FINAL CDEC RECOMMENDATION

DOXYCYCLINE MONOHYDRATE
(Apprilon – Galderma Canada Inc.)
Indication: Inflammatory Rosacea

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that 40 mg doxycycline modified-release capsules not be listed.

Reason for the Recommendation:
The Committee considered the comparative clinical benefit of 40 mg doxycycline modified-release (MR) capsules to be uncertain due to limitations in the design and analysis of the single randomized controlled trial (RCT) (ROSE-401) that compared 40 mg doxycycline MR capsules with 100 mg doxycycline immediate-release (IR) capsules.

Background:
Doxycycline monohydrate has a Health Canada indication for the treatment of inflammatory lesions (papules and pustules) of rosacea in adult patients. Doxycycline has been shown to inhibit neutrophil activity and several pro-inflammatory reactions that may be involved in the pathophysiology of rosacea. Apprilon is available as 40 mg MR capsules (30 mg IR and 10 mg delayed-release beads).

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind, active-controlled RCTs of doxycycline monohydrate and a critique of the manufacturer's pharmacoeconomic evaluation. The manufacturer submitted a confidential price for 40 mg doxycycline MR capsules.

Patient Input Information
No patient groups responded to the CDR call for patient input.

Clinical Trials
The review included one 16-week, double-blind RCT (ROSE-401; N = 91) that compared 40 mg doxycycline MR capsules with 100 mg doxycycline IR capsules once daily in patients with moderate to severe inflammatory rosacea. Both groups were treated concurrently with open-label 1% metronidazole topical gel. The proportion of randomized patients who discontinued treatment in the 40 mg MR group was greater than in the 100 mg IR group (*[confidential data removed at manufacturer's request]*).

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following:

- Total inflammatory lesion count — the sum of the papule count, pustule count, and nodule count.
- Investigator Global Assessment — a scale ranging from 0 (clear) to 5 (very severe) based on the number of papules, pustules, and nodules present.
- Clinical Erythema Assessment — a scale ranging from 0 (none) to 4 (severe) based on the level of redness. It is used to evaluate five facial regions: forehead, chin, nose, right cheek, and left cheek.
- Serious adverse events; total adverse events; gastrointestinal adverse events; opportunistic infections, such as vaginal candidiasis; antibiotic resistance; and withdrawals due to adverse events.

In ROSE-401, the primary efficacy end point was the change in total inflammatory lesion count from baseline to study end point (i.e., week 16 or last available post-baseline visit for each patient). The trial was designed to assess non-inferiority between 40 mg MR and 100 mg IR in total inflammatory lesion count. The study protocol specified that an observed mean difference between treatments of less than five lesions would support a conclusion of non-inferiority of 40 mg MR versus 100 mg IR based on a one-sided 90% confidence interval (CI) boundary.

The design and analysis of the ROSE-401 trial was limited by the following factors: there were a high proportion (*[confidential data removed at manufacturer's request]*) of early discontinuations; there was no per-protocol analysis conducted, which is important to include for non-inferiority trials; the validity and clinical significance of the non-inferiority margin of five lesions was uncertain, and the number of participants randomized (91) was less than the number of patients pre-specified in the study protocol (approximately 100 participants).

Results

Efficacy or Effectiveness

- The mean difference (MD) in change from baseline in total inflammatory lesion count at study end point between 40 mg MR and 100 mg IR was –0.3 (95% CI, –4.6 to 4.0), *P* = 0.830. The pre-specified non-inferiority margin of five lesions was achieved. However, given the questionable validity of the non-inferiority margin, the relatively high rate of premature discontinuation (total of *[confidential data removed at manufacturer's request]*), and the lack of a per-protocol analysis, the Committee concluded that the results of the ROSE-401 trial did not definitively demonstrate non-inferiority of 40 mg MR with 100 mg IR.
- There was no statistically significant difference in change from baseline of the Clinical Erythema Assessment total scores [MD (95% CI) = –0.2 (–1.9 to 1.5); *P* = 0.500] or change from baseline in the Investigator Global Assessment total scores [MD (95% CI) = 0.0 (–0.5 to 0.5); *P* = 0.857].

Harms (Safety and Tolerability)

- The proportion of patients with at least one adverse event was similar in both the 40 mg MR group (43%) and the 100 mg IR group (47%).
- Serious adverse events were reported for two patients (4.5%) in the 40 mg MR group and no patients in the 100 mg IR group (0%).
- Five patients (11.4%) in the 40 mg MR group discontinued due to adverse events compared with four patients (8.5%) in the 100 mg IR group.
- Two patients (4.5%) in the 40 mg MR group and 12 patients in the 100 mg IR group (25.5%) experienced gastrointestinal adverse events. The difference was primarily attributable to nausea, which occurred in eight patients in the 100 mg IR group and no patients in the 40 mg MR group.
- There were no events of vaginal candidiasis reported in either treatment group.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-effectiveness analysis comparing 40 mg MR with 100 mg IR during a 48-week time horizon. The results were reported in terms of an incremental cost per success, where success was defined as the percent reduction in inflammatory lesions without the presence of adverse events — a composite of clinical efficacy and harms. The validity of using this composite was unclear to the Committee. The manufacturer's input parameters for the relative efficacy and harms of 40 mg MR compared with 100 mg IR were based on assumptions that were inconsistent with available clinical trial data. The manufacturer reported that 40 mg MR is associated with an incremental cost for each percent reduction in inflammatory lesion count without adverse events of $845 compared with 100 mg IR.

CDR noted the following limitations with the manufacturer's analysis:

- The manufacturer assumed a reduced relapse rate and reduced incidence of vaginal candidiasis for 40 mg MR compared with 100 mg IR; however, the ROSE-401 trial did not assess these outcomes between 40 mg MR and 100 mg IR.
- The choice of outcome measure, "percent reduction in inflammatory lesion count without adverse events," does not coincide with the clinical trial outcome measure in ROSE-401. It is uncertain whether it represents a clinically meaningful outcome to patients, which complicates the interpretation of the incremental cost-effectiveness ratio.

The daily cost of doxycycline (40 mg MR) is *[confidential price removed at manufacturer's request]*. Other drugs used to treat rosacea, but without an indication, are less expensive (doxycycline 100 mg IR, $0.59; minocycline 100 mg to 200 mg, $0.62 to $1.24; and tetracycline 250 mg to 500 mg, $0.07 to $0.13.

Other Discussion Points:

The Committee noted the following:

- Doxycycline 40 mg MR was shown to be superior to placebo in three double-blind RCTs. The efficacy rates reported in the placebo-controlled RCTs were similar to those reported in the ROSE-401 trial.

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.

Regrets:

January 16, 2013 Meeting
None

March 20, 2013 Meeting
One CDEC member could not attend the meeting.

Conflicts of Interest:

None

About this Document:

CDEC provides formulary listing recommendations or advice to CDR participating drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a Record of Advice. 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 requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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