Canadian Expert Drug Advisory Committee
Final Recommendation – Plain Language Version

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

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that Invega Sustenna, which is also called paliperidone palmitate, not be listed for the treatment of schizophrenia by Canada's publicly funded drug plans at the resubmitted price.

Reason for the Recommendation:
In one medical study reviewed by CEDAC that used Health Canada-approved doses, Invega Sustenna was not worse than Risperdal Consta (also called risperidone long-acting injection), based on similar reductions in the Positive and Negative Syndrome Scale (PANSS). However, Invega Sustenna was shown to be no worse than Risperdal Consta at a dose equivalency ratio of approximately *[confidential information removed at manufacturer's request]*, at which Invega Sustenna would cost more than Risperdal Consta. This confidential information was used to make the CEDAC recommendation, and the manufacturer has requested that this information be kept confidential in agreement with the CDR Confidentiality Guidelines.

Background:
Invega Sustenna belongs to a class of drugs called antipsychotics. Antipsychotic medications affect the chemicals that allow communication between nerve cells (neurotransmitters). These chemicals are called dopamine and serotonin. It is unknown how Invega Sustenna exactly works. However, it seems to readjust the balance of dopamine and serotonin. It is approved by Health Canada for the treatment of schizophrenia. Antipsychotic drugs cannot cure schizophrenia. Rather, they are used to keep the symptoms under control and reduce the risk of relapse as the patient continues treatment.

Invega Sustenna is available in single-use, ready-to-use syringes in dose strengths 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. The two first injections into the deltoid (shoulder) muscle are given on Day 1 (150 mg) and then on Day 8 (100 mg). Following that, Invega Sustenna is given either in the buttock muscle or the deltoid muscle once per month at a usual recommended dose of 75 mg (range: 25 mg to 150 mg).

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

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

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 Invega Sustenna and a review of economic information prepared by the manufacturer of Invega Sustenna. 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 Invega Sustenna.

Clinical Trials
CEDAC reviewed three studies of adult patients with schizophrenia (PSY-3002, PSY-3006, and PSY-3008). Two of the studies (PSY-3002 and PSY-3006) were designed so that patients and assessors were not aware of which treatment was being given and, in one study (PSY-3008), patients were aware of which treatment they were getting, but the assessors were not aware.

PSY-3002 with 749 patients was a 53-week study that compared Invega Sustenna with Risperdal Consta. Invega Sustenna injections into the buttock muscle were given as follows: 50 mg on days one and eight, then 25 mg to 75 mg on day 36, followed by 25 mg to 100 mg every four weeks. Risperdal Consta injections were given into the buttock muscle as follows: 25 mg on days eight and 22, followed by 25 mg to 50 mg every two weeks. Risperidone by mouth was given in addition to Risperdal Consta as follows: 1 mg to 6 mg per day for the first 28 days, and then 1 mg to 4 mg per day for up to 21 days, following an increase in the dose of Risperdal Consta. The median doses of Invega Sustenna and Risperdal Consta at the end of the study were *[confidential median doses removed at manufacturer's request]*, respectively. A larger percentage of patients taking Invega Sustenna compared with Risperdal Consta (59% versus 50%, respectively) stopped taking part in the study.

PSY-3006 with 1,220 patients and PSY-3008 with 452 patients were 13-week studies that compared Invega Sustenna with Risperdal Consta. Doses of Invega Sustenna were as follows: 150 mg and 100 mg given into the deltoid muscle (on days one and eight, respectively), followed by injections into the deltoid or buttock muscle of 50 mg or 100 mg (on day 36) and 50 mg, 100 mg, or 150 mg (on day 64). Risperdal Consta was given by injection into the buttock muscle as follows: 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). Risperidone by mouth was given in addition to Risperdal

Consta as follows: 1 mg to 6 mg per day for the first 28 days and then 1 mg to 2 mg per day for up to 21 days, following an increase in the dose of Risperdal Consta.

In PSY-3006, the median doses of Invega Sustenna and Risperdal Consta at the end of the study were *[confidential median doses removed at manufacturer's request]*, respectively. In PSY-3008, the median doses of Invega Sustenna and Risperdal Consta at the end of the study were *[confidential median doses removed at manufacturer's request]*, respectively. A larger percentage of patients taking Invega Sustenna compared with Risperdal Consta stopped taking part in the study; 25% versus 23% in PSY-3006, and 28% versus 17% in PSY-3008.

PSY-3006 was thought to provide the most relevant results. Results of the other trials were not considered as relevant because of the following factors:

- Lower than Health Canada-recommended initial doses of Invega Sustenna in PSY-3002.
- Patients in PSY-3008 knowing which treatment they were receiving.
- PSY-3008 was conducted only in China and included only a small percentage of patients who had previously used medications for mental illness.

Because of the aforementioned factors, the Committee mostly considered the results of study PSY-3006 in making its decision.

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

Outcomes

The main purpose of all three studies was to measure the change (from the start of the study) in the total PANSS score. The PANSS is a 30-item scale which measures the severity of positive symptoms (e.g., delusions), negative symptoms (e.g., lack of emotional expression), and general psychopathology (mental illness) symptoms on a seven-point scale; total scores range from 30 to 210, with higher scores meaning greater severity of symptoms. A lowering of 10 to 15 points on the PANSS is about the same as "minimal improvement" on the Clinical Global Impression – Improvement scale. Invega Sustenna would be considered not worse than Risperdal Consta if the change in the PANSS score was likely not more than 5 points less (studies PSY-3002 and PSY-3006) or 5.5 points less (study PSY-3008) for Invega Sustenna compared with Risperdal Consta.

