 provided and analyzed the use of supportive analgesic medication; specifically, ibuprofen 400 mg tablets to a maximum allowable 1,200 mg per day.

Less than 10% of patients withdrew from any trial, and the frequency of withdrawal was similar between treatment groups in all trials. Neither study AU19 nor the Harada study provided hormonal add-back therapy to patients randomized to leuprolide acetate or buserelin, respectively, to minimize the adverse events associated with these treatments. No RCTs compared dienogest with combined hormonal contraceptives or other progestins.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: pelvic pain, quality of life, analgesic use, adverse events, serious adverse events, and withdrawal due to adverse events.

The primary outcome in study AU19 was the absolute change in pelvic pain from baseline to end of treatment on the visual analog scale (VAS; 0 = absence of pain, 100 = unbearable pain); dienogest would be considered non-inferior to leuprolide if results for the between-treatment difference did not exceed the pre-specified non-inferiority margin of 15 on the VAS scale. The co-primary outcomes in study A32473 were absolute change in pelvic pain from baseline to end point on the 0 to 100 VAS, and rescue analgesic use. The primary outcome in the Harada study was change from baseline to end of treatment in symptom severity score (five symptoms; scored 0 = none to 4 = severe).

Quality of life was assessed using the 36-item Short Form Health Survey (SF-36) in all trials. Studies AU19 and A32473 assessed quality of life and functional status using the Biberoglu and Behrman severity profile, which rates three symptoms (dysmenorrhea, dyspareunia, and pelvic pain) and two signs (pelvic pain and induration).

Results

The Committee focused its discussion on the two trials employing the Health Canada–approved formulation and dose of dienogest; studies AU19 and A32473.

Efficacy or Effectiveness

- In study A32473, the average reduction in pelvic pain, from baseline to end point on the VAS, was statistically significantly greater for dienogest than for placebo (–27.4 versus –15.1, respectively); mean difference (MD) (95% confidence interval [CI]):12.3 (6.4 to 18.1). In study AU19, dienogest was reported to be non-inferior to leuprolide acetate, based on the reduction in pelvic pain from baseline to end of treatment on the VAS (–47.5 versus –46.0, respectively); MD (95% CI): –1.5 (–9.3 to 6.3).
- There were no notable differences between dienogest and leuprolide acetate, or between dienogest and placebo, in terms of the change from baseline in the mental and physical summary scores of the SF-36 or the Biberoglu and Behrman severity profile; no statistical analysis of the results was reported.
- Use of concomitant analgesic medication was similar between dienogest and leuprolide groups in study AU19 and between dienogest and placebo groups in study A32473.

Harms (Safety and Tolerability)

- The proportion of patients experiencing serious adverse events in the trials was low. Serious adverse events were numerically higher with dienogest than with leuprolide in study AU19 (4.2% versus 0.8%, respectively). No serious adverse event was reported in study A32473.
- The proportion of patients with adverse events was 68% versus 74% for dienogest and leuprolide acetate, respectively, in study AU19 and 33% versus 26% for dienogest and placebo, respectively, in study A32473.
- Withdrawal due to adverse events was relatively infrequent and the incidence was similar between treatment arms in the included trials.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing dienogest with leuprolide for the management of pelvic pain associated with endometriosis based on an open-label RCT (AU19). The manufacturer considered costs of drug treatment, administration cost of leuprolide, and the cost of add-back therapy for patients receiving leuprolide for bone-mineral density loss (based on the results of AU19) in its analysis. The manufacturer considered a 24-month time frame, and assumed 18 months of treatment and an additional six months clinical benefit with dienogest; and 5.1 months of treatment and an additional 18.9 months of clinical benefit with leuprolide. The manufacturer's analysis was limited by the lack of information on combined hormonal contraceptives, which are commonly used as first-line therapy for management of pain associated with endometriosis. In addition, the Committee felt there was uncertainty in the likely cost of treatment, given the lack of information on long-term use (e.g., duration of treatment).

At the submitted price, the daily drug cost of dienogest (\$1.96) is less than all alternatives approved for the treatment or hormonal management of endometriosis (\$2.09 to \$13.86), with the exception of generic injectable medroxyprogesterone (\$1.29). Dienogest is more costly than combined hormonal contraceptives (\$0.33 to \$0.64 daily).

Patient Input Information:

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

- Symptoms of pain and fatigue were reported as being particularly important for women with endometriosis. Symptoms of endometriosis were noted to negatively affect quality of life by

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preventing women from carrying out daily activities, resulting in feelings of isolation and depression.

- The negative impact of endometriosis on fertility was noted.

Other Discussion Points:

- The Committee noted there are no RCTs comparing dienogest with combined hormonal contraceptives for this indication.
- The Committee noted that endometriosis is a chronic condition for which long-term treatment of symptoms may be required; however, trials included in the systematic review were limited by their short duration (maximum 24 weeks).

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

March 21, 2012 Meeting

Regrets:

None

Conflicts of Interest:

None

About this Document:

CDEC 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 CDEC made its recommendation. 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 in conformity with the *CDR Confidentiality Guidelines*.

The Final CDEC 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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