**INVEGA® (paliperidone ER)**
**INVEGA Dosing - Conversion to/from Another Antipsychotic**

## SUMMARY

- **Dose Equivalents:** With the exception of INVEGA SUSTENNA® (paliperidone palmitate)[1], there is no strict dose equivalency ratio between INVEGA® and any other antipsychotic, including RISPERDAL® (risperidone).[2,3]
- **Conversion:** No systematically collected clinical data is available on switching patients on INVEGA to/from another antipsychotic. The decision of how to convert/switch antipsychotics must be based on clinical judgement, individual patient assessment, and pharmacokinetic (PK) properties of the drugs involved.
- **Proposed Equivalency:** Based on a consensus building series of surveys sent to research and clinical experts (N=43) to determine dosing estimates that result in similar efficacy, Gardner et al (2010)[3] proposed that oral olanzapine 20 mg/day is equivalent to: aripiprazole 30 mg/day, clozapine 400 mg/day, INVEGA 9 mg/day, quetiapine 750 mg/day, risperidone (oral) 6.0 mg/day, risperidone long-acting injection 50 mg/14 days, and ziprasidone 160 mg/day.
- **Efficacy Comparison with RISPERDAL®:** Six randomized, double-blind, placebo-controlled trials in schizophrenia were used to compare the efficacy and tolerability of INVEGA and risperidone (three trials per product) using propensity score methodology. Treatment with INVEGA 6-12 mg and oral risperidone 4-6 mg/day resulted in similar completion rates and improvement on PANSS total scores at endpoint.[4]
- **Pivotal Studies in Schizophrenia:** In a pooled analysis of 3 placebo-controlled, 6-week, phase III clinical studies of adult patients with schizophrenia (N=1,306), patients were randomized to receive INVEGA (3, 6, 9, 12, or 15 mg/day), placebo, or olanzapine 10 mg/day. Ninety-seven percent (97%) of patients had received prior treatment with one or more psychotropic medications, and 68% of the total patient population had received an atypical antipsychotic.[5] The dose of INVEGA patients received was not stratified based on the dose of any prior psychotropic treatment. Among the total patient population, which includes patients who received prior psychotropics, 6 mg/day offered the best balance of tolerability and efficacy for most patients.[6]
- **Concomitant Use with Risperidone:** Concomitant use of INVEGA with risperidone has not been studied. Since paliperidone is the major active metabolite of risperidone, consideration should be given to the additive paliperidone exposure if risperidone is co-administered with INVEGA.[7]

## PROPOSED DOSE EQUIVALENCY

### Clinically Equivalent Dose:

**Gardner et al (2010)**[3] conducted a broad, two-stage, survey of research and clinical experts (N=43) to determine a representative set of clinically equivalent dosing estimates for most typical and atypical antipsychotics. The survey presented oral olanzapine 20 mg/day as the reference treatment for all equivalency estimates, and participants received instructions to prioritize efficacy over tolerability in estimates of dose equivalency. In comparison with olanzapine 20 mg/day, the median reported dose equivalency of INVEGA was 9.0 mg/day. This proposed equivalency results in an approximate equivalency ratio of 2.22 mg/day oral olanzapine equal to 1.00 mg/day INVEGA. Please see the table: Dose Equivalency of Atypical Antipsychotics to Oral Olanzapine for additional dose equivalencies of oral and long-acting atypical antipsychotics.

**Dose Equivalency of Atypical Antipsychotics to Oral Olanzapine**[3]

| Drug | Dose Equivalent to Olanzapine 20 mg/day | Milligrams of Olanzapine Equivalent to 1 mg of Drug |
|---|---|---|
| Aripiprazole | 30 mg/day | 0.67 |
| Clozapine | 400 mg/day | 0.050 mg |
| INVEGA | 9.0 mg/day | 2.22 |
| Quetiapine | 750 mg/day | 0.027 |
| Risperidone (oral) | 6.0 mg/day | 3.33 |
| Risperidone Long-acting Injection | 50 mg/14 days | - |
| Ziprasidone (oral) | 160 mg/day | 0.125 |

The authors note several limitations to the proposed criteria including, 1) a reliance on experience-based opinions, 2) the unrealistic assumption that antipsychotic dosing does not vary by diagnoses, and 3) the unrealistic assumption of linearity across the dosing range of dissimilar drugs.

