INVEGA® (paliperidone ER)
Adverse Event of INVEGA - Weight Change

SUMMARY

Adults With Schizophrenia or Schizoaffective Disorder

Meta-analysis

- A meta-analysis of double-blind (DB), randomized controlled trials with ≥3 weeks duration showed that INVEGA SUSTENNA and INVEGA were associated with a higher incidence of weight gain and increased body weight than placebo (PBO) in adults with acute symptoms of schizophrenia.[1]

Long-Term Studies

- In a study reporting results from three 1-year open-label extension (OLE) studies of three 6-week DB studies in patients with schizophrenia,[2-4] the average weight gain from DB baseline to OLE endpoint was 1.9 kg in patients receiving INVEGA 3-15 mg/d.[5]
- In the safety analysis set of a long-term, PBO-controlled trial in patients with schizophrenia, 12% vs 20% of patients receiving PBO vs INVEGA experienced a mean weight increase of ≥7% from run-in to DB endpoint.[6]

Short-Term Studies

- In pooled data from three 6-week, pivotal, PBO-controlled, fixed-dose studies in patients with schizophrenia, a similar incidence of ≥7% body weight gain was observed in patients receiving INVEGA 3 and 6 mg (7% and 6%, respectively) and PBO (5%), whereas those receiving INVEGA 9 and 12 mg experienced higher incidences (9% and 9%, respectively).[7]
  - In pooled data from three 6-week, pivotal, PBO-controlled, schizophrenia trials,[2-4] the average weight gain was 0.6-1.1 kg in patients treated with INVEGA 3-12 mg.[7]
- In pooled data from two 6-week PBO-controlled studies in patients with schizoaffective disorder, a higher percentage of INVEGA-treated subjects (5%) had a ≥7% increase in body weight than PBO-treated subjects (1%). In a study that examined the high- and low-dose groups, an increase in body weight of ≥7% was reported in 3%, 7%, and 1% of patients in the low-dose, high-dose, and PBO groups, respectively.[8,9]
  - An average weight gain was 0.8-1.4 kg in adult patients treated with INVEGA during the 6-week schizoaffective clinical trials.

Adolescents (Aged 12-17 Years) With Schizophrenia

- In a 2-year open-label (OL) study, a weight gain of ≥7% above baseline was reported in 43% of adolescents treated with INVEGA, and mean weight gain was 4.7 kg.[10]
- In a 6-week, DB, PBO-controlled study, weight increases of ≥7% were reported in 3 (6%), 6 (13%), 6 (13%), and 1 (2%) patients in the INVEGA low-dose, medium-dose, high-dose, and PBO groups, respectively. The mean weight change from baseline to endpoint was 0.3, 1.1, 1.4, and 0.0 kg, respectively.[11]
- A 26-week, randomized, DB study reported a weight gain of ≥7% above baseline in 26% vs 18% of patients in the INVEGA vs aripiprazole group. The mean weight increase was 2.3 vs 0.4 kg after 6 months of treatment.[12]

ADULTS - SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

Meta-analysis

Primary Author/Study Design	Weight Change Results
Kishi et al (2022)[1] conducted a systematic review and meta-analysis to compare the efficacy and safety of INVEGA SUSTENNA with that of INVEGA in adults with acute symptoms of schizophrenia spectrum and other psychotic disorders. • DB, RCT of INVEGA or INVEGA SUSTENNA (duration ≥3 weeks) published before August 4, 2022, were included. • Studies including children and adolescents, or dual diagnosis were excluded.	• A total of 5 and 7 studies on INVEGA SUSTENNA and INVEGA,[2-4,8,9,13,14] respectively, involving 4970 patients, were included. • INVEGA SUSTENNA and INVEGA were associated with a higher incidence of weight gain and increased body weight compared with PBO. • No significant difference was observed in weight gain between the effect size (RR [95% CI]) of INVEGA (1.90 [1.08-3.37]; *P*=0.03) and INVEGA SUSTENNA (2.36 [1.51-3.69]; *P*<0.01) and in weight change (MD [95% CI]) of INVEGA (1.16 [0.71-1.60] kg; *P*<0.01) and INVEGA SUSTENNA (1.80 [1.14-2.45] kg; *P*<0.01).
Abbreviations: CI, confidence interval; DB, double-blind; MD, mean difference; PBO, placebo; RCT, randomized control trials; RR, risk ratio.	

