Maintenance dose conversion between oral risperidone and paliperidone palmitate 1 month: Practical guidance based on pharmacokinetic simulations

Alberto Russu\textsuperscript{1} | Jennifer Kern Sliwa\textsuperscript{2} | Paulien Ravenstijn\textsuperscript{1} | Arun Singh\textsuperscript{3} | Maju Mathews\textsuperscript{3} | Edward Kim\textsuperscript{2} | Srihari Gopal\textsuperscript{3}

\textsuperscript{1}Janssen Research & Development, a Division of Janssen Pharmaceutica NV, Beerse, Belgium
\textsuperscript{2}Janssen Scientific Affairs, LLC, Titusville, NJ, USA
\textsuperscript{3}Janssen Research & Development, Titusville, NJ, USA

Summary

Aim: We assessed the dosage strengths of paliperidone palmitate 1-month (PP1M) long-acting injectable resulting in similar steady-state (SS) exposures to the dosage strengths of oral risperidone using pharmacokinetic (PK) simulations.

Methods: Population PK simulations of SS PK were performed using the PK models of oral risperidone and PP1M. The concentrations of active moiety (risperidone + paliperidone) from risperidone were compared to paliperidone concentrations resulting from PP1M administration. Similarity was assessed via graphical evaluation of median and 90% prediction intervals of SS PK profiles over 28 days.

Results: Oral risperidone doses of 1, 2, 3, 4, and 6 mg/d are expected to result in similar SS PK as PP1M doses of 25, 50, 75, 100, and 150 mg eq. (which correspond to 39, 78, 117, 156, and 234 mg of paliperidone palmitate) respectively (ie 25-fold dose conversion factor from oral risperidone to PP1M).

Conclusions: This study provides clinicians with a practical guidance to establish suitable maintenance dose levels of PP1M and oral risperidone when transitioning patients from one formulation to another.

1 INTRODUCTION

Schizophrenia is a chronic debilitating illness, often with high relapse rates and a chronic course.\textsuperscript{1} Most patients require long-term treatment with antipsychotic medications.\textsuperscript{2} Frequent switching of antipsychotic medications due to lack of efficacy, tolerability and non-adherence issues are common in schizophrenia treatment.\textsuperscript{2}

Long-acting injectable (LAI) formulations provide an advantage over oral antipsychotics with improved treatment outcomes including improved medication adherence and persistence, lower rates of hospitalisations, and a pharmacokinetic (PK) profile characterised by a prolonged terminal phase that helps delay relapse compared to oral formulations.\textsuperscript{3}

Paliperidone (9-hydroxyrisperidone) is the major metabolite of risperidone, with a similar serotonin (5HT\textsubscript{2A}) and dopamine (D2) antagonism and receptor binding profile.\textsuperscript{4} Patients taking risperidone are therefore exposed as well to paliperidone following in vivo conversion and the clinical effects of oral risperidone result from the combined concentrations of risperidone and paliperidone (ie active-moiety).\textsuperscript{5}

Paliperidone palmitate is a long-acting injectable formulation of paliperidone that is available in 1-month and 3-month formulations. The paliperidone palmitate 3-month formulation (PP3M) can be administered after patients are adequately treated and symptomatically stabilised for at least 4 months on the paliperidone palmitate 1-month formulation (PP1M). The corresponding PP3M dose is 3.5 times the maintenance PP1M dose. The corresponding oral paliperidone to PP1M maintenance dose has already been established (PP1M prescribing information).\textsuperscript{6} However, data are not available...
2 of 6
RUSSU et al.

2 | METHODS

To estimate the maintenance dose conversion between formulations, model-based PK simulations were performed using the population PK models of oral risperidone and PP1M, which were developed and validated based on extensive clinical study data, ie 780 patients from 9 studies for risperidone12 and 1795 patients from 11 trials for PP1M.13

For oral risperidone, the PK of the active antipsychotic fraction (ie active moiety, risperidone plus paliperidone) was characterised by a first-order absorption process with delay, describing absorption from gut to the central (plasma) compartment, and by a two-compartment disposition model with linear elimination. Variability in PK was described via covariate effects of body mass index (BMI) on volume of distribution (ie larger volume for heavier patients) and of body weight, age, and renal function on oral clearance (ie reduced clearance for older patients and for patients with reduced renal function, as measured by creatinine clearance, and greater clearance for heavier patients), as well as via random inter-individual variability terms accounting for unexplained variability sources on absorption and disposition. While risperidone metabolism is known to be influenced by CYP2D6 genotype, the PK of the active moiety has been shown to be on average similar across different metabolic phenotypes, ie poor, intermediate, and extensive metabolisers.14 Therefore, no inter-patient variability in CYP2D6 metabolic status needed to be accounted for in the active moiety PK model of oral risperidone.

