CEDAC FINAL RECOMMENDATION

TAPENTADOL
(Nucynta CR – Janssen Inc.)
Indication: Pain, Moderate to Moderately Severe

This document was originally issued on September 28, 2011. It was corrected on March 25, 2014. The price of hydromorphone has been corrected in the last paragraph on page three, under the heading “Cost and Cost-Effectiveness”.

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that tapentadol controlled release (CR) not be listed.

Reason for the Recommendation:
The Committee considered the data from three active-controlled double blind randomized controlled trials (RCTs) to be insufficient to determine the relative efficacy of tapentadol CR compared with oxycodone CR, due to the high and unbalanced frequency of patient withdrawals (tapentadol CR range, 44% to 48%; oxycodone CR range, 60% to 65%), much of which occurred during the initial three-week titration phase.

Of Note:
There are no RCTs comparing tapentadol CR with less costly long-acting opioid formulations of codeine, morphine, or hydromorphone.

Background:
Tapentadol has a Health Canada indication for the management of moderate to moderately severe pain in adults who require continuous treatment for several days or more. Tapentadol is a centrally acting synthetic opioid analgesic thought to act as a mu-opioid agonist and through the inhibition of norepinephrine reuptake. It is available as 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg CR tablets. The Health Canada-recommended dose of tapentadol CR is 100 mg to 250 mg twice daily, taken approximately every 12 hours; opioid-naive patients should initiate treatment with 50 mg twice daily, and then be individually titrated to an optimal dose within the recommended range.

Summary of CEDAC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind RCTs of tapentadol CR, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients. The manufacturer submitted a confidential price for tapentadol CR.

Clinical Trials
The systematic review included four double-blind RCTs of patients with moderate to severe pain related to osteoarthritis of the knee (studies 3008 and 3009), the lower back (study 3011), and diabetic peripheral neuropathy (study 3015).

Active-controlled Trials
Studies 3008 (N = 1,030), 3009 (N = 990), and 3011 (N = 981) were similarly conducted trials of 15 weeks duration. Following a three- to seven-day washout of previous analgesic medications, patients were randomized to tapentadol CR, oxycodone CR, or placebo for 15 weeks. After randomization, patients entered a maximum three-week titration phase (during which doses were titrated to 100 mg to 250 mg twice daily for tapentadol CR, and 20 mg to 50 mg twice daily for oxycodone CR) and a subsequent maintenance phase. Included patients were required to have had pain for a minimum of three months. Mean daily doses during the maintenance phases of the three trials ranged from 315 mg to 382 mg for tapentadol CR and 54 mg to 71 mg for oxycodone CR. All three studies had a high frequency of withdrawal, with differences between treatment groups: placebo (range: 36% to 53%), tapentadol CR (range: 44% to 48%), and oxycodone CR (range: 60% to 65%). The Committee considered the high and unbalanced patient withdrawals to have severely limited the validity of the comparison of tapentadol CR with oxycodone CR.

Placebo-controlled Trials
Study 3015 (N = 395) used an enrichment design; following a three- to 14-day washout of previous analgesic medications, patients entered a three-week open-label tapentadol CR run-in phase, during which the dose was titrated to 100 mg to 250 mg twice daily. Patients who had a ≥ 1 point improvement on the 11-point Numerical Rating Scale (NRS-11) for pain were randomized to continuation of tapentadol CR or placebo for 12 weeks. The mean daily dose of tapentadol CR during the double-blind phase was 419 mg. Approximately 32% of patients withdrew from the trial, with similar frequency between tapentadol CR and placebo. The Committee considered the trial to have limited generalizability.

Outcomes
Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: pain scores, the proportion of patients with ≥ 50% reduction in pain from baseline, quality of life, adverse events, withdrawal, and withdrawal due to adverse events.