Long-term Data (>24 Weeks)

Primary Author/Trial Design	Weight Change Results
Double-Blind Trials	
Rui 2014[15] conducted a multicenter, randomized, DB, PBO-controlled study to evaluate the long-term efficacy of INVEGA in preventing relapse in Chinese patients with schizophrenia for ≥1 year. There were 3 phases of the study: an 8-week run-in phase (n=201); a 6-week stabilization phase (n=161); and a variable-duration DB phase (n=136).	• Increased body weight was reported as an AE in 6.5% of patients during the OL run-in and stabilization phases. Increased body weight was reported as an AE in 1.4% and 1.6% of patients treated with PBO and INVEGA, respectively, during the DB phase. • In the DB phase, body weight increased in 42% and 30% of patients treated with INVEGA (mean, 3.9 kg) and PBO (mean, 2.05 kg), respectively.

Kramer 2007[6] conducted a long-term, DB, randomized, multicenter, PBO-controlled trial to assess symptom recurrence in patients with an acute episode of schizophrenia. The study was terminated early owing to significant efficacy results. Two OL phases (8-week run-in [N=530]; 6-week stabilization) preceded the DB phase (variable duration). During the DB phase (n=207), patients were randomized to PBO (n=101) or INVEGA (n=104) (flexible dose: 3, 6, 9, 12, or 15 mg/d).	• Mean weight change during the DB phase (average total treatment time >24 weeks):
	  ○ *PBO*: +0.2 kg; *INVEGA*: +1.8 kg
	• Mean weight increase of ≥7% from run-in to DB endpoint (safety analysis set):
	  ○ *PBO*: 12%; *INVEGA*: 20%
	• Clinically significant weight gain (reported as an AE):
	  ○ *PBO*: 2%; *INVEGA*: 2%

Open-Label Studies	
Schreiner 2014[16] conducted a 2-year, OL, randomized, rater-blinded, active-controlled study in patients recently diagnosed with schizophrenia (1-5 years before screening) to compare INVEGA SUSTENNA (n=352) with other OAP (n=363, including 77 patients who were treated with INVEGA).	• Of the 77 patients treated with INVEGA, 19.7% had at least a 7% increase in body weight from baseline to study endpoint (LOCF). • Over 2 years, weight increased in 15.9% of patients treated with INVEGA SUSTENNA. The mean weight

Dose: The mean modal dose of INVEGA was 7.5 mg.	change (SD) from baseline to the study endpoint was 2.3 (5.9) kg.
Kramer 2010[17] conducted a 52-week, OLE study of a DB, multicenter, PBO-controlled trial[6] (safety analysis set, n=235). ***Dose***: All patients received flexibly dosed INVEGA (3-15 mg/d). The starting dose of INVEGA was 9 mg/d.	• Mean weight gain in all treatment groups was 1.5 kg. • A total of 19% of patients in all groups experienced a weight increase of ≥7% from BL. • A total of 11% of patients in the INVEGA (DB phase)/INVEGA group experienced a weight increase of ≥7% from BL.
Emsley 2008[5] reported pooled data from 52-week OLE phases of three 6-week DB studies[2, 3, 4] in patients with schizophrenia (n=1083). ***Dose***: During the OLE studies, all patients received flexibly dosed INVEGA (3-15 mg/d). The starting dose of INVEGA was 9 mg/d. • During the 6-week DB studies, patients either received PBO, INVEGA (3-15 mg), or OLA (10 mg).	• Mean weight change in all patients (n=918) from DB BL to OLE endpoint was +1.9 kg. • Mean weight change from OLE BL to endpoint (grouped by previous treatment): ○ *INVEGA/INVEGA*: +1.2 kg; *OLA/INVEGA*: +0.3 kg; *PBO/INVEGA*: +1.8 kg • Change in body weight from OLE BL to endpoint: ○ *INVEGA*: +1.1 kg • Mean change in BMI was 0.4 kg/m^2. • A weight increase of ≥7% occurred in 15% of patients (n=137), and weight gain was reported as an AE in 5% of patients (n=53).
Abbreviations: AE, adverse event; BL, baseline; BMI, body mass index; CI, confidence interval; D, day; DB, double-blind; LOCF, last observation carried forward; OL, open-label; OLA, olanzapine; OLE, open-label extension; PBO, placebo; RIS, risperidone; SD, standard deviation.	

