INVEGA® (paliperidone ER)
Adverse Event of INVEGA - Movement Disorders

SUMMARY

- This information is intended to be a concise summary of representative clinical data; not all available published literature is incorporated into this response.
- Please refer to the following sections of the Full Prescribing Information which are relevant to your inquiry: WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS.[1]

Schizophrenia

Adult patients

- A pooled analysis of 3 placebo (PBO)-controlled, 6-week, fixed-dose studies in patients with an acute episode of schizophrenia (N=1,682),[2-4] found extrapyramidal symptom (EPS)-related adverse events (AEs) in 11%, 13%, 10%, 25%, 26%, and 24% of patients in the PBO, INVEGA 3 mg, 6 mg, 9 mg, 12 mg, and 15 mg groups, respectively.[5]
  - A post hoc analysis of this pooled data sets from INVEGA vs INVEGA SUSTENNA studies (N=2,256) found lower rates of spontaneously reported EPS-related treatment-emergent adverse events (TEAEs; tremor, dystonia, dyskinesia, parkinsonism), except for hyperkinesia, with INVEGA SUSTENNA than with INVEGA. The highest incidence was seen as early as the first week of INVEGA treatment (except parkinsonism and tremor).[6]
- An analysis of pooled data from 3 separate 52-week open-label extension (OLE) studies (N=1083) in patients that previously completed one of the three 6 weeks double-blind (DB) studies[2-4] found that EPS-related AEs were reported in 25% of patients treated with INVEGA (3-15 mg/day).[7]
- In the DB phase (n=206) of a long-term, randomized, multicenter, PBO-controlled study in patients with acute schizophrenia treated with flexible doses of INVEGA (3-15 mg/day) or PBO, EPS-related AEs were reported in 7% and 3% of patients in the INVEGA and PBO groups, respectively.[8] Patients entered the OLE study from the DB phase or directly from the run-in or stabilization phase of the earlier study. In the 52-week OLE phase (n=235), tremor (13%) and akathisia (6%) were the most frequently reported EPS-related TEAEs. There were no reports of tardive dyskinesia in either the DB or the OLE study periods.[9]
- A 6-week DB study (N=201) evaluated the efficacy and safety of INVEGA at low (1.5 mg) and high doses (6 mg) vs PBO to determine the lowest effective dose and potentially mitigate the risk of certain dose-related adverse effects. INVEGA caused higher incidences of tremor, dyskinesia, muscle rigidity, and restlessness compared to PBO. Akathisia, tremor, and dystonia were more common with INVEGA 6 mg than 1.5 mg. EPS-related assessment scales (Simpson-Angus Rating Scale [SAS], Abnormal Involuntary Movement Scale [AIMS], and Barnes Akathisia Rating Scale [BARS]) showed no changes from baseline to endpoint.[10]
- In a 6-week study in patients with a recent exacerbation of schizophrenia (n=397), comparing treatment with INVEGA (6-12 mg/day), quetiapine (QUE; 50-800 mg/day), and PBO, hypertonia and tremor were the most common movement-related AEs reported in all treatment groups (INVEGA, 12% and 19.6%; QUE, 3.8% and 7.5%; PBO, 3.8% and 15%, respectively). The EPS symptom ratings on the SAS were higher with INVEGA than with QUE ($P<0.001$).[11]
- The long-term efficacy and safety of INVEGA (flexible doing 3-12 mg/day) in Chinese patients (N=201) was evaluated in a study consisting of a 14-week open label run in period followed by a DB, PBO-controlled period and an OLE for 24 weeks. In the DB

phase (N=135), the following were reported in the INVEGA (3-12 mg) vs PBO group: EPS-related TEAEs (9.4% vs 4.2%), hyperkinesia (6.3% vs 0%), akathisia (5% vs 0%), tremor (3.1% vs 0%), dyskinesia (0% vs 2.8%), parkinsonism (0% vs 1.4%), and agitation (0% vs 3%). A higher proportion of patients in the INVEGA group (48%) were taking anti-EPS medications compared with placebo (38%) in the DB phase.[12] The most common EPS-related TEAEs from the 24-week OLE of this study (N=106) were hyperkinesia (5.7%), akathisia (3.8%), and restlessness (1.9%).[13]

