INVEGA® (paliperidone ER)
Adverse Event of INVEGA - Cerebrovascular Effects

SUMMARY

- As stated in the WARNINGS AND PRECAUTIONS section of the Invega Prescribing Information, in placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. INVEGA was not marketed at the time these studies were performed. INVEGA is not approved for the treatment of patients with dementia-related psychosis.[1]
- A post hoc analysis of 64 randomized, double-blind clinical trials and post marketing surveillance reports found a statistically significantly higher risk of cerebrovascular events in the risperidone/paliperidone group compared to placebo.[2]
- A report of a 39-year-old Taiwanese man who received INVEGA 15 mg/day was reported to develop a pons infarction confirmed via a computerized tomography of the brain.[3]

CLINICAL STUDIES

Post Hoc Analysis

Gopal et al (2013)[2] conducted a post-hoc analysis of 64 randomized, double-blind clinical studies and post marketing surveillance reports to determine the risk of cardiovascular morbidity and sudden death due to cardiac causes in patients treated with risperidone or paliperidone compared to placebo. The analysis consisted of 64 placebo- and active-controlled studies, including 11,096 patients (3554 were treated with paliperidone). Out of the 64 studies, 43 studies utilized oral risperidone and 13 studies utilized oral paliperidone; 3 studies employed risperidone long-acting injection (LAI) and 5 studies employed paliperidone LAI. Most paliperidone-treated patients included in the analysis had a diagnosis of either schizophrenia (67%), bipolar I disorder (19%), or schizoaffective disorder (12%). The mean modal oral dose of paliperidone was 8.5 mg with a median treatment duration of 42 days. Outcomes measured included medically important treatment-emergent adverse events prior to cardiovascular death, which consisted of cerebrovascular disorders. The results combined risperidone and paliperidone and were not stratified by formulation.

Based on the analysis, there was a significantly higher risk of cerebrovascular events in the risperidone/paliperidone group compared to placebo (odds ratio [OR], 3.7; 95% CI, 2.2, 6.4). The odds ratio was numerically higher for elderly vs non-elderly (3.8 vs 3.7, respectively) patients and for patients without previous cardiovascular disease history vs those with a cardiovascular disease history (5.5 vs 2.7, respectively). The risks of dysarthria and transient ischemic attack (TIA) were significantly increased with the risperidone/paliperidone group compared with placebo (dysarthria [OR, 3.7; 95% CI, 1.7, 8.2]; TIA [OR, 3.6; 95% CI, 1.2, 10.7]). A total of 5 patients (<0.1%) of patients treated with risperidone or paliperidone died due to a cerebrovascular event in the clinical studies. No post marketing reports of cerebrovascular death due to risperidone or paliperidone were reported in the analysis.

Case Reports

Chang et al (2014)[3] reported a case of pons infarction in a 39-year-old Taiwanese man treated with INVEGA 15 mg/day. The patient had a 12-year history of schizophrenia and, during a psychiatric hospitalization, was also found to have hypertension and hyperlipidemia. He began treatment with amlodipine 5 mg/day and INVEGA 6 mg/day, which was increased to 9 mg/day on day 2, and 15 mg/day on day 7. On day 9, the patient

complained of right-sided limb weakness and slurred speech. Brain computerized tomography showed an acute infarction involving the left paramedian pons and an echocardiogram showed irregular heartbeat with atrial fibrillation. His blood pressure was 160/98 mm/Hg with a pulse rate of 126/min. The author advocated that with adequate intravenous (IV) hydration to increase cerebral perfusion, the patient could gradually recover without a limp or dysarthria.

OTHER RELEVANT LITERATURE

In addition to the above summarized data, other relevant literature were identified.[4]

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 07 August 2024.

REFERENCES

1. INVEGA (paliperidone) [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc;https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-d30da9a4-d8a4-4e37-b8e8-d52589dfe597.

2. Gopal S, Hough D, Karcher K, et al. Risk of cardiovascular morbidity with risperidone or paliperidone treatment: analysis of 64 randomized, double-blind trials. *J Clin Psychopharmacol*. 2013;33(2):157-161.

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4. Wang JY, Wang CY, Tan CH, et al. Effect of different antipsychotic drugs on short-term mortality in stroke patients. *Medicine*. 2014;93(25):e170.