The cost-effectiveness of paliperidone palmitate compared to olanzapine pamoate in the treatment of schizophrenia in Sweden

Hanna Pudal \textsuperscript{1,2}, Michiel Hemels \textsuperscript{3,4}, Angelika Mehnert \textsuperscript{5}, Sylvain Druey \textsuperscript{6}, Monique Martin \textsuperscript{7}

\textsuperscript{1}Janssen-Cilag Oy, Helsinki, Finland, \textsuperscript{2}Janssen-Cilag A/S, Copenhagen, Denmark, \textsuperscript{3}Janssen Pharmaceuticals NV, Beerse, Belgium \textsuperscript{4}Innovus, Uxbridge, UK

Background
Schizophrenia is a chronic, severe and recurrent brain disorder that requires continuous, long-term treatment with antipsychotic medication to minimise relapse and provide clinical benefits to patients.\textsuperscript{1} For patients with schizophrenia, non-adherence to medication is a major risk factor for relapse and re-hospitalisation.\textsuperscript{2} Long-acting injectable (LAI) formulations of antipsychotics provide consistent medication delivery and the potential for improved adherence.\textsuperscript{3}

Objective
To compare from the Swedish societal perspective the cost-effectiveness of paliperidone palmitate (PP) administered monthly (75 mg eq every month) with olanzapine pamoate (OP) every 2 weeks (150 mg) or every 4 weeks (300 mg).

Methods
The Markov model is based on the premise that the long-term goal of treatment is to prevent relapses, which affect the patients’ clinical outcomes and generate substantial costs. Treatment efficacy from clinical trial data has been adjusted in the model based on level of compliance to reflect real-world effectiveness. Treatments are differentiated in terms of side-effects and switch rates (i.e. whether the patients will switch to another treatment, continue with the same treatment anyway or stop the treatment altogether). All direct medical costs of the management of schizophrenia are included. Markov states included relapse state, a stable state, and outcomes. Gender were generated for the duration in each health state. Four types of treatment-related side-effects were considered: the three side effects included in an economic model in the recent NICE guidelines: extrapyramidal symptoms (EPS), weight gain, and diabetes, as well as tardive dyskinesia (TD), chronic side effects that can significantly impact patients’ health-related quality of life.

Clinical parameters
Adherence and relapse risk
In this model “relapse” reflects both symptomatic worsening such as a clinically meaningful exacerbation of symptoms and/or an event of psychiatric hospitalization. The baseline relapse (the untreated risk of relapse) in the schizophrenia patient population was derived from the NICE report on mixed treatment comparison calculating the probability of relapse in patients with schizophrenia over 52 weeks on placebo treatment (43.6\% (NICE 2008)).\textsuperscript{6}

The clinical trial treatment effect for PP was based on relative relapse risk and calculated based on Garett et al 2010 (establishing relative relapse risks for RLAI in OLAI over 3 years) and Leucht et al 2009 (reporting evidence of similar relapse risk for OLE and OLL) thereby allowing to apply the NICE relative risk for RLAI over placebo to generate the relative relapse risk for RLAI over placebo: (RLAI/OLE)\textsuperscript{(relative risk)} = (RLAI/OLAI)\textsuperscript{(relative risk)} = RLAI/placebo.\textsuperscript{5,6}

Because lack of clinical studies with PP and OP, relapse risk ratio was estimated using the head-to-head trial of OP and olanzapine oral. Relapse rates by treatment arms are presented in table 2.

Compliance
The compliance data for the general schizophrenia population were derived from Glimmer 2004 and Oliven et al 2007. PP and OP are assumed to have the same risk as RLAI. RLAI risk ratio (1.26) is based on Oliven et al 2007, leading to a compliance of 52.9\% (1.26\%×\% = 52.9\%, with 41% being the proportion of compliant patients in the general population (Glimmer 2004). The same approach was applied for the risk for non-compliance (Oliven et al 2007) however, due to estimated compliance issues RLAI vs RLAI, AAR hazard ratio was discounted by proportion of non-compliant patients (0.11\%×\%×\% = 4.1\%). The probability and risk ratio for partially compliant patients was then calculated using the other risks (Table 2).

Results
It was assumed that the compliance level of OP is equal to risperidone long-acting injection. Regarding compliance level of OP, it was decided not to be higher than on PP because of the strong monitoring requirements for patients receiving OP. Because no evidence or studies that 3-hour post-monitoring of OP would decrease the compliance level it was assumed that compliance level of OP is equal to PP.

Side effects
Antipsychotic drugs are associated with dose-dependent risks of extrapyramidal symptoms, tardive dyskinesia, weight gain and diabetes. Annual probabilities of side-effects of OP were assumed to be equal to oral olanzapine. Side-effects probabilities of PP and OP are presented in table 3.

Methods
Switch rates
Switch rates are dependent on treatment and health states. Four possible reasons for switches were distinguished: lack of efficacy, lack of compliance, side-effects, patient request. The probability of switch due to lack of efficacy was assumed to affect patients with relapse only. Therefore, the probability of switch due to lack of efficacy among patients with relapse was calculated as the ratio of the probability of switch due to lack of efficacy over the probability of relapse in any cycle.

Utilities
Since we were unable to find a study reporting on utility data from Swedish schizophrenia patients, utility scores for health states and utility decrements for side-effects were taken from a UK study Briggs et al. 2010.

Results
All results are provided for a time horizon of 55 years. The discount rates for costs, QALYs and rehospitalisations were set at 3\%. Costs were reported in 2010 Swedish kronor (1 SEK = 0.159 Euro). In tables 5 and 6, total costs, discounted QALYs and discounted rehospitalisations are shown. Paliperidone palmitate dominates olanzapine pamoate by being less costly and more effective.

Limitations
• Relapses avoided: PP is dominated by OP in 8\% and dominates OP in about 92\% of cases (picture was run with 1.000 simulations to compare the cost-effectiveness between PP and OP).

Conclusions
• This cost-effectiveness analysis suggests that use of paliperidone palmitate resulted in improved clinical outcomes and lower health care costs compared with olanzapine pamoate.
• Paliperidone palmitate leads to fewer relapses and greater QALY’s gained compared with olanzapine pamoate.
• Paliperidone palmitate appears to be a cost-effective treatment option vs olanzapine pamoate for patients with schizophrenia.

References