The primary outcome in all four trials was the change from baseline in the average pain intensity using the NRS-11. Outcomes of importance to patients were included in the trials. These included quality of life (as assessed by the 36-item Short Form Health Survey [SF-36] and the European Quality of Life – 5 Dimensions) and function (as assessed as part of the SF-36 and the Western Ontario and McMaster Universities Arthritis Index).

Results

Given the large number of alternative agents within the same therapeutic class (i.e., opioid analgesics), the Committee focused its deliberations on comparisons of active treatments in studies 3008, 3009, and 3011, the results of which are described below.

Efficacy or Effectiveness

- Compared with oxycodone CR, tapentadol CR produced statistically significantly greater reductions in pain scores (NRS-11) in studies 3008 and 3009 (–0.4 points in both), which the Committee did not consider clinically important. In study 3011, tapentadol CR and oxycodone CR produced similar reductions in pain scores.
- A preplanned pooled analysis of the three trials conducted by the manufacturer reported a statistically significantly higher percentage of patients achieving a ≥ 50% reduction in pain score by the end of the maintenance phase with tapentadol CR compared with oxycodone CR: 30% and 21%, respectively. The Committee did not consider meta-analysis appropriate due to the limitations of the individual studies noted above.
- Improvements in quality of life or functioning with tapentadol CR, compared with oxycodone CR, were not consistently demonstrated across all three trials.

Harms (Safety and Tolerability)

- The frequency of withdrawal due to adverse events was statistically significantly greater for patients randomized to oxycodone CR compared with tapentadol CR in all three trials, ranging from 33% to 41%, compared with 16% to 19%, respectively.
- The frequency of gastrointestinal adverse events, including each of nausea, constipation, and vomiting, was observed more frequently in oxycodone CR groups compared with tapentadol CR in all three trials.
- There was no notable difference in the frequency of serious adverse events between tapentadol CR and oxycodone CR in any of the included trials.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing tapentadol CR with oxycodone CR over a one-year time frame, for the management of chronic pain. The analysis was based on a meta-analysis of three double-blind, parallel group RCTs (3008, 3009, 3011), wherein the manufacturer found that tapentadol CR is non-inferior compared with oxycodone CR in terms of pain relief and associated with fewer gastrointestinal adverse events. The manufacturer reported that tapentadol CR was less costly ($45.03) and associated with better outcomes than oxycodone CR.

The Committee considered that the trial data used to support similar pain relief in the pharmacoeconomic submission were limited by high and unbalanced withdrawals.

Based on recommended doses and current prices, the daily cost of tapentadol CR *[confidential information removed at manufacturer's request]* oxycodone CR and similar to longer-acting comparators such as hydromorphone ($2.02 to $4.03), fentanyl patch ($1.22 to $4.02), and tramadol ($1.60 to $4.00). Tapentadol CR is, however, more expensive than other long-acting analgesics such as codeine CR ($0.61 to $2.44), hydromorphone CR ($1.30), and sustained-release morphine ($0.46 to $0.70).

Patient Input Information:
The following is a summary of information provided by five patient groups who responded to the CDR Call for Patient Input:

- Chronic pain was noted to affect all aspects of life, including patients' emotional and mental health and their ability to perform daily activities.
- It was suggested that adverse effects of some analgesics (e.g., constipation, nausea, vomiting, itching) and fear of addiction may lead patients to discontinue or reduce the dosage of analgesics, resulting in inadequate treatment of pain.
- Compared with analgesics taken multiple times per day, patients expect long-acting formulations to reduce "peaks and valleys" and thus result in reduced suffering, adverse effects, potential for abuse and addiction, and improved compliance, function, and, ultimately, quality of life.

Other Discussion Points:
- The Committee noted that there are a large number of available opioid formulations.

CEDAC Members:
Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. James Silvius.

June 15, 2011 Meeting

Regrets:
Three CEDAC members did not attend

Conflicts of Interest:
None

September 21, 2011 Meeting

Regrets:
Two CEDAC members did not attend

Conflicts of Interest:
None

About this Document:
CEDAC 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 CEDAC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CEDAC 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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