Switching to Paliperidone Palmitate[1,2] from Other Depot Antipsychotics: Guidance Based on Pharmacokinetic Simulations

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Introduction

- ✓ Paliperidone Palmitate (PP), [INVEGA® SUSTENNA®, Ortho-McNeil-Janssen Pharmaceuticals, Inc.], the palmitate ester of paliperidone, is a long-acting injectable antipsychotic designed for intramuscular injection[1,2]
- ✓ The safety and efficacy of deltoid or gluteal muscle injections of PP 25, 50, 75, 100 or 150 mg eq. in the treatment of schizophrenia have been demonstrated in several randomized, double-blind, controlled trials[3–7]
- ✓ Recommended dosing regimen for PP is as follows: PP is administered on Day 1 as a dose of 150 mg eq. and Day 8 as dose of 100 mg eq. via a deltoid intramuscular injection, followed by a 75 mg eq. (25–150 mg eq.) intramuscular injection in either the gluteal or deltoid muscles on Day 36, and then once every month thereafter[8,9]
- ✓ PP is administered by intramuscular injection only, using appropriate needle sizes. For deltoid injection, 1½-inch 22G needle for patients ≥ 90 kg (≥ 200 lb) or 1-inch 23G needle for patients < 90 kg (< 200 lb) is used. For gluteal injection, 1½-inch 22G needle is used regardless of patient weight.
- ✓ There are limited data to address switching from other depot antipsychotics to PP
- ✓ Since risperidone long acting injection (RLAI) [RISPERDAL® CONSTA®, Ortho-McNeil-Janssen Pharmaceuticals, Inc.] has a similar active moiety to PP, specific strategies for switching patients from RLAI to PP can be established using simulations.
- ✓ The objective of this exercise is to describe the suggested optimal strategy to use when switching patients to PP from other long-acting injectable antipsychotics

Methods

- ✓ A 1-compartment model with zero/1st-order absorption best described the PK of PP[10] The model has been used to determine initiation and maintenance regimens for PP[8,9]
- ✓ A 1-compartment model with 3 parallel absorption pathways best described RLAI PK[11]
- ✓ Active moiety plasma concentrations were simulated based on final estimates of the population PK models using PK profiles for 5000 patients
- ✓ To evaluate the outcome of simulations, the population median and 90% prediction intervals of simulated PK profiles after multiple doses were graphically displayed
- ✓ In addition to the simulation-based analysis, a literature search was also performed to understand the PK characteristics of other long-acting injectable antipsychotics.

Results & Discussion

- ✓ The literature search results[12-16] (Table 1) show that, for all other depot antipsychotics, the dosing interval is in the range of 1-2 half-lives for each product.
- ✓ This indicates that at the time of switching to PP (in place of the next scheduled injection of the previous antipsychotic) there will be sustained therapeutic levels of the prior drug in the systemic circulation. This is true because it takes 4 to 5 half-lives for drugs to be disposed of from the systemic circulation based on 1st order PK principles.
- ✓ Given that significant levels of the previous antipsychotic would be present in the circulation there would be no need to administer the 2nd initiation dose of PP on Day 8, which is otherwise needed to elevate concentrations to therapeutic levels quickly.
- ✓ This concept, of not needing a Day 8 loading dose when switching to PP from other long-acting antipsychotics, can be easily illustrated through simulations using RLAI.
- ✓ RLAI is administered at doses of 25, 37.5 and 50 mg every 2 weeks. Therapeutic concentrations of active moiety are maintained for 4–5 weeks after the last dose of RLAI at steady-state and decline thereafter with a mean plasma half-life of 4–6 days[12].
- ✓ Plasma concentrations were simulated with PP injection, 2 weeks after the last RLAI dose, i.e. in place of the next scheduled injection, followed by monthly injections of PP
- ✓ Results are presented for 2 scenarios in Figure 1: [A] Low dose scenario where 25 mg RLAI is switched to 50 mg eq. PP followed by monthly injections of 50 mg eq. PP; and [B] High dose scenario where 50 mg RLAI is switched to 100 mg eq. PP followed by monthly injections of 100 mg eq. PP.
- ✓ The results in Figure 1 indicate that, for both low and high dose scenarios, drug levels are maintained close to steady-state concentrations right after the switch from RLAI.
- ✓ Thus this simple strategy of (a) initiating PP in place of the regularly scheduled injection of the previous depot antipsychotic; and (b) following up with monthly injections of PP, is considered to be both convenient and practical for the prescriber.
- ✓ Using the appropriate PP doses, (Table 2) determined by previous RLAI dose, may result in similar PK profiles for the active moiety before and after the switch from RLAI
- ✓ Simulations suggest that this switching strategy requires no oral supplementation.
- ✓ Finally, it should be indicated that a switching strategy has been proposed previously.[17] While both switching strategies result in comparable exposure the current proposal is more practical than the previous one. Moreover, the current strategy is in agreement with the switching recommendation in the US PP prescribing information.[1]

Summary

- ✓ When switching from RLAI to PP, treatment should be tailored for the patient based on their previous dose of RLAI
- ✓ No oral supplementation is required when switching from long-acting anti-psychotics
- ✓ When switching patients from previous long-acting injectable antipsychotics, initiate PP therapy in place of the next scheduled injection. PP should then be continued at monthly intervals.
- ✓ The 1-week initiation dosing regimen as described under introduction is not required when switching from long-acting injectable antipsychotics.
- ✓ Patients previously stabilized on different doses of RLAI can attain similar paliperidone steady-state exposure during maintenance treatment with PP according to Table 2.

