Canadian Agency for Drugs and Technologies in Health

COMMON DRUG REVIEW

CEDAC FINAL RECOMMENDATION

PALIPERIDONE PALMITATE
(Invega Sustenna – Janssen Inc.)
Indication: Schizophrenia

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that paliperidone palmitate not be listed at the resubmitted price.

Reason for the Recommendation:
In one double-blind randomized controlled trial (RCT) employing Health Canada-approved doses, paliperidone palmitate was reported to be non-inferior to risperidone long-acting injection (LAI) based on similar reductions in the Positive and Negative Syndrome Scale (PANSS). However, non-inferiority of paliperidone palmitate compared with risperidone LAI was demonstrated at an approximately [redacted] dose equivalency ratio, and therefore, at this dose equivalency, paliperidone palmitate would be more costly. This confidential information was used to make the CEDAC recommendation and the manufacturer requested that this information be kept confidential pursuant to the CDR Confidentiality Guidelines.

Background:
Paliperidone palmitate is the palmitate ester prodrug of paliperidone, a selective, monoaminergic antagonist that exhibits dopamine (D_2) and serotonin type 2A ($5\text{-}HT_{2A}$) antagonism; paliperidone is the active metabolite of risperidone. Paliperidone palmitate is approved by Health Canada for the treatment of schizophrenia. After two initial intramuscular (deltoid) injections (150 mg on day one and 100 mg on day eight), paliperidone (as palmitate) is administered through either deltoid or gluteal intramuscular injection monthly, at a recommended maintenance dose of 75 mg (range: 25 mg to 150 mg).

Paliperidone palmitate is available in single-use prefilled syringes in dose strengths of paliperidone base of 50 mg per 0.5 mL, 75 mg per 0.75 mL, 100 mg per 1 mL, or 150 mg per 1.5 mL (as 78 mg, 117 mg, 156 mg, or 234 mg of paliperidone palmitate, respectively). Where doses of paliperidone palmitate are specified below, they refer to the dose of the paliperidone base.

Submission History:
Paliperidone palmitate was originally reviewed by CEDAC for the indication of schizophrenia on November 17, 2010. CEDAC further considered paliperidone palmitate on January 19, 2011.

During the embargo period, the manufacturer filed a resubmission based on a reduced price. On March 23, 2011, CEDAC reviewed paliperidone palmitate at the resubmitted price.

Summary of CEDAC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind, and open-label, RCTs of paliperidone palmitate, 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 paliperidone palmitate.

Clinical Trials
The systematic review included three manufacturer-sponsored, non-inferiority RCTs of adult patients with schizophrenia (PSY-3002, PSY-3006, and PSY-3008). Two of the trials (PSY-3002 and PSY-3006) were double-blind, and one trial (PSY-3008) was open-label with blinded assessors.

PSY-3002 (N = 749) was a 53-week trial that compared paliperidone palmitate with risperidone LAI. Doses of paliperidone palmitate as intragluteal injection were 50 mg (days one and eight), then 25 mg to 75 mg (day 36), followed by 25 mg to 100 mg every four weeks. Risperidone LAI was administered by intragluteal injection of 25 mg (days eight and 22), followed by 25 mg to 50 mg every two weeks; risperidone LAI was supplemented, in blinded fashion, by oral risperidone at 1 mg to 6 mg per day for the first 28 days and 1 mg to 4 mg per day for up to 21 days following a dose increase in risperidone LAI. The median final doses of paliperidone palmitate and risperidone LAI were [redacted], respectively. Withdrawal was more frequently observed in the paliperidone palmitate treatment group compared with the risperidone LAI group: 59% versus 50%, respectively.

