INVEGA® (paliperidone ER)
Use of INVEGA in Autistic Disorder

SUMMARY

- INVEGA tablets are not indicated for the treatment of autistic disorder in adults, children, or adolescents.
- An open-label study enrolling adolescents and young adults with autism and severe irritability found that INVEGA significantly improved Clinical Global Impression-Improvement (CGI-I) scores and Aberrant Behavior Checklist-Irritability subscale (ABC-I) scores after 8 weeks of treatment. The most common adverse events (AEs) were excessive appetite, weight gain, tiredness, and rhinitis/cough.[1]
- An observational study reported increased rates of extrapyramidal symptoms related to the use of INVEGA in patients with autism spectrum disorder (ASD) and comorbid intellectual disability (ID).[2]
- Two cases have been reported of patients with autism and co-morbid mental retardation who were treated with INVEGA, which resulted in improvement in irritability and aggression associated with autistic disorder.[3]

PRODUCT LABELING

Please refer to the following sections of the enclosed Full Prescribing Information that are relevant to your inquiry: USE IN SPECIFIC POPULATIONS.

PUBLISHED LITERATURE

Clinical Studies

Stigler et al (2012)[1] evaluated the effectiveness and tolerability of INVEGA in the treatment of the irritability associated with autistic disorder in an 8-week, open-label study that enrolled adolescents and young adults (N=25).

Study Design/Methods

- Prospective study enrolling patients 12-21 years old with autism and significant irritability. Enrollment criteria included:
  - CGI-Severity scale score ≥4 focused on severe tantrums, aggression, and self-injury
  - ABC-I score ≥18
- Patients had not been treated with other antipsychotics for at least 2 weeks.
- Other psychotropic medication was allowed during the study if the dose was stable for at least 2 months.
- Patients started the study on INVEGA 3 mg/day. Over the next 4 weeks, the dose was increased by 3 mg/week based on response and tolerability up to a maximum dose of 12 mg/day.
- Maintenance phase lasted 4 weeks at the optimum dose.
- Primary endpoints were the change from baseline in the CGI-I and ABC-I scores.

Results

Patient Characteristics

- Mean age 15.3 years; 84% males.
- Concomitant psychotropic medication was taken by 56% of the study population.
- Mean final INVEGA dose was 7.1 mg/day (range 3-12 mg/day).
- Twenty-three patients completed the 8-week study.
  - One patient discontinued due to sedation and the other due to no response.

Efficacy

- Twenty-one (84%) patients were responders (defined as CGI-I score of 1-2 and ≥25% improvement in ABC-I subscale score).
  - Baseline vs Endpoint CGI-I score: 4.0 vs 1.8 (*P*=0.0002)
  - Baseline vs Endpoint ABC-I score: 30.3 vs 12.6 (*P*=0.0002)
  - Baseline vs Endpoint ABC-Hyperactivity score: 34.7 vs 17.4 (*P*=0.001)
  - Baseline vs Endpoint ABC-Social Withdrawal score: 17.2 vs 7.6 (*P*=0.02)
  - Baseline to Endpoint VABS Maladaptive Behavior subscale - total score: 37.4 vs 25.1 (*P*=0.0001)

Safety

- Most common AEs: excessive appetite (n=9), weight gain (n=9), tiredness (n=6), and rhinitis/cough (n=4).
- No clinically significant changes from baseline to endpoint in ECG parameters including QTc interval.
  - Baseline vs endpoint mean heart rate: 93±19.2 vs 85±18.5 beats per minute (*P*≤0.026)
- Baseline vs endpoint mean prolactin: 5.3±3.4 vs 41.4±26.8 ng/mL (*P*<0.0001)
- There were no observed or reported AEs related to hyperprolactinemia.
- Mean weight gain: 2.2±2.6 kg (range -3.6 to 7.9 kgs)
- No significant change in fasting glucose, cholesterol, triglycerides, or low-density lipoprotein.

Ballester et al (2022)[2] conducted a 36-month, observational, multicenter study in Spain to evaluate adverse events in adult patients with ASD and comorbid ID taking medications, including antipsychotics such as INVEGA.

