**Introduction**

Ziconotide is an intrathecal (IT) nonopioid analgesic approved in the United States for the management of severe chronic pain in adult patients for IT therapy who are warrantied and is interoate to other treatment, such as systemic anesthetics, adjuvant therapies, or IT morphine. Ziconotide is also approved in the European Union for the treatment of severe chronic pain in adult patients who require IT analgesia.

The most frequently reported adverse events (AEs) that occurred in >10% of patients and more commonly with ziconotide than placebo in a clinical trial (that is a double-blind study 301) were dizziness, nausea, asthenia, diarrhea, somnolence, vomiting, constipation, peripheral edema, and urinary retention.

Patients who are candidates for IT therapy often receive ≥1 concomitant non-IT pharmacotherapies.

- In 3 double-blind, placebo-controlled, multicenter ziconotide clinical trials, which comprised 457 patients, almost all patients received concomitant non-IT medications, including antidepressants (60%), anticonvulsants (53%), antihypertensives (46%), and sedatives (34%).

- Concomitant use of IT and agents that produce similar AEs may increase the incidence of AEs.

- Common AEs with antidepressants include nausea/vomiting, dizziness, somnolence, chest pain, excessive sweating, and impaired urination.

**Objectives**

- To investigate whether AEs associated with treatment with IT ziconotide increase when it is used with the same AEs profile or mechanism of action are taken concomitantly.

**Methods**

**Study Design and Participants**

The current study was a post hoc analysis of 401 patients who participated in an open-label extension study (mean 252 days; range 129-563 days). The study included patients with severe chronic pain (N=301), headache chronic pain (N=95) or who had completely or gradually or who completed short-term (3-4 weeks) therapy with IT ziconotide or placebo (Figure 1).

- 6 patients who did not complete the last study visit of study 301, 301 or the last dose in ziconotide or placebo (Figure 1).

**Statistical Analysis**

Ziconotide is an analgesic with a well-established safety profile. The incidence of AEs was reported by patients who received ziconotide or placebo.

- The mean IT ziconotide daily dose and mean days of ziconotide treatment were greater in patients who received concomitant use of antidepressants, anticonvulsants, and both ziconotide and antidepressants or anticonvulsants compared with patients who received ziconotide and no antidepressants or anticonvulsants (Table 2).

**Figure 1: Open-Label Extension Study Design**

**Results**

**Mean (SD) duration of the open-label extension study was 198.5 days (22.4 days).**

- 200 patients received IT ziconotide in the open-label extension study.

- 20 patients had ≥3 adverse events (AEs) in IT ziconotide treatment in a patient.

- Patients received concomitant anticonvulsants and antidepressants (n=42, 21.1%), antidepressants but not anticonvulsants (n=50, 25.0%) and anticonvulsants but not antidepressants (n=32, 16.0%) during the long-term extension study.

**Concomitant medications and AEs**

The incidence of these AEs for patients who received ziconotide was greater in patients with concomitant use of antidepressants, but not anticonvulsants, or anticonvulsants and no antidepressants compared with patients who received ziconotide and either of these medications alone (Table 3).

**Table 1: Baseline Demographics and Characteristics By Concomitant Medications and AEs**

- Overall, 2163 patients (20.1%) experienced ≥1 AEs during the long-term extension study.

- AEs were reported by patients receiving ziconotide in combination with antidepressants and anticonvulsants, and neither anticonvulsants or antidepressants, but not anticonvulsants (n=37, 18.8%) or neither antidepressants nor anticonvulsants (n=37, 18.7%).

**Conclusions**

- These findings suggest a higher prevalence of somnolence, depression, ephedrine, hypertension, accidental injury, heart rate, taking anticonvulsants and antidepressants concomitantly with IT ziconotide.

- The incidence of these AEs for patients who received ziconotide and other antidepressants or anticonvulsants was generally lower in patients who received ziconotide alone compared with patients who received neither, with the exception of sweating (higher in the antidepressant but not anticonvulsant group) and urinary tract infection (higher in the anticonvulsant but not antidepressant group).

- Patients receiving ziconotide and antidepressants, but not anticonvulsants, had a greater incidence of specific AEs (eg, nausea, vomiting, and sweating); compared with patients receiving ziconotide and no antidepressants or anticonvulsants; conversely, the incidence of other AEs (eg, poor appetite and constipation) was greater in patients receiving ziconotide and antidepressants or anticonvulsants compared with patients who received ziconotide and neither of these medications alone (Table 3).

**Table 2: Characteristics of Ziconotide Use, By Concomitant Medication Use**

- The incidence of these AEs for patients who received ziconotide and other antidepressants or anticonvulsants was generally lower in patients who received ziconotide alone compared with patients who received neither, with the exception of sweating (higher in the antidepressant but not anticonvulsant group) and urinary tract infection (higher in the anticonvulsant but not antidepressant group).

- Concomitant ziconotide use was considered acceptable for patients in the present study; treating and interpreting AEs in patients receiving IT ziconotide was not anticonvulsants, versus ziconotide and no anticonvulsants or antidepressants concomitantly, the incidence of other AEs (eg, back pain, lower extremity pain) was lower in patients receiving ziconotide and anticonvulsants, but not antidepressants, compared with patients receiving ziconotide and no anticonvulsants or antidepressants (Figure 4).

**Figure 2: Patients With Adverse Events, By Concomitant Medication Use**

**Figure 3: Patients With Adverse Events, By Concomitant Medication Use**

- Patients receiving ziconotide and antidepressants, but not anticonvulsants, had a greater incidence of specific AEs (eg, nausea, vomiting, and sweating); compared with patients receiving ziconotide and no antidepressants or anticonvulsants; conversely, the incidence of other AEs (eg, poor appetite and constipation) was greater in patients receiving ziconotide and antidepressants or anticonvulsants compared with patients who received ziconotide and neither of these medications alone (Table 3).