CDEC FINAL RECOMMENDATION

OXYCODONE HYDROCHLORIDE/NALOXONE HYDROCHLORIDE RESUBMISSION
(Targin – Purdue Pharma)
Indication: Relief of Moderate to Severe Pain and Opioid-Induced Constipation

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that oxycodone hydrochloride/naloxone hydrochloride controlled release (CR) (Targin) not be listed.

Reason for the Recommendation:
The comparative clinical benefit of oxycodone/naloxone CR in patients with moderate to severe chronic pain and opioid-induced constipation is not established, because there are no randomized controlled trials (RCTs) comparing oxycodone/naloxone CR with less expensive opioid treatment in combination with an optimized laxative regimen.

Background:
Targin is a fixed-dose combination of an opioid analgesic (oxycodone hydrochloride) and an opioid antagonist (naloxone hydrochloride). The oxycodone component is indicated for the relief of moderate to severe pain in adults who require continuous around-the-clock opioid analgesia for several days or more. The naloxone component is indicated for the relief of opioid-induced constipation. The product is available as CR tablets in the following dose combinations of oxycodone hydrochloride and naloxone hydrochloride, respectively: 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg.

Health Canada recommends that the product be administered twice daily and doses be individualized based upon the status of each patient. Single doses should not exceed 40 mg/20 mg, and the maximum daily dose should not exceed 80 mg/40 mg of oxycodone hydrochloride and naloxone hydrochloride, respectively.

Submission History:
Oxycodone/naloxone CR was previously submitted to the Common Drug Review (CDR) and discussed by the Canadian Expert Drug Advisory Committee at the May 2011 meeting; however, the manufacturer elected to file a resubmission before the Notice of Final Recommendation was issued. Thus, the original submission was stopped. The basis for this resubmission is a new, confidential reduced price. The manufacturer did not submit new clinical information.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the CDR: a systematic review of double-blind RCTs of oxycodone/naloxone CR, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials
The systematic review included four double-blind RCTs of patients with moderate to severe malignant (OXN2001) or non-malignant (OXN3401, OXN3001, OXN3006) chronic pain; patients in all trials except OXN3401 were also required to have opioid-induced constipation.

Patients in all studies were to discontinue pre-study laxatives, with the exception that continuation of bulk-forming laxatives was permitted in OXN2001, OXN3001, and OXN3006. In three trials the double-blind phase was preceded by a run-in phase, during which all patients were titrated to optimized analgesia with oxycodone immediate release (OXN3401) or oxycodone CR (OXN3001, OXN3006). The run-in periods were 14 days in study OXN3401, and ranged from seven to 28 days in studies OXN3001 and OXN3006. The double-blind phases of all studies are described below:

- OXN3401 (N = 464) randomized patients to placebo, oxycodone/naloxone CR, or oxycodone CR every 12 hours for 12 weeks; oxycodone dose assignment ranged from 20 mg to 40 mg per day based on patients' optimized dose during the run-in period. Dose titration of randomized treatments was not permitted during the trial.
- OXN2001 (N = 185) randomized patients to oxycodone/naloxone CR or oxycodone CR every 12 hours for four weeks; oxycodone dose assignment ranged from 20 mg to 80 mg per day based on patients' pre-study opioid dose. Oxycodone could be added to achieve a maximum dose of 120 mg per day during the trial.
- OXN3001 (N = 322) randomized patients to oxycodone/naloxone CR or oxycodone CR every 12 hours for 12 weeks; assignment of oxycodone dosage ranged from 20 mg to 50 mg per day, based on patients' optimized dose during the run-in period. Dose titration to a maximum dose of oxycodone 50 mg per day was permitted during the trial.
- OXN3006 (N = 278) randomized patients to oxycodone/naloxone CR or oxycodone CR every 12 hours for 12 weeks; assignment of oxycodone dosage ranged from 60 mg to 80 mg per day based on patients' optimized dose during the run-in period. Oxycodone could be added to achieve a maximum dose of 120 mg per day during the trial.

Rescue analgesia with oxycodone immediate release was allowed in all trials. In OXN2001, OXN3001, and OXN3006, oral bisacodyl 10 mg per day was permitted for rescue laxation (maximum five doses within seven consecutive days). In OXN3401, laxative use was at the discretion of the investigator.

Study withdrawal ranged from 13% to 28% across the four trials but did not differ substantially between treatment groups within the trials. The major limitation of the trials that enrolled patients with opioid-induced constipation is the trials' questionable external validity, as an optimized laxative regimen (which is considered standard care for patients with opioid-induced

constipation) was not included as a comparator to the naloxone component of the combination product.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: constipation as measured by subjective and objective measures (Bowel Function Index [BFI], Patient Assessment of Constipation Symptoms [PAC-SYM], and complete spontaneous bowel movements), quality of life, patient global assessment, pain score, and need for rescue laxatives.

The three-item BFI was developed by the manufacturer specifically for use in the oxycodone/naloxone CR trials and the minimal clinically important difference was determined to be ≥ 12 points (scaled from 0 to 100), based on an analysis of the standard error of measurement and the half standard deviation. The PAC-SYM is a widely used measure for constipation symptom assessment; higher scores indicate worse bowel function. However, the minimal clinically important difference for this measure has not been established.