Figure 1: Switching From RLAI to PP

Top and bottom panels represent low and high dose scenarios. Simulations for the middle dose are not shown because those results can be simply interpolated between the 2 panels. Lines and shaded areas (violet region) represent medians and 90% prediction intervals.

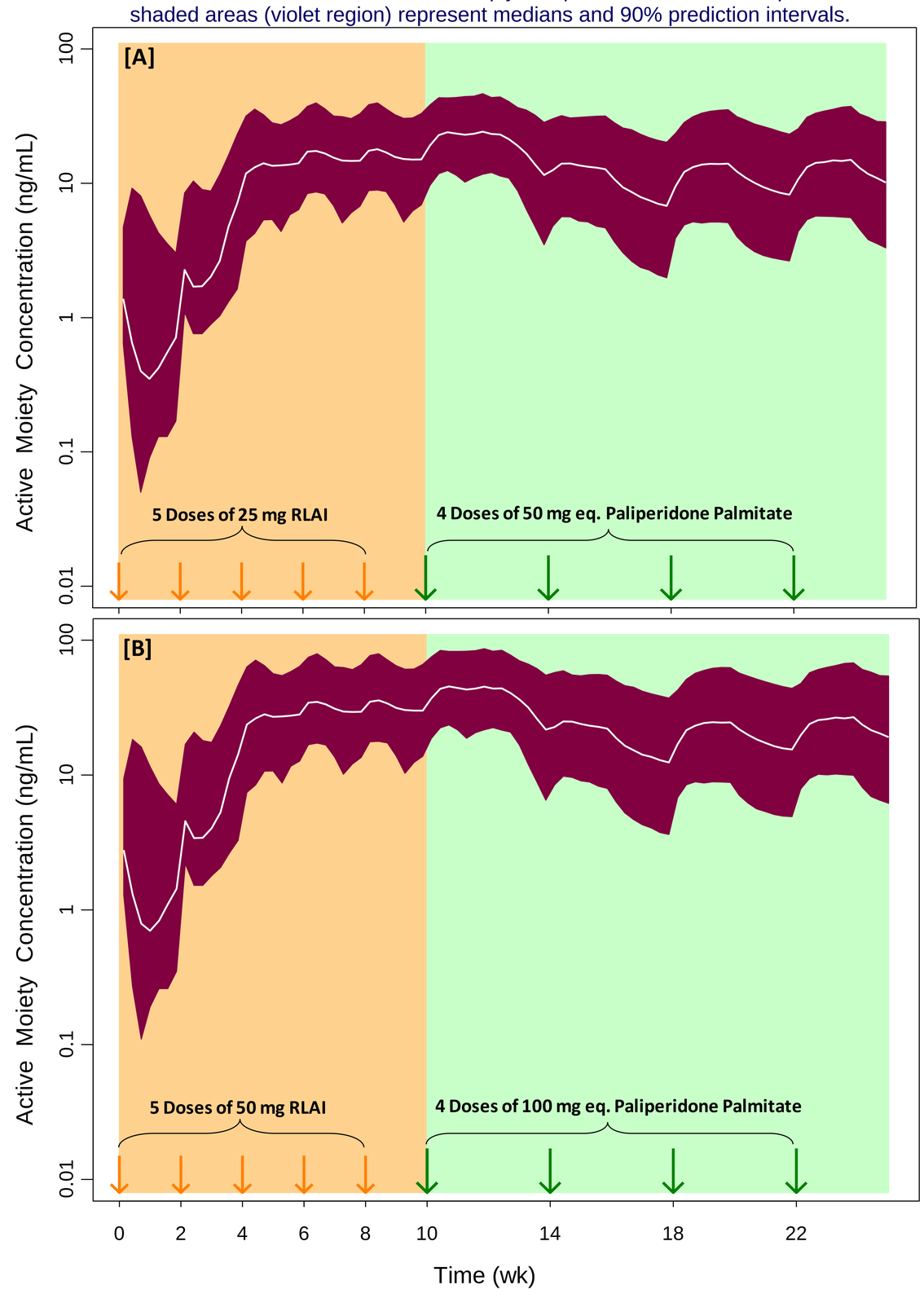

Table 1: Properties of Other Long-Acting Antipsychotics

Depot Antipsychotic	Dosing Interval	Half-life†	Reference
Clopenthixol deconoate	2-4 weeks	10 days	13
Flupenthixol deconoate	2-4 weeks	17 days	14
Fluphenazine decanoate	2-5 weeks	14 days	14
Fluphenazine enanthate	1 week	4 days	15
Fluspirilene	1 week	7 days	13
Haloperidol deconoate	4 weeks	21 days	13
Olanzapine pamoate	2-4 weeks	26 days	16
Perphenazine enanthate	2 weeks	4-6 days	13
Pipothiazine palmitate	4 weeks	15-16 days	13
Risperidone long acting injection	2 weeks	4-6 days	12
Zuclopenthixol deconoate	2-4 weeks	19 days	13

†Apparent terminal half-life after multiple dosing

Table 2: Doses of RLAI & PP Needed to Attain Similar Exposure

Previous RLAI Dose	PP Injection†
25 mg every 2 weeks	50 mg monthly
37.5 mg every 2 weeks	75 mg monthly
50 mg every 2 weeks	100 mg monthly

†If PP is discontinued, its prolonged-release characteristics must be considered. As with other antipsychotics, the need for continuing existing extrapyramidal symptom medication should be re-evaluated periodically

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