Study Design/Methods

- Adult patients with ASD (established by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5]) and comorbid ID (patients with intelligence quotient <70 scores and with underdeveloped communicative abilities) were included.
- A 24-month retrospective analysis was conducted to identify AEs, described as symptoms, from the local electronic health records (EHR) followed by a 12-month prospective pharmacovigilance monitoring period.
- The causality of observed symptoms was attributed to the potential side effects of the drugs by evaluating the summary of product characteristics (SmPC) of each drug.
- The AEs observed-to-expected (O/E) ratio (defined as a ratio of the frequency of AEs "observed" in the EHR to the "expected" side effects based on each drug's SmPC safety data) was evaluated.

Results

- A total of 83 adult patients with ASD and comorbid ID, predominantly male (86%), and aged between 20 to 40 years were included. Epilepsy was reported as the highest-occurring comorbidity (33%).
- A total of 365 prescriptions were recorded (median [interquartile range] medications per patient, 4 [3-6]), 50% of which were antipsychotics, including 47% with >1 antipsychotic simultaneously.
- Sixty-four AEs were identified in the sample, with 51% of AEs associated with an antipsychotic.
- Antipsychotic-related AEs primarily affected the nervous system (39%) followed by the endocrine (17%), metabolic (15%), and cardiovascular (7%) systems.

- In the O/E analysis in this sample, INVEGA was associated with increased rates of extrapyramidalism (O/E, 13.25) and decreased rates of headache (O/E, 0.12).

Case Reports

Stigler et al (2010)[3] described 2 cases of patients diagnosed with autism and co-morbid mental retardation. The first case was a 20-year-old male diagnosed with autism and moderate mental retardation. In this patient, the core symptoms of autism were further complicated with daily episodes of aggression, tantrums, and self-injurious behavior (SIB), described as significant head banging. Prior medication trials with fluvoxamine, mirtazapine, olanzapine, chlorpromazine, haloperidol, quetiapine, and lithium were ineffective. After a 7-month trial on risperidone 4 mg twice daily, guanfacine 1 mg twice daily, and valproic acid ER 1500 mg/nightly, the patient continued to exhibit severe SIB. The patient was switched to INVEGA 12 mg/day without a titration period due to the intensity of his behavior. The patient experienced significant improvement in aggression, SIB, and tantrums and was judged to be much improved with a CGI-I.

The second case reported a 16-year-old female diagnosed with autism, mild mental retardation, and intermittent explosive disorder. The patient's severe irritability included impulsive aggression, SIB, and intermittent explosive episodes. The patient's history also included a seizure disorder diagnosed at a young age which was controlled with a stable dosage of oxcarbazepine 300 mg/day. On initial assessment, the patient received a regimen of ziprasidone 80 mg twice daily, naltrexone 75 mg/day, and diazepam 10 mg three times a day. As the patient's behavior continued to deteriorate, ziprasidone was tapered and discontinued. INVEGA 3 mg/day was initiated and continued for 4 weeks with modest improvement. INVEGA was increased to 6 mg/day resulting in significant improvement in the patient's symptoms of irritability and was rated as "very much improved" with a CGI-I score of 1. The effectiveness in the control of the patient's symptoms resulted in the taper and discontinuation of the naltrexone and diazepam. The patient was maintained at this dose for 50 weeks with no AEs reported.

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 13 February 2024.

REFERENCES

1. Stigler KA, Mullett JE, Erickson CA, et al. Paliperidone for irritability in adolescents and young adults with autistic disorder. *Psychopharmacology (Berl)*. 2012;223(2):237-245.

2. Ballester P, Espadas C, Londoño AC, et al. The challenge of detecting adverse events in adults with autism spectrum disorder who have intellectual disability. *Autism Res*. 2022;15(1):192-202.

3. Stigler KA, Erickson CA, Mullett JE, et al. Paliperidone for irritability in autistic disorder. *J Child Adolesc Psychopharmacol*. 2010;20(1):75-78.