CDEC FINAL RECOMMENDATION

AZILSARTAN MEDOXOMIL
(Edarbi — Takeda Canada Inc.)
Indication: Mild to Moderate Essential Hypertension

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that azilsartan medoxomil not be listed at the submitted price.

Reason for the Recommendation:
At the submitted price, azilsartan medoxomil ($1.19 per day) is more costly than other angiotensin II receptor blockers (ARBs) available in Canada ($0.17 to $1.10 per day).

Of Note:
Based on a review of the clinical evidence, CDEC noted that a reduction in price would increase the likelihood of a recommendation to list in a manner similar to other ARBs.

Background:
Azilsartan medoxomil (Edarbi) is a selective ARB indicated for the treatment of mild to moderate essential hypertension. It may be used alone, concomitantly with thiazide diuretics, or concomitantly with calcium channel blockers. The recommended starting dose of azilsartan medoxomil is 40 mg once daily, which can be increased to a maximum of 80 mg once daily.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the Common Drug Review (CDR): a systematic review of randomized controlled trials (RCTs) focused on azilsartan medoxomil, 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. With proper diagnosis and treatment, the risk of stroke and heart attack can be considerably reduced.
- 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 systematic review included three multicentre, double-blind RCTs of adults with mild to moderate essential hypertension. Study TAK-491-301 compared azilsartan medoxomil 40 mg or 80 mg once daily against valsartan 320 mg once daily (N = 984; 24 weeks). Study TAK-536-CCT-001 compared azilsartan 40 mg or 80 mg once daily with candesartan 12 mg once daily or placebo (N = 588; 12 weeks). TAK-536-CCT-005 compared azilsartan 40 mg once daily with candesartan 12 mg once daily (N = 636; 16 weeks).

Outcomes

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

- change from baseline in 24-hour mean systolic blood pressure (SBP)
- change from baseline in 24-hour mean 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 24-hour mean SBP was the primary outcome in TAK-491-301. Change from baseline in trough sitting DBP was the primary outcome in TAK-536-CCT-001 and TAK-536-CCT-005.

Results

CDEC focused their discussion on the results of study TAK-491-301 which investigated the Health Canada-approved formulation and dosing for azilsartan medoxomil (i.e., 40 mg and 80 mg per day).

Efficacy

- The mean difference (MD) (95% confidence interval [CI]) in the change from baseline in 24-hour SBP was reported as follows:
  - azilsartan medoxomil 40 mg versus valsartan 320 mg: –3.6 mmHg (–5.6 to –1.7)
  - azilsartan medoxomil 80 mg versus valsartan 320 mg: –4.0 mmHg (–6.0 to –2.1).
- The MD (95% CI) in change from baseline in 24-hour DBP was reported as follows:
  - azilsartan medoxomil 40 mg versus valsartan 320 mg: –2.2 mmHg (–3.4 to –0.9)
  - azilsartan medoxomil 80 mg versus valsartan 320 mg: –2.7 mmHg (–4.0 to –1.4).
- The MD (95% CI) in change from baseline in trough SBP was reported as follows:
  - azilsartan medoxomil 40 mg versus valsartan 320 mg: –3.3 mmHg (–5.9 to –0.6)
  - azilsartan medoxomil 80 mg versus valsartan 320 mg: –5.3 mmHg (–8.0 to –2.7).
- The MD (95% CI) in change from baseline in mean trough DBP was reported as follows:
  - azilsartan medoxomil 40 mg versus valsartan 320 mg: –2.5 mmHg (–4.1 to –1.0)
  - azilsartan medoxomil 80 mg versus valsartan 320 mg: –2.8 mmHg (–4.3 to –1.2).

Harms (Safety and Tolerability)

- At least one adverse event was reported for 65.4% of patients treated with azilsartan medoxomil 40 mg, 65.3% of patients treated with azilsartan medoxomil 80 mg, and 59.2% of patients treated with valsartan 320 mg. The most commonly reported adverse events in the azilsartan medoxomil treatment groups were headache, dizziness, and urinary tract

infection. Hyperkalemia and hypokalemia were reported for less than 1% of patients across the three treatment groups.
- Serious adverse events were reported for 2.4% of patients treated with azilsartan medoxomil 40 mg, 1.5% of patients treated with azilsartan medoxomil 80 mg, and 2.5% of patients treated with valsartan 320 mg.
- Withdrawals due to adverse events were reported for 7.0% of patients treated with azilsartan medoxomil 40 mg, 8.2% of patients treated with azilsartan medoxomil 80 mg, and 6.1% of patients treated with valsartan 320 mg.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis, where only drug costs were considered, comparing 40 mg and 80 mg azilsartan medoxomil with other ARBs. The manufacturer assumed equivalent efficacy and safety for azilsartan medoxomil compared with other ARBs, based on several studies ranging from six weeks to six months in duration in which azilsartan medoxomil was compared with placebo, olmesartan and valsartan (other ARBs), or an angiotensin-converting enzyme inhibitor (ramipril) in patients with mild to moderate essential hypertension. The manufacturer submitted a flat price of $1.1923 per 40 mg or 80 mg tablet, or $1.19 per day. Azilsartan medoxomil was more expensive than other ARBs ($0.17 to $1.10 per day), yielding incremental costs for azilsartan medoxomil that ranged from $0.09 to $1.02 per patient per day.

Other Discussion Points:

CDEC noted the following:
- A CDR analysis suggested that the submitted price of azilsartan medoxomil would need to be reduced by 8% to be equivalent to the highest priced ARB, or reduced by 72% to equal the weighted average cost of other ARBs.
- The proportion of patients who experienced at least one adverse event appeared to be greater with azilsartan medoxomil than with valsartan.

Research Gaps:

CDEC noted that there is an absence of evidence regarding the following:
- Data comparing azilsartan medoxomil with other antihypertensive drugs on cardiovascular events, cerebrovascular events, end-organ damage, or mortality.
- The sustained effect of azilsartan medoxomil 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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