## Dose Equivalency to Oral Risperidone

### *Prior Risperidone Exposure in Pivotal Trials:*

In a post hoc analysis of three 6-week, double-blind, placebo-controlled studies of patients with schizophrenia receiving INVEGA 3-12 mg/day antipsychotic monotherapy or placebo, a subset of patients had received oral risperidone for at least four weeks and within two weeks of study entry (n=198). Patients in this subset received a mean prior dose of risperidone 4.1-4.4 mg/day for a mean duration of 418.8-527.0 days. Approximately two-thirds of these patients received risperidone as part of antipsychotic polypharmacy. The improvements in PANSS (Positive and Negative Syndrome Scale), CGI-S (Clinical Global Impressions - Severity), and PSP (Personal and Social Performance) scores in this subset were similar to the improvements among the subset of patients who did not receive prior risperidone (n=995). These results suggest that prior oral risperidone treatment at doses of 4.1-4.4 mg/day does not meaningfully affect the efficacy results among patients receiving INVEGA compared with patients switching from other antipsychotic(s) and no antipsychotic.[8]

### *Doses of Risperidone and INVEGA That May Result in Similar Efficacy:*

Six randomized, double-blind, placebo-controlled trials in schizophrenia were used to compare the efficacy and tolerability of INVEGA and risperidone (three trials per product) using propensity score methodology. Treatment with INVEGA 6-12 mg and oral risperidone 4-6 mg/day resulted in similar completion rates and improvement on PANSS total scores at endpoint.[4]

### *Doses of INVEGA After Switching from Oral Risperidone:*

1. An open-label, 6-month study enrolled 694 schizophrenic patients who were non-responsive, non-compliant, or non-tolerant to oral risperidone and switched to flexibly-dosed INVEGA (3-12 mg/day). The recommended starting dose of INVEGA was 6 mg/day without titration, if possible. The mean baseline risperidone dose was lowest (3.9 mg/day) in patients who switched due to non-compliance and highest (4.6 mg/day) in patients who switched due to non-response. The mean initial dose of INVEGA was 5.3 mg/day (mean mode dose of 7.1 mg/day). The mean duration of INVEGA use was 154 days and during the study the dose was increased in 57% of patients and decreased in

16% of patients. Those patients finishing the study on INVEGA 3 mg/day had received a mean dose of risperidone of 2.8 mg/day before enrollment, patients finishing on INVEGA 6 mg/day had received risperidone 3.9 mg/day, patients finishing on INVEGA 9 mg/day had received risperidone 4.6 mg/day, and patients finishing on INVEGA 12 mg/day had received risperidone 6.2 mg/day.[9]

2. In a naturalistic, observational, open-label study, schizophrenic patients who were non-responsive or partial responders to risperidone (oral or long-acting injection) were directly switched to INVEGA (range 6-12 mg/day). The mean prior risperidone dose was 5.7 mg/day for oral risperidone and 43 mg (last injection) for long-acting injectable risperidone. After 3 weeks, the mean dose of INVEGA was stabilized at 9.1 mg/day.[10]
3. In a blinded-initiation study, patients with schizophrenia sub-optimally responsive to oral risperidone who had received oral risperidone 4 or 6 mg/day (mean prior risperidone dose 4.3 mg/day for 1.2-1.3 years), received INVEGA 6-12 mg/day (flexibly dosed). After 4-6 weeks, patients received a mean modal dose of INVEGA 6.6 mg/day.[11]
4. In a flexible-dose (INVEGA 3-12 mg/day) study of up to 6 months in patients with schizophrenia unsuccessfully treated with oral risperidone, patients who had received a mean dose of risperidone 4.3 mg/day transitioned to a mean mode dose of INVEGA 7.1 mg/day.[12]
5. In a case report, one patient switched from risperidone 8 mg/day to INVEGA 12 mg/day.[13]

**Dopamine D2 Receptor Occupancy**

Studies of the D2 receptor occupancy ED50 suggest an equivalent daily dose ratio of ~2:1 for INVEGA and risperidone.[14]

