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Paliperidone Palmitate Long-Acting Injectable Given Intramuscularly in the Deltoid Versus the Gluteal Muscle *Are They Therapeutically Equivalent?*

To the Editors:

In the report by Yin et al,¹ the statement that “many clinicians may misinterpret these directions (in paliperidone palmitate product monograph) to mean that these intramuscular sites (deltoid or gluteal) are interchangeable, and thus therapeutically equivalent” is, in our opinion, not correct. We are writing to clarify some statements from the Yin et al article concerning the deltoid versus gluteal intramuscular injection of paliperidone palmitate.

The recommended initiation as stated in the product label of paliperidone palmitate 1-month injection is with a dose of 150 mg eq on treatment day 1 and 100 mg eq 1 week later, both administered in the deltoid muscle. Here, the deltoid and gluteal injection sites are not interchangeable, and from a clinical point of view, it is important to reach therapeutic concentrations quickly when starting a new antipsychotic. However, after the second initiation dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle. The injection sites of the maintenance doses can be used interchangeably, but for deltoid injections, the appropriate needle length is based on the patient's weight (1-in 23G needle for patients weighing <90 kg and 1.5-in 22G needle for patients weighing ≥90 kg). For gluteal injection, regardless of patient weight, the use of a 1.5-in 22G needle is recommended. The use of differently sized needles depending on the weight of the patient for injection into the deltoid muscle is recommended to limit the risk of drug administration into the subcutaneous tissues, which would result in a decreased rate of absorption from the intramuscular site of injection.

Different distributions of muscle and adipose tissue, as well as difference in blood flow between the deltoid and gluteal sites,^{2–4} may affect the uptake rate of paliperidone into the circulation from the site of injection. At the deltoid site, the likelihood of an injection that is purely intramuscular is higher compared with that at the gluteal injection site. The hypovascularity of subcutaneous adipose tissue compared with

muscle tissue may result in a slower uptake of paliperidone from the gluteal compared with the deltoid injection site. We agree that there is a different rate of absorption between the deltoid and gluteal injection sites, as presented in the articles cited by Yin et al,^{4–6} as well as in a more recent publication,⁷ but we do not consider these differences therapeutically relevant after multiple doses as discussed hereinafter.

The statement made by Yin et al,¹ “This is concerning as the observed C_{max} for the 150 mg dose is considerably higher (i.e., 65%) than the average value reported in the product monograph,” is based on a single dose pharmacokinetic study by Cleton et al.⁶ In the study described by Rossenu et al,⁷ a C_{max} difference was also observed after the first and fourth injections (30% higher C_{max} after deltoid injection compared with gluteal injection). However, Rossenu et al⁷ showed that steady state was not reached entirely after the 4 gluteal injections, and so this difference in C_{max} cannot be extrapolated to C_{max} at steady state. In addition, Samtani et al⁸ have shown that the median peak paliperidone concentrations at steady state for repeated gluteal and deltoid injections were 46 versus 50 ng/mL, respectively, for a dose strength of 150 mg eq, which is only a 9% difference. Thus, the statistics obtained from only a single dose or even a few doses at initiation cannot be extrapolated to the steady state condition during maintenance therapy.

The following statement made by Yin et al¹ is taken out of context: “the observed C_{max} and AUC were 20% to 50% higher after injection in the deltoid muscle compared with the gluteal muscle.” The 50% higher area under the curve (AUC) is not total exposure but a partial AUC (AUC_{0-36} days) from Study USA-03, which studied deltoid dosing with a longer 1.5-in needle length. Yin et al fail to mention that the AUC_{∞} in the same study was similar between deltoid and gluteal dosing (4% higher AUC_{∞} after deltoid injection of 150 mg eq, which is a commonly used PP1M dose).⁹ This similarity in AUC_{∞} for deltoid versus gluteal dosing was also observed in the study by Cleton et al⁶ where the AUC_{∞} was only 3% to 18% higher across the 4 dose strengths after a single deltoid dose compared with a single gluteal dose.

The population pharmacokinetic model (built on 1795 subjects from 6 phase 1 trials and 5 phase 2 and 3 trials, with a total of 18 530 pharmacokinetic samples from many different countries and ethnicities) confirmed not only the observed differences

in pharmacokinetics upon the initiation of paliperidone palmitate treatment but also that differences between the gluteal and deltoid injection sites become less apparent after multiple injections.¹⁰ The final covariate model indicated that, among other variables, injection site had a significant influence also on the first-order absorption rate constant (k_a), indicating a slower absorption rate after gluteal injection. However, paliperidone palmitate offered complete bioavailability of paliperidone at all dose strengths and from both injection sites.¹⁰ Taken together, these data confirm that the total exposure at steady state is similar between the deltoid and gluteal injection sites.

