



Canadian Agency for
Drugs and Technologies
in Health

COMMON DRUG REVIEW

CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

PALIPERIDONE (Invega[™] – Janssen Ortho Inc.)

Description:

Paliperidone, the active metabolite of risperidone, is approved for the treatment of schizophrenia.

Dosage Forms:

3 mg, 6 mg and 9 mg extended release tablets. The recommended dose is 6 mg taken once daily.

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that paliperidone not be listed.

Reasons for the Recommendation:

1. There are no clinical trials comparing paliperidone with risperidone and there are no clinical trials that specifically enrolled patients who have failed treatment with risperidone. The Committee considers that such comparisons with risperidone, the metabolic precursor of paliperidone, would have been useful in assessing the clinical role of paliperidone.
2. The manufacturer proposed that paliperidone be listed on formularies for use in specific patient populations. The manufacturer has requested that the specifics of this proposal remain confidential, pursuant to the Confidentiality Guidelines of the Common Drug Review. However, there are no clinical trials which have specifically evaluated paliperidone in these patients.
3. Clinical trials of paliperidone are inadequate to assess the effectiveness and safety of paliperidone relative to other antipsychotic agents.
4. The cost of paliperidone ranges from \$3.38 to \$10.12 per day when taken at a dose range of 3 mg to 12 mg, which is significantly higher than the price of generic risperidone (\$1.92 to \$4.79 at 4 mg to 10 mg daily). The Committee felt that there was insufficient evidence for a clinical advantage of paliperidone to support this price difference.

Summary of Committee Considerations:

The Committee considered a systematic review of double-blind randomized controlled trials (RCTs) of paliperidone in patients with schizophrenia. Six placebo controlled trials met the inclusion criteria for the systematic review. One of these also included quetiapine as an active comparator arm and three of the trials included olanzapine as an active control, though these trials do not provide an analysis comparing

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paliperidone with olanzapine. Five of the six trials lasted only six weeks and the discontinuation rates ranged from 14 to 57%.

Compared to placebo, paliperidone demonstrated statistically significant but clinically small improvements for the following outcomes:

- symptoms of schizophrenia measured by the Positive and Negative Syndrome Scale (PANSS), in five of the six trials that measured this;
- social functioning measured by the Personal and Social Performance (PSP) scale in four of the five trials that measured this;
- quality of life measured by the Symptoms and Quality of Life in Schizophrenia (SQLS) in three of the five trials that measured this.

Although paliperidone demonstrated statistically significant improvement in PANSS compared to quetiapine (-33.2 ± 19.0 vs -27.6 ± 22.2), the clinical relevance of this difference is questionable because of the short duration of the trial and because this difference is smaller than what is usually considered to be clinically important. Overall, the Committee felt that clinical trials of paliperidone were inadequate to assess the effectiveness and safety of paliperidone relative to other antipsychotic agents.

There were no statistically significant differences in the number of patients experiencing a serious adverse event between paliperidone treatment groups and any of the comparators. The rate of adverse extrapyramidal effects appeared to be greater with higher doses of paliperidone when compared to lower doses. The trials were too short to assess clinical manifestations of the hyperprolactinemia associated with paliperidone use.

Paliperidone is more costly than generic risperidone and similar in cost to quetiapine and generic olanzapine. The manufacturer submitted an economic evaluation which compared paliperidone with risperidone, olanzapine and quetiapine. The evaluation reported that paliperidone was associated with greater clinical benefit and lower cost versus each of the comparators. Given the lack of comparative clinical trials demonstrating a therapeutic advantage for paliperidone and its higher cost compared to generic risperidone, the Committee felt that these analyses and results were based on unrealistic assumptions.

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.
2. The Committee was aware that antipsychotic agents are widely used to treat agitation and behavioural problems in elderly patients with dementia, but concerns have been raised regarding the benefit:harm ratio of this use.

Background:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication's effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.

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