Short-term Data (≤24 Weeks)

Primary Author/Trial Design	Weight Change Results
Double-Blind Trials	
Canuso 2010b[18] conducted a 6-week, prospective, DB, multicenter study to assess the observed change in the MSQ scores in patients with schizophrenia suboptimally responsive to oral RIS. Patients were randomized to either immediate or delayed initiation of therapy with INVEGA (safety analysis set, n=197). ***Dose***: Immediate initiation INVEGA: mean modal dose, 6.8 mg/d. Delayed initiation: 2 weeks on RIS; mean dose, 4.3 mg/d, followed by 4 weeks of treatment with INVEGA; mean modal dose, 6.3 mg/d.	• Mean weight change from baseline to week 6: ○ Immediate initiation: 0.37 kg ○ Delayed initiation: 0.38 kg
Meltzer 2008[7] reported a pooled analysis of 3 similarly designed 6-week, DB, randomized, multicenter, fixed-dose, PBO-controlled studies[2-4] in patients with an acute episode of schizophrenia (safety analysis set, n=1318). ***Dose***: Patients were randomized to PBO or INVEGA (3, 6, 9, 12, or 15 mg/d).	• Mean weight change at endpoint: ○ *PBO*: -0.4 kg ○ *INVEGA*: 3 mg, 0.6 kg; 6 mg, 0.6 kg; 9 mg, 1.0 kg; 12 mg, 1.1 kg; 15 mg, 1.9 kg

Open-Label Studies (>12 Weeks)	
Chen 2018[19] conducted a 24-week, OL, single-arm, multicenter, phase 4 trial to evaluate the efficacy and safety of switching to INVEGA in Taiwanese patients with schizophrenia who were unresponsive or intolerant to previous AP therapy. A total of 297 patients were enrolled in the study and 178 completed the 24-month treatment. ***Dose***: Patients received a INVEGA daily dose of 10.0±2.38 mg (mean±SD) over the entire treatment period.	• Body weight (mean± SD) decreased from 66.2±14.7 to 65.5±14.5 kg, and the decrease was nonsignificant.
Na 2013[20] conducted a 24-week, multicenter, noncomparative, OL study in Korea to assess subjective symptom changes in patients with schizophrenia who switched to INVEGA (safety analysis set, n=387; mean age, 36.7 years; female, 55.3%). Mean doses of INVEGA at baseline and endpoint were 5.4 and 8 mg/d, respectively.	• For the ITT population (n=321), 84.1% of patients were abruptly switched to INVEGA, 7.8% were cross-tapered within 1 week, and 8.1% were prescribed previous APs up to 4 weeks after study initiation. • From baseline to endpoint, mean body weight significantly increased from 67.8 to 69 kg (P=0.009), whereas mean waist circumference significantly increased from 87.25 to 88.21 cm (P=0.029).
Kim 2012[21] conducted a 24-week OL study to evaluate the subjective well-being and attitudes toward AP medication in patients with schizophrenia who switched to INVEGA (N=243; mean age, 36.4 years; female, 52.7%). ***Dose***: All patients received flexibly dosed INVEGA (3-12 mg/d). During the first 4 weeks of the study, INVEGA doses were initiated at 6 mg/d and adjusted at the discretion of the investigator while previous AP was tapered off. Mean doses of INVEGA at endpoint and week 24 were 8.4 and 9.2 mg/d, respectively.	• Mean doses of INVEGA at endpoint and week 24 were 8.4 and 9.2 mg/d, respectively. • A clinically relevant increase in body weight (≥7%) was observed in 49 LOCF patients (20.2%) and 40 patients who completed the 24-week study (25%), whereas a clinically relevant decrease was observed in 6 LOCF patients (2.5%) and 4 patients who completed the study (2.5%). • Mean weight gain from baseline to endpoint was statistically significant (P<0.001) for LOCF patients (+1.4 kg) and for those who completed the 24-week study (+1.7 kg). • Previous RIS and non-RIS users experienced a statistically significant increase in mean body weight from baseline to endpoint after switching to INVEGA (+1.4 vs +1.3 kg; P<0.001).
Abbreviations: AP, antipsychotic; BMI, body mass index; D, day; DB, double-blind; HAL, haloperidol; ITT, intent-to-treat; LOCF, last observation carried forward; MSQ, Medication Satisfaction Questionnaire; OAP, oral antipsychotic; OL, open-label; OLA, olanzapine; PBO, placebo; RIS, risperidone; SD, standard deviation.	