The primary efficacy outcomes in the four trials are described below:

- OXN3401 – time from initial dose of study drug to multiple (recurring) pain events. A pain event was defined as an average pain intensity score (on an 11-point numerical rating scale – higher scores indicate greater pain) over 24 hours of ≥ 5; or pain intensity score right now of ≥ 5 accompanied by rescue analgesic use (two or more doses per day); or study discontinuation due to lack of efficacy
- OXN2001 – mean BFI and Brief Pain Inventory Short Form scores (co-primary outcomes)
- OXN3001 and OXN3006 – mean BFI score.

Results

Efficacy or Effectiveness

Pain scores were not statistically significantly different between oxycodone/naloxone CR and oxycodone CR treatment groups in any of the four trials. Given that the analgesic efficacy of oxycodone is well established, CDEC focused its discussion on the three trials that enrolled patients with opioid-induced constipation (OXN2001, OXN3001, and OXN3006), results of which are described below:

- Improvements (reductions) in BFI scores were statistically significantly greater for oxycodone/naloxone CR compared with oxycodone CR at week four; mean differences (MD) were –12.6, –15.2, and –14.9 in studies OXN2001, OXN3001, and OXN3006, respectively, which exceed the minimal clinically important difference.
- PAC-SYM scores were statistically significantly improved (lower) for oxycodone/naloxone CR compared with oxycodone CR after four weeks in OXN2001, and after 12 weeks in studies OXN3001 and OXN3006, but the minimal clinically important difference for this outcome is not known.
- In studies OXN3001 and OXN3006, compared with oxycodone CR, patients in the oxycodone/naloxone CR group had a statistically significantly greater increase in the number of complete spontaneous bowel movements. However, the between-treatment difference was approximately one complete spontaneous bowel movement per week, which the Committee considered to be of uncertain clinical importance.

- Rescue laxative use was statistically significantly lower in oxycodone/naloxone CR groups compared with oxycodone CR groups in non-cancer patients (OXN3001 and OXN3006), but was not statistically significantly different between treatment groups in cancer patients (OXN2001).
- No notable differences in quality of life or Patient Global Impression of Change between oxycodone/naloxone CR and oxycodone CR were reported in any of the reviewed trials.

Harms (Safety and Tolerability)

- The proportion of patients with serious adverse events, adverse events, and withdrawal due to adverse events was not statistically significantly different between oxycodone/naloxone CR and oxycodone CR in any of the four trials.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing oxycodone/naloxone CR with oxycodone CR alone over a one-year time horizon, in patients with opioid-induced constipation. The model was based on a pooled analysis of OXN3001 and OXN3006. Patient data from the trials were used to model the progression of patients' opioid-induced constipation over the 12-week study period and last observation carried forward was used to model beyond 12 weeks. Pain control was assumed to be similar between the two treatments. Quality-of-life data (36-item Short Form Health Survey [SF-36] scores) gathered during the trial were converted to utility values to calculate quality-adjusted life-years (QALYs). The manufacturer reported that treatment with oxycodone/naloxone CR is associated with an incremental cost per QALY of $9,504 when compared with oxycodone CR; however, the results varied when the trials were considered separately: $3,063 per QALY based on OXN3001 and $30,836 based on OXN3006.

The manufacturer's economic evaluation was limited by the lack of an active comparator for the treatment of constipation and by insufficient evidence to support improvements in quality of life. Further, the generalizability of the results to individuals requiring higher doses of oxycodone, such as patients with cancer, was undocumented.

At recommended doses of oxycodone (20 mg to 80 mg daily), the daily cost of oxycodone/naloxone CR ranges from *[confidential price removed at manufacturer's request]*. The daily cost of oxycodone CR ranges from $1.76 to $4.23 at the same dose; available oral laxatives cost less than $1 daily. 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

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

- Patients with chronic pain were noted to suffer from associated symptoms, such as concentration problems, chronic fatigue, and depression, which reduce patients' quality of life and their ability to meet their life responsibilities.
- Patient groups identified quality of life as a key issue and expressed an expectation that oxycodone/naloxone would improve patients' quality of life by reducing the incidence or severity of constipation. The practice of some patients of limiting their intake of opioids to avoid opioid-induced constipation, thus resulting in inadequate pain management, was identified as an important concern.

- Patients expect the combination of an opioid and treatment for opioid-induced constipation to be more convenient than separately available treatments.
- Given that patients often suffer chronic pain at end of life, it was suggested that the Committee consider the unique needs of palliative care patients.

Other Discussion Points:

- The Committee noted that statistically significant differences, favouring oxycodone/naloxone, in the BFI and number of complete spontaneous bowel movements were not associated with improvements in quality of life, a key issue identified by patient groups.
- The Committee noted the potential for considerable off-label use of oxycodone/naloxone CR, for prevention of opioid-induced constipation.

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

November 16, 2011 Meeting

Regrets:

One CDEC member did not attend.

Conflicts of Interest:

None

January 18, 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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