CDEC FINAL RECOMMENDATION

LINAGLIPTIN / METFORMIN HYDROCHLORIDE
(Jentadueto – Boehringer Ingelheim Canada Ltd.)
Indication: Type 2 Diabetes Mellitus

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that linagliptin/metformin (Jentadueto) be listed for patients if the following clinical criterion is met:

Clinical Criterion:

- Patients for whom insulin is not an option and who are already stabilized on therapy with metformin, a sulfonylurea and linagliptin, to replace the individual components of linagliptin and metformin for these patients.

Reason for the Recommendation:
At the submitted price, Jentadueto ($[redacted] per day) is less costly than linagliptin and metformin administered separately ($2.67 to $2.79 per day), and less costly than Janumet (sitagliptin/metformin, $3.20 per day).

Background:
Jentadueto is a fixed-dose combination of linagliptin and immediate-release metformin, indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus in the following scenarios:

- When treatment with both linagliptin and metformin is appropriate, in patients inadequately controlled on metformin alone, or in patients already being treated and well controlled with the free combination of linagliptin and metformin.
- In combination with a sulfonylurea in patients inadequately controlled on metformin and a sulfonylurea.

Jentadueto is available as 2.5 mg/500 mg, 2.5 mg/850 mg, and 2.5 mg/1,000 mg (linagliptin/metformin) oral tablets. The product monograph recommends twice daily dosing.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the Common Drug Review (CDR): a systematic review of linagliptin/metformin and a critique of the manufacturer's pharmacoeconomic evaluation. No patient groups responded to the CDR call for patient input. There were no randomized controlled trials (RCTs) that met the minimum inclusion criteria for

the CDR systematic review. Therefore, CDEC considered a summary of information relevant to linagliptin/metformin, prepared by CDR, which included:

- trials of linagliptin and metformin that did not meet the CDR systematic review protocol
- pharmacokinetic and bioavailability data.

Summary of Findings:

Additional Studies

There were no RCTs that met the inclusion criteria for the CDR systematic review. Specifically, no studies were identified that evaluated the safety and efficacy of Jentadueto; however, several studies have examined the combination of linagliptin 2.5 mg twice daily or 5 mg once daily added-on to metformin or metformin and a sulfonylurea. These studies have demonstrated the following:

- Linagliptin in combination with metformin and a sulfonylurea was superior to placebo in combination with metformin and a sulfonylurea for glycemic control (Study 1218.18).
- Linagliptin in combination with metformin was superior or equivalent for glycemic control to the following comparator regimens: placebo in combination with metformin (Studies 1218.6, 1218.62, and 1218.17), glimepiride in combination with metformin (Studies 1218.6 and 1218.20), linagliptin monotherapy (Studies 1218.40 and 1218.46), and metformin monotherapy (Studies 1218.52 and 1218.46).

Pharmacokinetic Data

The pharmacokinetic characteristics of the fixed-dose combination linagliptin/metformin tablets have been tested against the single tablets administered together in phase I studies of healthy volunteers. The three fixed-dose combination strengths (2.5 mg/500 mg, 2.5 mg/850 mg, and 2.5 mg/1,000 mg) have been shown to be bioequivalent to the individual drugs administered separately in accordance with standard bioequivalence criteria.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing the drug costs of Jentadueto (2.5 mg/500 mg, 2.5 mg/850 mg, 2.5 mg/1,000 mg, twice daily) to the individual components, linagliptin and metformin, as well as to Janumet, a fixed-dose combination of sitagliptin (50 mg) and metformin (500 mg, 850 mg, or 1,000 mg). At the submitted price of $[redacted] per tablet ($[redacted] per day), the average annual cost of Jentadueto ($[redacted] per patient) was lower than the equivalent dose combinations of the individual components, metformin and linagliptin ($974 to $1,016). The average annual cost of Jentadueto was also lower than that of Janumet ($1.60 per tablet, twice daily; $1,169 per patient per year).

Research Gaps

CDEC noted that there is an absence of evidence regarding the following:

- Direct or indirect comparisons assessing the comparative efficacy of linagliptin versus other antihyperglycemic drugs for the prevention of macrovascular and microvascular diabetes-related complications.

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 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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