ELDERLY – SCHIZOPHRENIA

Short-Term Data

Primary Author/Trial Design	Weight Change Results
Tzimos 2008[22] conducted a 6-week, DB (n=114), randomized, multicenter, flexible-dose, PBO-controlled trial with an optional 24-week OL extension (n=88) in elderly patients (≥65 years old) with an acute episode of schizophrenia. ***Dose***: Flexible, once-daily doses of INVEGA (3-12 mg/d) or PBO (2:1) during the DB treatment; INVEGA only during the OL treatment.	• There were no noteworthy changes in mean body weight or BMI at endpoint in the INVEGA and PBO groups. • Mean change in body weight from baseline to DB endpoint was 0 kg in the INVEGA and PBO groups and from OL baseline to endpoint was 0.4 kg in the PBO/INVEGA and INVEGA/INVEGA groups.

	• Three patients reported weight gain as an AE.
Abbreviations: BMI, body mass index; D, day; DB, double-blind; OL, open-label; PBO, placebo.	

ADOLESCENTS – SCHIZOPHRENIA

Long-term Data (>24 Weeks)

Primary Author/Trial Design	Weight Change Results
Savitz 2015[12] conducted a 26-week, DB, randomized trial in adolescents 12-17 years old with schizophrenia and compared INVEGA (n=113) with ARI (n=115). The study had an AC period (8 weeks) and a maintenance period (18 weeks). ***Dose***: INVEGA 6 mg/d for 1 week and then flexibly dosed at 3-9 mg/d for remainder of study. Median mode dose of INVEGA was 6 mg/d. ARI dose initiated at 2 mg/d and titrated up to 10 mg/d over 1 week and then flexibly dosed at 5-15 mg/d for the remainder of study. Median mode dose of ARI was 15 mg/d.	• In the total study population, the mean BL weight was 59.8 kg, and 73% of the adolescents had normal weight. • Median duration of exposure was 181 and 182 days in the INVEGA and ARI groups, respectively. • Increased weight was reported in 10.6% and 6.1% of patients in the INVEGA and ARI groups, respectively. • Mean weight increase at day 182: ○ *INVEGA*: 2.3 kg; *ARI*: 0.4 kg • Weight increase of ≥7% from BL: ○ *INVEGA*: 26%; *ARI*: 18%
Savitz 2015[10] conducted a 2-year OL study in 400 adolescents 12-17 years old with schizophrenia to evaluate the long-term safety and tolerability of INVEGA. This trial was an extension of a 6-week DB study. ***Dose***: INVEGA 6 mg/d initially and then flexibly dosed at 1.5-12 mg/d. The most common dose (38% of patients) was 6 mg/d.	• For the total study population, the mean BL weight was 61.6 kg, and 68% of the adolescents had normal weight. • Median (range) duration of exposure was 604.5 (2-765) days, and 220 adolescents completed the study. • Increased weight was reported by 18.3%. • Mean weight gain from BL (n=386) was 4.7 kg. • Weight increase of ≥7% from BL was 43%.
Abbreviations: AC, acute treatment; ARI, aripiprazole; BL, baseline; D, day; DB, double-blind; OL, open label.	