For PP1M, a dual-input absorption process from the depot compartment was used to describe the poly-phasic release profile of paliperidone in the central compartment. Briefly, a zero-order absorption process directly in the central compartment (accounting for about 17% of the total dose) described the rapid appearance of paliperidone in the systemic circulation immediately following intramuscular injection. The remaining fraction of dose was assumed to be absorbed via a linear process following a given lag time (equal to the duration of the zero-order process, about 13 days). Disposition was described via a one-compartment model with linear elimination. As established in a previous study,13 the patient characteristics influencing inter-patient variability in PP1M PK were consistent with those identified for oral risperidone, eg covariate effects of body mass index (BMI) on volume of distribution (ie larger volume for larger BMI) and of renal function on apparent clearance (ie reduced clearance for patients with reduced renal function). Injection site (deltoid vs gluteal) was found to influence the absorption process of PP1M (ie slower first-order absorption process for gluteal vs deltoid site; higher fraction of dose absorbed via the “fast” zero-order process for deltoid vs gluteal site), which is likely due to different distribution of muscle and adipose tissues in the 2 injection sites. Additional covariate effects have been described elsewhere.13 Paliperidone is not significantly metabolised by the CYP2D6 enzyme and hence is also not impacted by this genotype.

The population PK models described above were used to simulate SS PK profiles according to the following dosing regimens:

- Oral risperidone once-daily at doses of 1, 2, 3, 4, and 6 mg;
- PP1M every 4 weeks (deltoid or gluteal injections) at doses of 25, 50, 75, 100, and 150 mg equivalents (mg eq.) of paliperidone (the corresponding doses of paliperidone palmitate substance are 39, 78, 117, 156, and 234 mg, respectively; the conversion factor from mg eq. to mg is 1.56). Initiation with deltoid injections of 150 mg eq. (234 mg) on day 1 and 100 mg eq. (156 mg) on day 8 was simulated.

Similarity between given doses of oral risperidone and PP1M was assessed via graphical evaluation of central tendency and variability in the population as median and 90% prediction interval of
3. RESULTS

The PP1M maintenance doses of 25, 50, 75, 100 and 150 mg eq. (injected either in the deltoid or gluteus) are expected to result in similar SS exposure range (based on median and 90% prediction interval) to oral risperidone doses of 1, 2, 3, 4, and 6 mg once-daily, respectively, which results in a 25-fold dose conversion factor from oral risperidone to PP1M. Table 1 summarises the PP1M dose levels that are projected to attain similar SS exposures to corresponding oral risperidone doses for maintenance treatment.

FIGURE 1 Comparison between oral risperidone 3 mg once-daily and PP1M 75 mg eq. (deltoid or gluteal injections) every 4 weeks. Top panel shows PP1M deltoid injections, while bottom panel shows PP1M gluteal injections. Simulations are shown as median and 90% prediction interval of 1000 individual simulated concentration-time profiles (oral risperidone: active moiety; PP1M: paliperidone palmitate once-monthly) over a hypothetical 28-day time frame at steady-state for both drugs. For PP1M, (dose in mg) = 1.56 × (dose in mg eq.)

TABLE 1 Doses of oral risperidone and PP1M expected to result in similar active moiety at steady-state based on pharmacokinetic simulations

| Oral risperidone (mg) | Paliperidone palmitate 1-mo (PP1M) |
|-----------------------|------------------------------------|
|                       | (mg eq.)                           | (mg) |
| 1                     | 25                                 | 39   |
| 2                     | 50                                 | 78   |
| 3                     | 75                                 | 117  |
| 4                     | 100                                | 156  |
| 6                     | 150                                | 234  |

*For PP1M the conversion factor from mg eq. to mg is 1.56.