Adolescent patients

- In a 6-week, PBO-controlled study in adolescents (12-17 years of age) with schizophrenia, akathisia and tremor were reported as the most common (>5%) TEAEs in the INVEGA weight-based treatment groups.[14]

Elderly patients

- A 6-week study in elderly patients (n=114) with acute schizophrenia found that INVEGA (3-12 mg/day) was associated with similar rates of movement disorder-related TEAEs compared to PBO. These included extrapyramidal disorder (EPD), hypertonia, tremor, and akathisia (3-5%). A total of 30% of patients received medication for EPSs at screening, and this decreased to 17% in the INVEGA group and 26% in the PBO group at the end of the DB portion of the study. No cases of tardive dyskinesia were reported. During the 24-week OLE of this study, 88 patients received INVEGA. The incidence of movement disorder-related TEAEs and the use of medication to manage EPS was also similar to that observed during the short-term phase of the study.[15]

Schizoaffective Disorder

Adult patients

- Movement-related disorders were reported in 2 PBO-controlled, 6-week studies in patients experiencing an acute exacerbation.[16,17] In 1 study (n=313), the following AEs were reported in the INVEGA 6 mg/day vs INVEGA 12 mg/day vs PBO group: EPS-related AEs (23.1% vs 22.4% vs 12.1%), tremor (12.0% vs 11.2% vs 3.7%), akathisia (3.7% vs 6.1% vs 7.5%), and hypertonia (8.3% vs 4.1% vs 2.8%).[16] In the other study (n=309), the following AEs were reported in the INVEGA (mean modal dose, 9 mg/day) vs PBO group: EPS-related AEs (16.8% vs 9.5%), akathisia (6.1% vs 1.1%), and hypertonia (4.7% vs 1.1%).[17]

Other Diagnoses

Adult patients

- Movement-related disorders were reported in 2 PBO- and active-controlled (olanzapine [OLA]: 5-20 mg/day[18] or QUE: 400-800 mg/day[19]), 15-[18] and 12-week[19] studies in patients with bipolar I disorder, who were given a 3-12 mg/day dose of INVEGA. During the maintenance phase of the INVEGA vs OLA vs PBO study (n=762), INVEGA patients reported EPS-related TEAEs at a rate of 4%, OLA-treated patients at a rate of 10%, and PBO-treated patients at a rate of 3%. Dyskinesia, akathisia, hypokinesia, tremor, and EPD were the EPS-related TEAEs reported in the INVEGA group. Parkinsonism and akathisia occurred at similar percentages in patients receiving INVEGA or OLA (6% and 1%, respectively).[18] In the INVEGA vs QUE vs PBO study (n=491), akathisia and hypertonia, were reported (INVEGA, 8% and 5%; QUE, 3% and 1%; PBO, 3% and 1%, respectively).[19] EPS-related AEs that occurred more frequently in the INVEGA group

(≥3% difference versus PBO) included hypertonia, drooling, EPD, akathisia, and muscle spasms.[19]

- A 3-week, fixed-dose, PBO-controlled study evaluated the efficacy and safety of INVEGA doses of 3, 6, or 12 mg/day in patients with acute manic or mixed episodes associated with bipolar I disorder (n=467). The incidences of EPS-related AEs, EPD, akathisia, dystonia, and dyskinesia were higher in patients who received the highest dose of INVEGA (12 mg/day vs 3 or 6 mg/day INVEGA doses). EPS-related AEs that occurred more frequently in at least 1 INVEGA group than in the PBO group (≥3% difference) were hypertonia, akathisia, and dystonia.[20]
- A 6-week, PBO-controlled study evaluated the efficacy and safety of INVEGA (flexible dose 3-12 mg/day) as adjunctive to mood stabilizers in patients with acute manic or mixed episodes associated with bipolar I disorder (n=299). EPS-related AEs that occurred more frequently in the INVEGA vs the PBO group included akathisia (8% vs 1%) and EPD (4% vs 1%).[21]

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 08 January 2024.

Open-label studies (with the exception of OLE studies of controlled trials), case reports, pharmacoeconomic/pharmacoepidemiology studies, pharmacokinetic studies, controlled trials with less than 50 enrolled patients, and review articles are not included in this scientific response.

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