Short-term Data (≤24 Weeks)

Primary Author/Trial Design	Weight Change Results
Singh 2011[11] conducted a 6-week, multicenter, randomized, DB, PBO-controlled study of INVEGA in adolescents 12-17 years old with schizophrenia (safety analysis set, n=201). Patients received 1 of 3 weight-based fixed doses of INVEGA (low: 1.5 mg, n=54; medium: 3-6 mg, n=48; high: 6 or 12 mg, n=47) or PBO (n=51).	• Mean increase in weight in each weight-based, fixed-dose group from BL to week 6: ○ *PBO*: 0 kg; *INVEGA* low: 0.3 kg; *INVEGA* medium: 1.1 kg; *INVEGA* high: 1.4 kg • Increase in weight of ≥7% in each group, n (%): ○ *PBO*: 1 (2%); *INVEGA* low: 3 (6%); *INVEGA* medium: 6 (13%); *INVEGA* high: 6 (13%) • Increases in weight measurements were dose related. • A decrease in weight of ≥7% occurred in 1 patient in both the PBO and INVEGA low-treatment groups.
Abbreviations: BL, baseline; DB, double-blind; OL, open label; PBO, placebo	

COMPARATIVE STUDIES

Comparison With Other Antipsychotics

Primary Author/Trial Design	Weight Change Results
Wang et al (2022)[23] conducted a 12-week, randomized, DB, parallel, multicenter study that compared the efficacy and safety of INVEGA with OLA in adults 18-45 years old with schizophrenia, who were reported to have treatment failure owing to inadequate response or intolerance to previous treatment. ***Final dose***: OLA, 10-30 mg/d; INVEGA, 6-15 mg/d.	• Of 86 patients enrolled in the study, 45 and 41 patients received INVEGA and OLA, respectively. • Increases in weight, waist circumference, and BMI within each group were statistically evident from baseline to endpoint (*P*<0.001). • In the INVEGA vs OLA group, no between group differences were observed in body weight change (mean [SD], 2.03 [2.76] vs 2.97 [2.60] kg; *P*=0.110) and BMI change (mean [SD], 0.82 [1.09] vs 1.06 [0.90] kg/m^2; *P*=0.280). However, a greater increase in waist circumference was observed in the OLA vs INVEGA group (mean [SD], 3.23 [2.48] vs 2.08 [2.36] cm; *P*=0.030).

Hu 2013[24] conducted a 12-week, randomized, OL, flexible-dose, parallel-group study in China to assess metabolic profile and weight gain in patients with schizophrenia receiving INVEGA (n=33; mean age, 25.24 years; male, 63.6%) and OLA (n=23).
Dose: Within the first 2 weeks, patients were titrated to the target doses of INVEGA (6 mg/d) and OLA (15 mg/d). At week 12, mean daily INVEGA and OLA doses were 7.55 and 15.87 mg, respectively.
Due to aggression, 25 INVEGA and 14 OLA patients received intramuscular HAL within the first 2 weeks of the trial.
	• From baseline to week 12, INVEGA and OLA patients experienced significant increases in weight and BMI, with no significant between-group differences.
	• Weight (baseline; week 12)
	  ○ *INVEGA*: 60.13 kg; 62.81 kg; *P*<0.001
	  ○ *OLA*: 62.28 kg; 66.94 kg; *P*<0.001
	• BMI (baseline; week 12):
	  ○ *INVEGA*: 21.21 kg/m^2; 22.17 kg/m^2; *P*<0.001
	  ○ *OLA*: 21.54 kg/m^2; 23.17 kg/m^2; *P*<0.001
	• Significant baseline to 12 week increases in subcutaneous fat were observed for INVEGA (16.15 vs 18.65 mm; *P*<0.001) and OLA (13.43 vs 17.09 mm; *P*<0.001) patients.
	• From baseline to week 12, waist and hip circumferences significantly increased for INVEGA and OLA; however, the change in waist-to-hip ratio was not significant.