We acknowledge that, in principle, the time to reach steady state is longer for the gluteal injection site. This is why the 2 initiation doses of once-monthly paliperidone palmitate are required to be administered in the deltoid muscle, in addition to the requirement for weight-based selection of the appropriate needle size for administration, to rapidly attain therapeutic concentrations. Therefore, Yin et al did not provide the appropriate background and context when they state that “The US Food and Drug Administration (FDA) also reviewed this data and commented that ‘compared with deltoid injections, repeated administration in the gluteal muscle resulted in a delayed time to achieve steady state (approximately 4 weeks longer)’.”¹¹

In summary, the results of multiple studies of paliperidone palmitate indicate that, at the initiation of treatment, injection in the deltoid muscle results in higher initial exposures compared with injection in the gluteal muscle. After multiple injections and at steady state, the difference in exposure between gluteal and deltoid muscles is less apparent. In view of the totality of the evidence as described in this letter, we do not agree with the statement by Yin et al¹ that the deltoid and gluteal injection sites are not interchangeable or therapeutically not equivalent.

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AUTHOR DISCLOSURE INFORMATION

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3-month formulations of paliperidone palmitate were developed by Janssen Research & Development, and the authors participated in the development programs. The company also provided a formal review of this letter before submission to the journal.

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Response to the Letter to the Editor on “Paliperidone Palmitate Long-Acting Injectable Given Intramuscularly in the Deltoid Versus the Gluteal Muscle: Are They Therapeutically Equivalent?”

To the Editors:

We would like to thank Dr Ravenstijn and her associates¹ from Janssen Pharmaceuticals for taking the time to comment on the issue of therapeutic equivalence between the deltoid and gluteal sites of administration for the once-monthly formulation of paliperidone palmitate (PP1M). Although they have brought up several points that supplement our article (eg, the importance of using appropriate needle lengths at the different sites), we do not agree with the premise of their argument.

The focus of our article, as stated in the title, is to address the issue of therapeutic equivalence between the deltoid and gluteal sites of administration for PP1M.² Generally speaking, therapeutic equivalence requires that the criteria for both pharmaceutical equivalence and bioequivalence be fulfilled. Because the product in question is the same, the issue of therapeutic equivalence is simply one of bioequivalence between the 2 injection sites. Bioequivalence is defined in section 320.1 of the Code of

Federal Regulations as “the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.”³ To our knowledge, Janssen have never shown data that demonstrate bioequivalence between the deltoid and gluteal injection sites, nor have they made any claims that the 2 sites are bioequivalent. Thus, we cannot assume that deltoid and gluteal injections of PP1M are therapeutically equivalent.

For PP1M, the rate and extent to which paliperidone becomes available at the site of action are likely to be similar between the 2 injection sites if the corresponding measures (ie, maximum plasma concentration [C_{max}] and area under the curve [AUC], respectively) are comparable. However, if there are large discrepancies between the 2 sites when comparing either of these pharmacokinetic parameters (ie, 90% confidence interval [CI] for geometric mean ratios is outside the range of 80.0%–125%), then therapeutic equivalence cannot be conferred even if the product monograph states that “monthly maintenance doses can be administered in either deltoid or gluteal muscle”. In a study sponsored by Janssen, the C_{max} observed after injecting 150 mg of PP1M in the deltoid muscle was 65% higher than the value observed after injecting the same dose in the gluteal muscle (ie, geometric mean C_{max} -based ratio: 164.9 [90% CI, 131.2–207.1]),⁴ suggesting that the injection sites are not bioequivalent. Ravenstijn et al downplayed the importance of these data by stating that they were derived from a single-dose study. They then referred to another Janssen sponsored study⁵ showing that after 4 injections in the deltoid muscle, C_{max} was 30% higher compared with the gluteal muscle (ie, geometric mean C_{max} -based ratio: 130% [90% CI, 100.6%–168.9%]). Once again, Ravenstijn et al seemed to dismiss the difference, stating that “this difference in C_{max} cannot be extrapolated to C_{max} at steady-state”. We would like to point out that the FDA Guidance for Industry with regard to bioavailability and bioequivalence actually recommends the use of single-dose studies to “assess bioavailability and bioequivalence because they are generally more sensitive than steady-state studies in assessing rate and extent of release of drug substance from drug product into the systemic circulation.”⁶ As such, the data referred to by Ravenstijn et al further strengthen our argument that the injection sites may not be bioequivalent. We believe that Janssen is in agreement with us on the topic of single-dose studies