Canadian Expert Drug Advisory Committee
Final Recommendation – Plain Language Version

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

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that Nucynta CR, which is also called tapentadol controlled release (CR), not be listed by Canada's publicly funded drug plans for the treatment of moderate to moderately severe pain.

Reason for the Recommendation:
The Committee considered that the data from three medical studies that compared Nucynta CR with oxycodone CR (also called OxyContin) were not sufficient to determine how the drugs compared in effectiveness. This was because a large percentage of patients stopped participating during the studies, ranging from 44% to 48% for Nucynta CR groups and 60% to 65% for oxycodone CR groups, and much of the stopping of participation occurred during the first three weeks.

Of Note:
There are no medical studies comparing Nucynta CR with long-acting opioid analgesics that cost less than Nucynta CR (for example, long-acting forms of codeine, morphine, or hydromorphone).

Background:
Nucynta CR belongs to a class of drugs called opioid analgesics, which act on the central nervous system. It relieves pain by acting on specific nerve cells of the spinal cord and brain. Nucynta is approved by Health Canada for the treatment of moderate to moderately severe pain in adults who require ongoing treatment for several days or more.

Nucynta CR is available as 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg tablets. The Health Canada recommended dose of Nucynta CR is 100 mg to 250 mg twice daily, taken approximately every 12 hours. Patients who have not had opioid analgesics before should start treatment with 50 mg twice daily, and then the dose should be adjusted within the recommended range to a dose that is best for each individual patient.

Summary of CEDAC Considerations:
To make their decision, the Committee considered the following information prepared by the Common Drug Review (CDR): a review of the medical studies of Nucynta CR and a review of economic information prepared by the manufacturer of Nucynta CR. Also, CEDAC considered information that patient groups submitted about outcomes and issues important to patients who have the condition for which the drug is indicated or who might use the drug. The manufacturer submitted a confidential price for Nucynta CR.

Clinical Trials
CEDAC reviewed four studies of patients with moderate to severe pain from osteoarthritis of the knee (studies 3008 and 3009), the lower back (study 3011), and diabetic peripheral neuropathy (study 3015).

Studies Comparing Nucynta CR with other Medications
Study 3008 (with 1,030 patients), study 3009 (with 990 patients), and study 3011 (with 981 patients) were similar studies, each lasting 15 weeks. After stopping all pain medications for three to seven days, patients were given one of Nucynta CR, oxycodone CR, or placebo (a pill containing no active medication) for 15 weeks. During the first three weeks, the doses of the medications were increased as necessary (between 100 mg to 250 mg twice daily for Nucynta CR, and between 20 mg to 50 mg twice daily for oxycodone CR). After three weeks, the doses were kept constant for the remainder of the study. Only patients who had already had pain for a minimum of three months were allowed in the studies. Average daily doses during the constant dose part of the three studies ranged from 315 mg to 382 mg for Nucynta CR and 54 mg to 71 mg for oxycodone CR. Disadvantages of the studies included the large percentage of patients who stopped participating, with differences depending upon which treatment the patient was receiving: placebo (range, 36% to 53%), Nucynta CR (range, 44% to 48%), and oxycodone CR (range, 60% to 65%). Because of the high and unbalanced stopping of participation in the aforementioned studies, the Committee was not confident in the results comparing Nucynta CR with oxycodone CR.

Studies Comparing Nucynta CR with Placebo
Study 3015 included 395 patients. After three to 14 days of not taking any pain medication, all patients were given Nucynta CR for three weeks. During the three weeks, the dose of Nucynta CR was adjusted to between 100 mg to 250 mg twice daily. Patients who had at least a one point improvement on the 11-point numerical rating scale (NRS-11) for pain were then allowed to continue in the study and were given either Nucynta CR (at the same dose) or placebo for 12 weeks. The average daily dose of Nucynta CR, during the Nucynta CR versus placebo part of the study, was 419 mg. Approximately 32% of patients stopped taking part in the study, regardless of whether they were on Nucynta CR or placebo. The Committee felt that the results of this study could not be applied to a wider group of patients.

Outcomes
Outcomes were defined in advance in the CDR review protocol. Of these, the Committee discussed the following: pain scores, the percentage of patients with a 50% or greater lowering of pain from the start of the study, quality of life, side effects, stopping participation in the study, and stopping participation due to side effects.

The main purpose in all four studies was to look at the change in the average pain intensity from study start, using the NRS-11. Various measurements which were important to patients were

included in the studies. 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 (measured as part of the SF-36 and the Western Ontario and McMaster Universities Osteoarthritis Index).