Other outcomes of interest were also decided in advance in the CDR systematic review. Of these, the Committee discussed the following: the Clinical Global Impression – Severity (CGI-S) scale, the Personal and Social Performance (PSP) scale, side effects, and injection site reactions.

Results which were important to patient groups included improvements in quality of life, ability to work and take on family responsibilities, and lowering of amount of work for the caregiver. The PSP scale includes measurement of the ability to work and take on family responsibilities, as well as the ability to care for oneself, which should lower the amount of work for the caregiver. Patients and caregivers also mentioned that they would like medications with fewer side effects; in particular, weight gain, problems with thought, sleep problems, and sexual problems. Side effects of weight gain and sexual problems were measured during the studies.

Results

Efficacy or Effectiveness

- In PSY-3006, both Invega Sustenna and Risperdal Consta showed important decreases (improvements) in the PANSS score, with the average changes from study start being –18.6 and –17.9, respectively. In PSY-3006, Invega Sustenna was found not to be worse than Risperdal Consta when the data was analyzed, either for all patients for whom data was available, or for only those patients who followed the study rules. Study PSY-3002, which used lower than Health Canada-recommended initial doses of Invega Sustenna, concluded that Invega Sustenna appeared worse than Risperdal Consta. PSY-3008 concluded that Invega Sustenna was not worse than Risperdal Consta when the data was analyzed for patients who followed the study rules, but appeared worse than Risperdal Consta when data was analyzed for all patients for whom data was available.
- Results for the CGI-S and PSP were similar to the results for the PANSS; that is, there was no real difference between Invega Sustenna and Risperdal Consta in PSY-3006 and PSY-3008, but, in PSY-3002, the results for Risperdal Consta were better than for Invega Sustenna.

Harms (Safety and Tolerability)

- Injection site pain occurred more often with Invega Sustenna compared with Risperdal Consta in all of the studies; the largest differences in the occurrence of injection site pain between Invega Sustenna and Risperdal Consta were in PSY-3006 and PSY-3008. This is probably because the first two doses of Invega Sustenna in PSY-3006 and PSY-3008 were given into the deltoid muscle as recommended by Health Canada, which is more painful than an injection into the buttock muscle. Health Canada recommends that Risperdal Consta be given into the buttock muscle.
- The percentage of patients with side effects, or who stopped taking part in the study because of side effects, was about the same for Invega Sustenna and Risperdal Consta in all of the studies.
- In PSY-3002, it was much more common for patients to stop taking part in the study because the treatment was not working if they were on Invega Sustenna (23%) compared with Risperdal Consta (12%).
- The average change in body weight was small in all of the studies, and was about the same regardless of which treatment the patient received.

Cost and Cost-Effectiveness

The manufacturer submitted economic information to compare Invega Sustenna with Risperdal Consta based on claims of similar effectiveness and safety shown in medical studies, and doses based on a 1 mg Invega Sustenna to 1 mg of Risperdal Consta (1:1) ratio from the product monograph. The manufacturer also submitted economic information based on a 1.33:1 ratio that was based on the median final doses used in study PSY-3008. At the confidential submitted prices, the monthly cost of Invega Sustenna (monthly dose of 75 mg [$456] to 100 mg *[confidential information removed at manufacturer's request]*) is similar to Risperdal Consta (37.5 mg every other week [$469]).

The Committee felt that doses of Invega Sustenna and Risperdal Consta should have been taken from study PSY-3006, which looked to be the most relevant study. The final median doses from study PSY-3006 suggest a *[confidential information removed at manufacturer's request]* dose ratio which is greater than the 1.33:1 ratio. At the ratio suggested by study PSY-3006, the

monthly cost of Invega Sustenna *[confidential information removed at manufacturer's request]* is greater than Risperdal Consta (25 mg every other week [$313]).

The Committee felt that a cost comparison was not enough to evaluate the cost-effectiveness of Invega Sustenna compared with Risperdal Consta to account for the uncertainty regarding the effectiveness and dosing.

At recommended doses, the monthly cost of Invega Sustenna (75 mg to 150 mg given monthly [$456 to *(confidential information removed at manufacturer's request)]*) is greater than Risperdal Consta (25 mg to 50 mg given 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 in agreement with the CDR Confidentiality Guidelines.

Patient Input Information
The following is a summary of information provided by seven patient groups that responded to the CDR Call for Patient Input.

- Patient groups focused on the important effect that schizophrenia has on quality of life, the ability to work, and to have good personal relationships. Patients felt that it is necessary to have a choice of treatments available because treatments do not work the same for all patients.
- Patients stated that problems with current treatments include side effects (weight gain, poor sleep, sexual and nerve problems) and that it can be difficult to keep to the treatment schedule. Difficulty keeping to the treatment schedule was felt to be due to the need for frequent injections, as well as due to the fact that patients with schizophrenia may not recognize the need for treatment.
- Patients expect that, since Invega Sustenna only needs to be given once per month compared with every two weeks for Risperdal Consta, patients will be able to keep to the treatment schedule more easily and therefore have a lower chance of relapse (symptoms coming back). Patients expect that there would be less nerve side effects compared to older drugs, and less chance of interactions between Invega Sustenna and other drugs.

Other Discussion Points:

- It was noted that, unlike Risperdal Consta, which requires that the patients take additional medication by mouth when starting treatment, this is not necessary with Invega Sustenna. This is important because if patients need to take additional medication by mouth it may make it more difficult to keep to the treatment schedule.
- The Committee noted that the final mean doses from a published report of study PSY-3006 suggest a dose equivalency ratio of approximately 1.6:1 for Invega Sustenna to Risperdal Consta; however, the Committee considered that the actual 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. Anne Holbrook (Vice-Chair)

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

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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.