

CDEC FINAL RECOMMENDATION

AZILSARTAN MEDOXOMIL / CHLORTHALIDONE

(Edarbyclor — Takeda Canada Inc.)

Indication: Severe Hypertension

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that azilsartan medoxomil/chlorthalidone (AZL-M/CLD) not be listed.

Reason for the Recommendation:

CDEC considered the comparative clinical benefit of AZL-M/CLD for use as initial therapy in the treatment of severe hypertension to be uncertain due to limitations of the single randomized controlled trial (RCT) that was included in the review (Study 303). Specifically, only a minority of the study population were patients receiving initial therapy for severe hypertension, and the comparator, the combination of olmesartan and hydrochlorothiazide (OLM/HCTZ), is not indicated for use in the treatment of severe hypertension in Canada.

Background:

Edarbyclor is a fixed-dose combination of azilsartan medoxomil, an angiotensin II receptor blocker (ARB), and chlorthalidone, a diuretic. Edarbyclor has a Health Canada indication for initial therapy for patients with severe essential hypertension in whom the benefits of prompt blood pressure reduction exceed the risks of combination therapy. The typical starting combined dose is 40 mg/12.5 mg (AZL-M/CLD) taken orally once daily. The dose can be increased to 80 mg/12.5 mg or 40 mg/25 mg after two to four weeks as needed to control blood pressure.

Summary of CDEC Considerations:

CDEC considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of AZL-M/CLD, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Patient Input Information

The following is a summary of information provided by one patient group that responded to the CDR call for patient input:

- High blood pressure is the number one risk factor for stroke and a major risk factor for heart disease.

Common Drug Review

- Low adherence to prescribed medications is a concern and has been implicated as one of the major contributors to uncontrolled high blood pressure and risk of cardiovascular disease.

Clinical Trials

The CDR systematic review included one multinational, multicentre, double-blind, phase III RCT of 12 weeks duration (Study 303, N = 1,071), in which adults with moderate to severe essential hypertension received forced titrations of:

- AZL-M/CLD 40 mg/25 mg (20 mg /12.5 mg for 4 weeks, 40 mg/12.5 mg from week 4 to 8, and 40 mg/25 mg from week 8 to 12)
- AZL-M/CLD 80 mg/25 mg (40 mg/12.5 mg for 4 weeks, 80 mg/12.5 mg from week 4 to 8, and 80 mg/25 mg from week 8 to 12)
- OLM/HCTZ 40 mg/25 mg (20 mg/12.5 mg for 4 weeks, 40 mg/12.5 mg from week 4 to 8, and 40 mg/25 mg from week 8 to 12).

There was a relatively small number of patients with severe hypertension in Study 303: AZL-M/CLD 40 mg/25 mg (n = 31), AZL-M/CLD 80 mg/25 mg (n = 32), and OLM/HCTZ 40 mg/25 mg (n = 31). It should be noted that AZL-M/CLD 80 mg/25 mg is not an approved dose in Canada.

Outcomes

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

- change from baseline in mean clinic systolic blood pressure (SBP)
- change from baseline in mean clinic diastolic blood pressure (DBP)
- change from baseline in mean trough sitting DBP
- change from baseline in mean trough sitting SBP
- serious adverse events, total adverse events, and withdrawals due to adverse events.

Change from baseline in mean clinic SBP was the primary outcome in Study 303.

Results

Efficacy

- The mean difference (MD) (95% confidence interval [CI]) in the change from baseline in clinic SBP was reported as follows:
 - AZL-M/CLD 40 mg/25 mg versus OLM/HCTZ 40 mg/25 mg: -5.3 mmHg (-7.6 to -3.1)
 - AZL-M/CLD 80 mg/25 mg versus OLM/HCTZ 40 mg/25 mg: -6.9 mmHg (-9.2 to -4.6).
- The MD (95% CI) in change from baseline in clinic DBP was reported as follows:
 - AZL-M/CLD 40 mg/25 mg versus OLM/HCTZ 40 mg/25 mg: -2.3 mmHg (-3.6 to -1.0)
 - AZL-M/CLD 80 mg/25 mg versus OLM/HCTZ 40 mg/25 mg: -4.1 mmHg (-5.4 to -2.8).
- The MD (95% CI) in change from baseline in trough SBP was reported as follows:
 - AZL-M/CLD 40 mg/25 mg versus OLM/HCTZ 40 mg/25 mg: -7.0 mmHg (-9.4 to -4.7)
 - AZL-M/CLD 80 mg/25 mg versus OLM/HCTZ 40 mg/25 mg: -9.0 mmHg (-11.5 to -6.6).
- The MD (95% CI) in change from baseline in mean trough DBP was reported as follows:
 - AZL-M/CLD 40 mg/25 mg versus OLM/HCTZ 40 mg/25 mg: -3.9 mmHg (-5.4 to -2.4)
 - AZL-M/CLD 80 mg/25 mg versus OLM/HCTZ 40 mg/25 mg: -4.3 mmHg (-5.8 to -2.7).

- Post hoc subgroup analyses according to hypertension grade (1, 2, or 3) at baseline suggested that the larger effects of AZL-M/CLD 40 mg/25 mg compared with OLM/HCTZ 40 mg/25 mg on SBP were maintained regardless of initial hypertension severity, although the result for hypertension grade 3 patients (SBP of at least 180 mmHg) was not statistically significant.

Harms (Safety and Tolerability)

- Compared with OLM/HCTZ, a larger proportion of patients treated with AZL-M/CLD 40 mg/25 mg experienced at least one adverse event (71.3% versus 60.2%).
- Serious adverse events were reported for one patient in the AZL-M/CLD 40 mg/25 mg group (0.3%) and eight patients in the OLM/HCTZ 40 mg/25 mg group (2.2%).
- Withdrawals due to adverse events were reported for 8.7% of patients in the AZL-M/CLD 40 mg/25 mg group and 7.1% of patients in OLM/HCTZ 40 mg/25 mg group.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis, where only drug costs were considered, comparing 40 mg/12.5 mg, 40 mg/25 mg, and 80 mg/12.5 mg AZL-M/CLD to other ARB/diuretic fixed-dose combinations available in Canada. The manufacturer assumed that AZL-M/CLD is equivalent in terms of efficacy and safety compared with other ARB/diuretic fixed-dose combination products.

At the submitted price of \$1.19 per day, regardless of strength, AZL-M/CLD was more costly than other ARB/diuretic fixed-dose combinations (\$0.28 to \$1.10 per day), yielding incremental costs for azilsartan medoxomil that ranged from \$0.09 to \$0.91 per patient per day.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- Data comparing AZL-M/CLD with other antihypertensive drugs on cardiovascular events, cerebrovascular events, end-organ damage, or mortality.
- The sustained effect of AZL-M/CLD on blood pressure reduction beyond 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. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani

September 18, 2013 Meeting

Regrets:

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 not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice 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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