***Pharmacokinetic Exposure:***

Oral risperidone 4 mg/day and INVEGA 12 mg/day result in similar steady state exposure to the pharmacologically active fraction ($AUC_{0\text{-}24h}$ 760 ng·h/mL for risperidone [risperidone + 9-hydroxyrisperidone/paliperidone] vs. 896 ng·h/mL for paliperidone). However, other PK parameters (e.g., observed maximum plasma concentration, time to reach observed maximum plasma concentration, and fluctuation index) differed.[15]

A pharmacokinetic study evaluated plasma concentrations of risperidone and 9-hydroxyrisperidone in 25 patients with schizophrenia who received risperidone for at least 4 weeks (no changes in dose for 1 week prior to study initiation) and then were switched to open-label INVEGA for 6 weeks. The dose of INVEGA was 6 mg/day for the first week and then varied depending upon patient tolerability and clinical efficacy. Plasma concentrations of the active moiety (risperidone and/or 9-hydroxyrisperidone) were significantly higher when patients were taking risperidone 3 mg/day (n=12) than after they switched to INVEGA 6 mg/day for 1 week (16.4 vs 14.1 ng/mL; $P$ =0.002). For the total population (n=25), the concentration of the active moiety was significantly higher when patients were treated with risperidone (mean dose 4 mg/day) than after they were switched to INVEGA 6 mg/day (19.7 vs 15.9 ng/mL; $P$<0.001). At the end of 6 weeks, the mean dose of INVEGA had been increased to 9.6 mg/day. A significant reduction ($P$ =0.001) in the mean total PANSS total score and the CGI-S score was observed.[16]

**Dose Equivalency to Paliperidone Palmitate**

The following table describes the doses of INVEGA and INVEGA SUSTENNA needed to attain similar paliperidone exposure at steady state during maintenance dosing. Please refer to the DOSAGE AND ADMINISTRATION section of the INVEGA SUSTENNA Prescribing Information for dosing instructions on how to switch from oral INVEGA to INVEGA SUSTENNA. Please

contact the Janssen Medical Information Center at 1-800-526-7736 for further information pertaining to switching from INVEGA SUSTENNA to oral INVEGA.[1]

**Doses of INVEGA and INVEGA SUSTENNA Needed to Attain Similar Paliperidone Exposure at Steady State During Maintenance Dosing**

| Formulation | INVEGA Extended-Release Tablet | INVEGA SUSTENNA Injection |
|---|---|---|
| Dosing Frequency | Once Daily | Once every 4 weeks |
| Dose (mg) | 12 | 234 |
| | 9 | 156 |
| | 6 | 117 |
| | 3 | 39-78 |

### Dose Equivalency to Oral Olanzapine

#### *Prior Olanzapine Exposure in Pivotal Trials:*

In a post-hoc analysis of three 6-week, double-blind, placebo-controlled studies of patients with schizophrenia receiving INVEGA 3-12 mg/day or placebo, a subset of patients had received oral olanzapine for at least four weeks and within two weeks of study entry (n=153). Patients in this subset received a mean prior dose of olanzapine 16.4-17.0 mg/day for a mean duration of 490.1-556.3 days. Among patients randomized to INVEGA who had received prior olanzapine, PANSS total (-18.5 vs. -3.5; $P<0.001$), CGI-S (-1.1 vs. -0.09; $P<0.001$), and PSP (+8.6 vs. -2.8; $P<0.001$) scores improved compared with patients who had received prior olanzapine and randomized to placebo. Among patients randomized to INVEGA who had not received prior olanzapine (n=1040), PANSS (-17.5 vs. -5.0; $P<0.001$), CGI-S (-0.9 vs. -0.3; $P<0.001$), and PSP (+8.7 vs. +0.9; $P<0.001$) scores also improved compared with patients who had not received prior olanzapine and randomized to placebo.[17]

#### *Dose of INVEGA After Switching from Olanzapine:*

In a flexible-dose (INVEGA 3-12 mg/day) study of up to 6 months in patients with schizophrenia unsuccessfully treated with oral olanzapine, patients who had received a mean dose of olanzapine 14.2 mg/day transitioned to a mean mode dose of INVEGA 7.2 mg/day.[18]

### Dose Equivalency to Oral Aripiprazole

#### *Dose of INVEGA After Switching from Aripiprazole:*

In a flexible-dose (INVEGA 3-12 mg/day) study of up to 6 months in patients with schizophrenia unsuccessfully treated with aripiprazole, patients who had received a mean dose of aripiprazole 19.4 mg/day transitioned to a mean mode dose of INVEGA 6.8 mg/day.[19]