Results

As there are many drugs in the same category as Nucynta CR (i.e., opioid analgesics), the Committee focused their discussions on the studies that compared Nucynta CR with other opioid analgesics (studies 3008, 3009, and 3011). The results of these studies are described below.

Efficacy or Effectiveness

- Nucynta CR lowered pain more than oxycodone CR (on the NRS-11 scale) in studies 3008 and 3009 (–0.4 points in both), but this amount of additional lowering was not considered by the Committee to be important for patients. In study 3011, Nucynta CR and oxycodone CR produced similar lowering of pain scores.
- An analysis (planned in advance by the manufacturer) that pooled data from the three studies showed that a higher percentage of Nucynta CR patients compared with those on oxycodone CR achieved a 50% or greater lowering in pain score; 30% and 21%, respectively. The Committee did not consider the pooling of data to be appropriate because of the disadvantages of the individual studies noted previously.
- Improvements in quality of life or functioning with Nucynta CR, compared with oxycodone CR, were not constant across all three studies.

Harms (Safety and Tolerability)

- In all three studies, a greater percentage of patients on oxycodone CR compared with patients on Nucynta CR stopped taking part in the study because of side effects (ranging from 33% to 41% compared with 16% to 19%, respectively).
- In all three studies, there was a higher percentage of patients who experienced side effects related to the stomach and intestines (such as nausea, constipation, and vomiting) in oxycodone CR groups compared with Nucynta CR.
- There was roughly the same percentage of patients with serious side effects in Nucynta CR and oxycodone CR groups in each of the three studies.

Cost and Cost-Effectiveness

The manufacturer submitted economic information comparing Nucynta CR with oxycodone CR to evaluate the health benefit for the management of chronic pain. The manufacturer estimated the effect of therapy over a one-year time frame.

The analysis was based on pooled data from three studies (3008, 3009, 3011), where the manufacturer found that Nucynta CR is not worse than oxycodone CR for pain relief and also had fewer side effects related to the stomach or intestines. The manufacturer reported that Nucynta CR was less costly ($45.03) and had better results compared with oxycodone CR.

The Committee considered that the study data that was used to show that Nucynta CR was not worse than oxycodone CR had the disadvantage of being from studies with high percentages of patients who stopped participating, and the percentage of patients who stopped participating was different, depending on which treatment was received.

Based on recommended doses and current prices, the daily cost of Nucynta CR *[confidential information removed at manufacturer's request]* oxycodone CR and similar to longer-acting opioid analgesics such as hydromorphone (also called Jurnista, $2.02 to $4.03); fentanyl patch (also called Duragesic, $1.22 to $4.02); and tramadol CR (also called Zytram XL, $1.60 to $4.00). Nucynta CR is, however, more expensive compared to other long-acting analgesics such as codeine CR (also called Codeine Contin, $0.61 to $2.44), hydromorphone CR (also called Hydromorph Contin, $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' ability to perform daily activities and their emotional and mental health.
- It was suggested that side effects of some analgesics (e.g., constipation, nausea, vomiting, itching) and fear of addiction may lead patients to stop or decrease their analgesics, leading to not getting enough pain relief.
- Compared with analgesics which are taken multiple times per day, patients expect long-acting formulations to make it easier for them to stick to their dosing schedules. Patients also expect a reduction in peaks and valleys of pain, which would lead to less suffering, less side effects, and lower the chance of abuse and addiction, as well as improve their ability to perform daily tasks and their quality of life.

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

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
The information contained within this plain language version of the Canadian Expert Drug Advisory Committee (CEDAC) Recommendation about this drug is based on the information found within the corresponding technical version of the CEDAC Recommendation.

In making its recommendation, CEDAC considered the best clinical and pharmacoeconomic evidence available, up to that time. Health care professionals and those requiring more detailed information are advised to refer to the technical version available in the CDR Drug Database on the CADTH website (www.cadth.ca).

Background on CEDAC
CEDAC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). The committee is made up of drug evaluation experts and public members. CEDAC provides recommendations about whether or not drugs should be listed for coverage through the participating publicly funded drug plans; however, the individual drug plans make their own decision about whether or not to cover a drug.

In making its recommendations, CEDAC decides if the drug under review ought to be covered by the participating public drug plans based on an evidence-informed review of the medication's effectiveness and safety, and based on an assessment of its cost-effectiveness in comparison with other available treatments. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

The CEDAC Recommendation neither takes the place of a medical professional providing care to a particular patient, nor is it intended to replace professional advice. CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada, the federal government, any provincial or territorial government, or any pharmaceutical manufacturer.

The manufacturer has reviewed this document and has requested the deletion of confidential information.