



CDEC FINAL RECOMMENDATION

SILODOSIN

(Rapaflo – Watson Pharma Company)

Indication: Prostatic Hyperplasia, Benign

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that silodosin not be listed.

Reason for the Recommendation:

In the systematic review, the one double-blind randomized controlled trial (RCT) that included an active comparator reported that silodosin was non-inferior to tamsulosin, based on reductions in the International Prostate Symptom Score (IPSS); however, at the confidential submitted price, silodosin is more costly than tamsulosin controlled release (CR) and a number of other alpha blockers.

Background:

Silodosin has a Health Canada indication for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). It is an α_{1A} receptor antagonist available as 4 mg and 8 mg oral capsules. The Health Canada-recommended dose is 8 mg once daily; for patients with moderate renal impairment (creatinine clearance of 30 mL to 50 mL per minute), the dose recommended by Health Canada is 4 mg once daily.

Summary of CDEC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind RCTs of silodosin and a critique of the manufacturer's pharmacoeconomic evaluation. No patient groups responded to the CDR Call for Patient Input. The manufacturer submitted a confidential price for silodosin.

Clinical Trials

The systematic review included three 12-week double-blind RCTs in men aged 50 years or older with moderate to severe symptoms of BPH:

- SI04009 (N = 461) and SI04010 (N = 462) were identically designed trials that randomized patients to one of silodosin 8 mg once daily or placebo
- KMD3213-IT-CL 0215 (hereafter referred to as study 0215; N = 977) randomized patients to one of three treatment groups: silodosin 8 mg, tamsulosin 0.4 mg, or placebo,

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all once daily. Study 0215 was designed to test the superiority of silodosin compared with placebo and the non-inferiority of silodosin compared with tamsulosin.

In all three trials, a four-week single-blind placebo run-in phase preceded the double-blind treatment phase as a means to exclude placebo responders.

The mean age of patients enrolled in the trials was approximately 65 years and the mean baseline IPSS ranged from 19 to 21 across the three trials. Study completion was 90% or greater in all trials.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: change in the IPSS (both total and subscales), percent responders, maximum urinary flow rate, quality of life, and adverse events, including serious adverse events and withdrawals due to adverse events. The primary outcome in all three trials was the change from baseline to 12 weeks in the total IPSS. In study 0215, the non-inferiority margin for the primary outcome was -1.5 ; that is, silodosin would be considered non-inferior to tamsulosin if the lower limit of the 95% confidence interval (CI) for the between-treatment mean difference (MD) was greater than or equal to -1.5 .

The IPSS consists of seven symptom questions (scored 0 to 5, with higher scores indicating greater severity) and one question assessing the impact of urinary symptoms on quality of life (scored 0 to 6, with higher scores indicating worse quality of life). In addition to the total score (based on the seven symptoms), irritative and obstructive subscale scores may be calculated. The minimal clinically important difference has been reported to range from 3 to > 6 points on the total IPSS score, and from 2 to 3 points on the quality of life question.

Study 0215 defined a treatment response as both the percentage of patients achieving a $\geq 25\%$ decrease in the IPSS, and the percentage of patients achieving a $\geq 30\%$ increase in the maximum urinary flow rate.

Results

Efficacy or Effectiveness

- Reductions in the total IPSS and the irritative and obstructive subscale scores were statistically significantly greater for silodosin than for placebo in all three trials.
- In study 0215, mean reductions from baseline in the total IPSS score were -7.1 and -6.7 for silodosin and tamsulosin, respectively, at 12 weeks. Silodosin was reported to be non-inferior to tamsulosin; MD (95% CI): 0.3 (-0.4 to 1.0). Changes in the irritative and obstructive IPSS subscale scores were not statistically significantly different between silodosin and tamsulosin.
- In study 0215, the percentage of patients classified as responders ($\geq 25\%$ decrease on the IPSS) was not statistically significantly different between silodosin (67%) and tamsulosin (65%).
- Two studies (SI04010 and 0215) reported statistically significant between-treatment differences in quality of life scores favouring silodosin over placebo at 12 weeks; the between-treatment difference was not statistically significant in study SI04009.

- In two studies (SI04009 and SI04010), the increase in maximum urinary flow rate was statistically significantly greater for silodosin than for placebo; increases in maximum urinary flow rate were not statistically significantly different between silodosin and placebo in study 0215.
- Maximum urinary flow rate increases and improvements in quality of life scores, at 12 weeks, were not statistically significantly different between silodosin and tamsulosin in study 0215.

Harms (Safety and Tolerability)

- There were no statistically significant between-treatment differences in the proportions of patients experiencing a serious adverse event in any of the included studies.
- The proportion of patients experiencing any adverse event was statistically significantly higher in the silodosin groups than in the placebo groups in all three trials. The proportion of patients experiencing an adverse event was not statistically significantly different between silodosin and tamsulosin in study 0215.
- The most frequent adverse event associated with silodosin was retrograde ejaculation (range: 14% to 29% of patients across the three trials); 2.1% of tamsulosin-treated patients reported retrograde ejaculation in study 0215.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing silodosin with other selective alpha blockers for the treatment of BPH based on a non-inferiority RCT of silodosin and tamsulosin (study 0215). Only drug costs were considered and calculated over a one-year time horizon based on utilization information from the publicly funded drug plans. The manufacturer reported the cost of silodosin to be within the range of its comparators; however, the calculations likely overestimate the price of comparators, as the unit costs used were higher than those reported by public drug plans, and costs of brand and generic versions of the comparators were pooled.

Based on the confidential submitted price, the daily cost of silodosin (*confidential price removed at manufacturer's request*) is more expensive than tamsulosin CR (\$0.15 to \$0.24) and other alpha blockers (\$0.14 to \$0.50) such as alfuzosin, doxazosin, and terazosin. The confidential price was used by the Committee in making the listing recommendation and the manufacturer requested that this information be kept confidential pursuant to the CDR Confidentiality Guidelines.

Patient Input Information:

No patient groups responded to the CDR Call for Patient Input.

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 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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