Zhang 2012[25] conducted a 52-week, randomized, OL study in China to assess the metabolic influences of INVEGA, ARI, and ZIP during the treatment of first-episode schizophrenia (N=203; average age, 26.4 years; male, 61%).
Mean daily doses (BL, 13 weeks, 26 weeks, and 52 weeks):
INVEGA (n=63): 5.2, 6.4, 6.4, and 6.4 mg
ARI (n=71): 5.6, 12.4, 16.8, and 14.5 mg
ZIP (n=69): 25.4, 36.4, 68.2, and 65.3 mg
	• After 13, 26, and 52 weeks, weight gain was significantly greater in the ARI-treated patients vs INVEGA or ZIP-treated patients.
	• Mean weight (BL, 13 weeks, 26 weeks, and 52 weeks)
	  ○ *ARI*: 54.3, 57.6, 58.8, and 57.4 kg
	  ○ *INVEGA*: 53.4, 52.3, 53.1, and 53.6 kg
	  ○ *ZIP*: 54.7, 52.7, 51.9, and 50.5 kg
	• After 26 and 52 weeks, ARI-treated patients experienced significantly greater increases in BMI than INVEGA or ZIP-treated patients.
	• Mean BMI (BL, 13 weeks, 26 weeks, and 52 weeks)

	○ *ARI*: 22.4, 23.7, 24.3, and 24.5 kg/m^2 ○ *INVEGA*: 21.5, 21.2, 21.9, and 21.5 kg/m^2 ○ *ZIP*: 21.9, 20.2, 20.6, and 20.3 kg/m^2 • No significant changes in waist circumference were observed.
Shah 2011[26] conducted a 6-week, randomized, DB, multicenter study to compare the efficacy and safety of INVEGA (n=109) with those of OLA (n=105) in the treatment of acute schizophrenia (mean age, 34.25 years; males, 64.5%). The INVEGA arm received an initial dose of 3 mg once daily, which was titrated up to 12 mg once daily by week 6. The OLA arm received an initial dose of 5 mg once daily, which was titrated up to 20 mg once daily.	• A total of 102 AEs were reported in 54 patients receiving INVEGA, and 90 AEs were reported in 48 patients receiving OLA. • Increased appetite was one of the most commonly reported AEs for both INVEGA (8.8%) and OLA (10%). Mean body weight significantly increased from baseline to endpoint for both INVEGA (+1.5 kg; *P*=0.01) and OLA (+2 kg; *P*<0.01).
Canuso 2009[27] conducted a 6-week trial comparing INVEGA, QUE, and PBO in adult patients with a recent exacerbation of schizophrenia. Two weeks of monotherapy was followed by a 4-week additive therapy phase during which patients could receive additional psychotropic medications if necessary (safety analysis set, n=397). ***Dose***: INVEGA: 6 mg/d, days 1-3, up to 9 mg/d on day 4, and an optional dose increase to 12 mg/d on day 8. QUE: 50 mg/d, day 1; 100 mg/d on day 2, 200 mg/d on day 3, 400 mg/d on day 4, and 600 mg/d on day 5 with an optional dose increase to 800 mg/d on day 8.	• At the monotherapy phase endpoint, LSM weight gain was significantly higher with QUE vs INVEGA (*P*=0.028) or PBO (*P*=0.011): ○ *PBO*, 0.2 kg vs *INVEGA*, 0.4 kg vs *QUE*, 0.8 kg • Study endpoint, LSM weight gain: QUE vs INVEGA (*P*=0.004) or PBO (*P*=0.013): ○ *PBO*, 0.3 kg vs *INVEGA*, 0.4 kg vs *QUE*, 1.1 kg
Abbreviations: AE, adverse event; ARI, aripiprazole; BL, baseline; BMI, body mass index; D, day; DB, double-blind; OL, open-label; OLA, olanzapine; OLE, open-label extension; PBO, placebo; QUE, quetiapine; RIS, risperidone; ZIP, ziprasidone.	

OTHER RELEVANT LITERATURE

Additional studies enrolling Chinese patients with schizophrenia that compared INVEGA with second-generation antipsychotics and reported weight changes are referenced below.[28,29]

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 27 March 2025.

Please contact the Johnson & Johnson Medical Information department at 1-800-526-7736 from 9AM to 5PM EST for a comprehensive literature search.

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