PSY-3006 (N = 1,220) and PSY-3008 (N = 452) were 13-week trials that compared paliperidone palmitate with risperidone LAI. Doses of paliperidone palmitate were 150 mg and 100 mg (intradeltoid injections on days one and eight, respectively), followed by 50 mg or 100 mg (day 36), and 50 mg, 100 mg, or 150 mg (day 64) as intradeltoid or intragluteal injections. Risperidone LAI dosing was 25 mg (days eight and 22), 25 mg or 37.5 mg (days 36 and 50), and 25 mg, 37.5 mg, or 50 mg (days 64 and 78) as intragluteal injections. Risperidone LAI was supplemented (blinded in PSY-3006) by oral risperidone at 1 mg to 6 mg per day for days one to 28, and then 1 mg to 2 mg per day for up to 21 days following a dose increase in risperidone LAI.

In PSY-3006, the median final doses of paliperidone palmitate and risperidone LAI were [redacted], respectively. In PSY-3008, the median final doses of paliperidone palmitate and risperidone LAI were [redacted], respectively. Withdrawal was more frequently observed in the paliperidone palmitate treatment group compared with the risperidone LAI group: 25% versus 23% in PSY-3006, and 28% versus 17% in PSY-3008.

PSY-3006 provided the most internally and externally valid results based on the double-blind design and the appropriate site and dose of initial paliperidone palmitate injections. The external validity of PSY-3002 was limited because the initiation doses of paliperidone palmitate were lower than those recommended by Health Canada. The internal validity of PSY-3008 was limited because of the open-label design, which may have biased results. The external validity of PSY-3008 was limited because the trial was conducted exclusively in China and due to the low percentage of patients who had received previous treatment with psychotropic drugs. Given the limitations with studies PSY-3002 and PSY-3008, the Committee focused its deliberations on study PSY-3006.

Confidential information was used by CEDAC to make its listing recommendation, and the manufacturer requested that this information be kept confidential pursuant to the CDR Confidentiality Guidelines.

Outcomes

The primary outcome in all three trials was the change from baseline in the total PANSS. The PANSS is a 30-item scale that evaluates the presence or absence and severity of positive, negative, and general psychopathology symptoms on a seven-point scale; total scores range from 30 to 210, with higher scores indicating greater severity of symptoms. A reduction of 10 to 15 points on the PANSS corresponds to “minimal improvement” on the Clinical Global Impression — Improvement scale. Non-inferiority of paliperidone palmitate compared with risperidone LAI was to be concluded if the lower limit of the 95% confidence interval (CI) of the between-treatment difference in change from baseline exceeded −5 for PSY-3002 and PSY-3006, and −5.5 for PSY-3008.

Other outcomes were also defined a priori in the CDR systematic review. Of these, the Committee discussed the following: Clinical Global Impression — Severity (CGI-S) scale, Personal and Social Performance (PSP) scale, adverse events, and injection site reactions.

Outcomes of importance to patient groups included improvements in quality of life, ability to work and assume family responsibilities, and reduction in caregiver burden. The PSP scale includes the measurement of ability to work and assume family responsibilities, as well as the ability to carry out self-care, which is expected to reduce caregiver burden. Patients and caregivers also expressed a desire for medications with fewer adverse effects, specifically related to weight gain, cognitive impairment, sleep quality, and sexual dysfunction; the effects of treatments on weight gain and sexual dysfunction were examined in the trials.

Results

Efficacy or Effectiveness

- PSY-3006 reported clinically important reductions (improvements) in the PANSS score for both treatments (paliperidone palmitate and risperidone LAI); mean (standard deviation [SD]) changes from baseline were −18.6 (15.4) and −17.9 (14.2) for paliperidone palmitate and risperidone LAI, respectively. In PSY-3006, paliperidone palmitate was non-inferior to risperidone LAI (non-inferiority margin of −5.0 points) employing both a per-protocol and intention-to-treat analysis; mean difference (MD) = 0.4, 95% CI: −1.62 to 2.38 for the

per-protocol analysis. Paliperidone palmitate failed to demonstrate non-inferiority compared with risperidone LAI in reducing the PANSS score in PSY-3002, which employed lower-than-recommended loading dosing of paliperidone palmitate. Paliperidone palmitate was reported to be non-inferior to risperidone LAI in reducing the PANSS in the open-label trial (PSY-3008) for the per-protocol analysis, but not the intention-to-treat analysis.
- Results for the CGI-S and PSP were similar to the results for the PANSS; specifically, there were no statistically significant differences between paliperidone palmitate and risperidone LAI in PSY-3006 and PSY-3008, but there were statistically significant differences favouring risperidone LAI in PSY-3002.