### Dose Equivalency to Oral Ziprasidone

In a case report, one patient transitioned from ziprasidone 80 mg twice daily to INVEGA 6 mg/day.[13]

### Conversion/Titration - Methods

The recommended dose of INVEGA in the treatment of schizophrenia and schizoaffective disorder is 6 mg/day in the morning, and initial dose titration is not required. The decision

of how to convert/switch antipsychotics must be based on clinical judgement, individual patient assessment, and PK properties of the drugs involved. The Table: Initial Dose Selection and Titration presents processes that have been used in clinical trials and published case reports.

**Initial Dose Selection and Titration**[11,12,13]

| Study Description | Prior Antipsychotic Dose | Initial INVEGA Dose | Titration Method |
|---|---|---|---|
| **Oral Risperidone** | | | |
| Blinded-initiation study of patients with schizophrenia suboptimally-responsive to risperidone 4 mg/day (N=201)[11] | Risperidone 4 mg/day | INVEGA 6 mg/day | No titration |
| Flexible-dose study of up to 6 months in patients with schizophrenia unsuccessfully treated with risperidone (N=694)[12] | Risperidone 4.3 mg/day (mean dose) | INVEGA 5.3 mg/day | No titration |
| Case report[13] | Risperidone 8 mg/day | INVEGA 12 mg/day | No titration |
| **Oral Olanzapine** | | | |
| Flexible-dose study of up to 6 months in patients with schizophrenia unsuccessfully treated with olanzapine (N=396)[12] | Olanzapine 14.2 mg/day (mean dose) | INVEGA 5.3 mg/day | No titration |
| **Oral Aripiprazole** | | | |
| Flexible-dose study of up to 6 months in patients with schizophrenia unsuccessfully treated with aripiprazole (N=141)[12] | Aripiprazole 19.4 mg/day (mean dose) | INVEGA 5.1 mg/day | No titration |
| **Oral Ziprasidone** | | | |
| Case report[13] | Ziprasidone 80 mg twice-daily | INVEGA 3 mg/day | Ziprasidone tapered and discontinued over a month. |

**Pivotal Studies**: In three similarly designed 6-week, double-blind, randomized, fixed-dose, placebo-controlled studies designed to evaluate the efficacy and safety of INVEGA in patients with an acute episode of schizophrenia[6], and in a 6-week, double-blind, randomized, placebo-controlled study designed to evaluate the efficacy and safety of INVEGA in patients with schizoaffective disorder, patients discontinued any antipsychotic medication(s) for at least 2 days prior to receiving INVEGA.[20,21]

### Conversion/Titration - Pharmacokinetic Considerations

**Sheehan et al (2012)**[22] conducted a study reviewing the peak-to-trough fluctuation in plasma concentration of long-acting injectable antipsychotics and their oral equivalents. Selected Pharmacokinetic Parameters provides the time to maximum plasma concentration ($T_{max}$) and the terminal half-life ($T_{½}$) for long-acting injectable antipsychotics and their oral equivalents.

**Selected Pharmacokinetic Parameters**[22]

| Drug | $T_{max}$ | $T_{½}$ |
|---|---|---|
| **Long-Acting Injectable Antipsychotics** | | |
| Haloperidol Decanoate | 6 Days | 21 Days |
| Olanzapine Pamoate | 4 Days | 30 Days |
| Paliperidone Palmitate | 13 Days | 37 Days[b] |
| Risperidone Long-Acting Injection | 35 Days[b] | 4.5 Days[b] |
| Zuclopenthixol Decanoate | 3 Days | 7.4 Days |
| **Oral Antipsychotics** | | |
| Haloperidol | 4.9 Hours | 25.6 Hours |
| Oral Olanzapine | 6 Hours | 30 Hours |
| Oral Risperidone[a] | 1.3 Hours | 19.5 Hours |
| Paliperidone ER | 24 Hours | 23 Hours |

**Abbreviations:** T½, Terminal Half-life
[a]data reported for the active moiety (risperidone + (9-OH-risperidone)
[b]Where a range was reported, the midpoint of the range is presented here.

## LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 05 September 2024.

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