Figures 1 and 2 show the comparison of PK profiles between oral risperidone 3 mg and PP1M 75 mg eq., and between oral risperidone 6 mg and PP1M 150 mg eq. respectively. Graphical comparisons between the other 3 oral risperidone dose levels and the respective 25-fold PP1M dose levels are provided in Figures S1, S2, and S3.
Because the PK of the active moiety following oral risperidone treatment is linear, administering the same total daily dose in a twice-daily regimen (eg 6 mg/d administered as 3 mg twice-daily) is only expected to result in a reduced peak-trough ratio, compared to a once-daily regimen. The average plasma concentration over the dosing interval is not affected. Therefore, the above dose conversion results can be assumed to hold also for oral risperidone administered twice-daily for the same total daily dose.

4 | DISCUSSION

This work describes the exposure-matching between oral risperidone and paliperidone palmitate dose levels based on PK similarity at SS, using population PK simulations. Population PK approaches provide a comprehensive framework to characterise the PK of a compound from multiple studies while accounting for inter-subject variability. Dose conversion factors derived from population PK simulations have been accepted by the Health Authorities and are currently featured in label language of PP1M and PP3M worldwide.\footnote{RUSSU ET AL.}

Based on the population PK simulations presented here, a 25-fold dose multiple between oral risperidone and PP1M may be considered to attain similar SS exposures for the two formulations. These results are based on comparing the whole PK profile at steady-state between the two formulations, and not only a single PK parameter (such as eg trough concentration, or area under the concentration-time curve [AUC]). In addition, the model-based PK simulations presented here allowed characterising the variability of PK in the population, thereby providing stronger support to the dose conversion results compared to using only mean patient data.

The transition from oral risperidone to PP1M must include the recommended initiation regimen of 150 mg eq. (234 mg) and 100 mg eq. (156 mg) on Day 1 and Day 8, respectively, in the deltoid, in accordance with the approved prescribing information for PP1M to ensure attainment of adequate SS exposures, without oral antipsychotic supplementation.\footnote{RUSSU ET AL.} Once treatment with PP1M has been initiated (ie on day 1), oral antipsychotics can be discontinued.\footnote{RUSSU ET AL.}

Clinical factors related to adherence, efficacy and tolerability are critically important when establishing a suitable maintenance dose.
level in a given patient. The conversion does not take into account the potential effects of CYP2D6 inhibitors (i.e., paroxetine, sertraline or fluoxetine) or CYP3A and PgP inducers (i.e., carbamazepine) on active-moiety concentrations. Our results provide supplementary guidance to clinicians when considering the appropriate maintenance dose for patients transitioning from stable doses of oral risperidone to long-acting injectable PP1M.

5 | CONCLUSION

This analysis provides the clinician with a practical guidance to establish suitable maintenance dose levels of PP1M and oral risperidone when transitioning patients from one formulation to another, such that SS active-moiety exposures are similar between the two drugs. In addition to PK considerations, clinical symptoms should always be considered when switching medications. Patients undergoing a switch should be monitored closely before and after switching the medications.

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DISCLOSURES

The studies presented in this report were sponsored by Janssen Research & Development, LLC, USA. All authors are employees of Janssen Research & Development or Janssen Scientific Affairs, LLC and are shareholders in the parent company (Johnson & Johnson). The sponsor of the study had roles in the study design and conduct; collection, analysis and interpretation of the data.

AUTHOR CONTRIBUTIONS

Drs. Alberto Russu, Arun Singh, Maju Mathews, and Srihari Gopal were involved in study design, conduct, analysis and interpretation of data. Paulien Ravenstijn was the clinical pharmacokinetic leader, contributing to data analysis and interpretation. Alberto Russu was the pharmacometric leader for the study and had the primary role in pharmacokinetic analyses and data interpretation. Jennifer Kern Sliwa and Edward Kim identified the customer need for this pharmacokinetic analysis and contributed to the development and review of this manuscript. All authors contributed to data interpretation, development and review of this manuscript and confirm that they have read the journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. All authors meet ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors had access to the study data, provided direction and comments on the manuscript, made the final decision about where to publish these data and approved submission to this journal.

ORCID

Alberto Russu http://orcid.org/0000-0003-2095-4365

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

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