Harms (Safety and Tolerability)
- Injection site pain was more commonly reported for paliperidone palmitate compared with risperidone LAI in all trials; however, between-treatment differences were largest in studies PSY-3006 and PSY-3008. This is likely because the two initial paliperidone palmitate doses in studies PSY-3006 and PSY-3008 were administered through intradeltoid injections (as recommended in the product monograph), which are noted to be more painful than intragluteal injections; risperidone LAI is recommended to be administered through intragluteal injection.
- All three trials reported similar frequencies of adverse events and withdrawals due to adverse events between paliperidone palmitate and risperidone LAI.
- In PSY-3002, withdrawals due to inefficacy were noticeably more frequent for paliperidone palmitate (23%) compared with risperidone LAI (12%).
- Mean percentage weight changes were of small magnitude in all studies and did not differ substantially between treatments.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis of paliperidone palmitate and risperidone LAI based on claims of similar clinical efficacy and safety demonstrated in clinical trials, and doses based on a 1 mg paliperidone palmitate to 1 mg risperidone LAI (1:1) ratio from the product monograph and doses based on a 1.33:1 ratio (which reflects the median final doses in study PSY-3008). At the confidential submitted prices, the monthly cost of paliperidone palmitate (monthly dose of 75 mg [$456] to 100 mg [[redacted]) is similar to risperidone LAI (37.5 mg every other week; $469).

The Committee felt that doses of paliperidone palmitate and risperidone LAI should have been taken from study PSY-3006, which appeared to be the most relevant. The final median doses suggest a [redacted] dose ratio, which is greater than 1.33:1. At this ratio, the monthly cost of paliperidone palmitate ([redacted]) is greater than risperidone (25 mg every other week; $313).

The Committee felt that a cost-comparison analysis did not provide the necessary structure to fully evaluate the cost-effectiveness of paliperidone palmitate compared with risperidone LAI, to account for the uncertainty regarding clinical efficacy and dosing.

At recommended doses, the monthly cost of paliperidone palmitate (75 mg to 150 mg administered monthly; $456 to [redacted]) is greater than risperidone LAI (25 mg to 50 mg administered every other week; $313 to $626).

Confidential information including confidential pricing was used by CEDAC to make its 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 seven patient groups who responded to the CDR Call for Patient Input:

- The profound effect of schizophrenia on quality of life and the ability to work and have meaningful personal relationships was emphasized. The need to have a variety of drugs available because of differences in patient response was noted.
- Stated issues with current therapy included adverse effects (weight gain, poor sleep, sexual dysfunction, and neurological effects) and difficulties with medication adherence. Medication adherence was felt to be adversely affected by lack of insight intrinsic to the disease condition and the burden on patients and family members because of the need for frequent injections.
- Expectations of the new drug included improved medication adherence with a resultant reduction in relapse due to the reduced frequency of injections, fewer neurological adverse effects compared with older drugs, and less potential for drug-drug interactions.

Other Discussion Points:

- It was noted that oral supplementation recommended with the initiation of risperidone LAI is not required with initiation of paliperidone palmitate; the need for oral supplementation may adversely affect adherence with the former treatment.
- The Committee noted that the final mean doses from a published report of PSY-3006 suggest a dose equivalency ratio of approximately 1.6:1 for paliperidone palmitate to risperidone LAI, however the Committee considered that the ratio may be higher.

CEDAC Members Participating:
November 17, 2010
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, and Dr. Yvonne Shevchuk.

January 19, 2011
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, and Dr. Yvonne Shevchuk.

March 23, 2011
Dr. Robert Peterson (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, and Dr. Yvonne Shevchuk.

Regrets:
November 17, 2010
None

January 19, 2011
None

March 23, 2011
Dr. A. Holbrook (Vice Chair)

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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