Clinical Policy Bulletin: Ziconotide (Prialt)

Number: 0712

Policy

Aetna considers intrathecal administration of ziconotide (Prialt) medically necessary for members with severe chronic pain that is intolerant of or refractory to other treatments such as systemic analgesics, adjunctive therapies, or intrathecal morphine.

Aetna considers intrathecal administration (or other routes of administration) of ziconotide experimental and investigational as a treatment for autism, Irukandji syndrome, stroke and for other indications because its effectiveness for these indications has not been established.

Background

Voltage-sensitive calcium channel conductance is essential for the nervous system to signal a painful event. However, intrathecal administration of L-type calcium channel blockers does not provide analgesia. On December 28, 2004, ziconotide (Prialt), a peptide with analgesic and neuroprotective effect, gained approval from the Food and Drug Administration (FDA) for the treatment of severe chronic pain that is intolerant of or refractory to other treatments. Ziconotide is the synthetic equivalent of omega-MVIIA, a component of the venom of the marine snail, Conus magus. The mechanism of action underlying ziconotide’s therapeutic profile derives from its potent and selective blockade of a neuron-specific N-type voltage-sensitive calcium channels (N-VSCCs). Direct blockade of N-VSCCs inhibits the activity of a subset of neurons, including pain-sensing primary nociceptors. This mechanism of action distinguishes ziconotide from all other analgesics, including opioid analgesics. Clinical studies have reported that spinally administered ziconotide provides significant pain relief to severe chronic pain patients who have failed to obtain relief from opioid therapy. Systemic toxicity is markedly decreased by administration of smaller doses of ziconotide intrathecally. Furthermore, development of tolerance is not observed following chronic use of ziconotide in these subjects. Nevertheless, there are neurological...
adverse effects due to delay in clearance of ziconotide from the neural tissues (Miljanich 2004).

In a randomized, double-blind, pilot study, Atanassoff and colleagues (2000) evaluated the safety and analgesic effectiveness of intrathecal ziconotide in patients with acute post-operative pain following total abdominal hysterectomy, radical prostatectomy, or total hip replacement. After intrathecal injection of local anesthetic and before surgical incision, a continuous intrathecal infusion of either placebo or 1 of 2 doses of ziconotide (0.7 ug/hr or 7.0 ug/hr) was started and continued for 48 to 72 hrs post-operatively. Primary and secondary effectiveness variables were the mean daily patient controlled analgesia (PCA) morphine equivalent consumption and visual analog scale pain intensity (VASPI) scores, respectively. Of the 30 patients who received study drug; 26 were evaluable for effectiveness. Mean daily PCA morphine equivalent consumption was less in patients receiving ziconotide than in placebo-treated patients, and the difference was statistically significant between 24 and 48 hrs (p = 0.04). VASPI scores during the first 8 hrs post-operatively were markedly lower in ziconotide-treated than in placebo-treated patients. In 4 of 6 patients receiving the 7 ug/hr-dose of ziconotide, side effects such as dizziness, blurred vision, nystagmus and sedation contributed to discontinuation of drug after 24 hrs. These symptoms resolved following ziconotide discontinuation. Ziconotide showed analgesic activity, as indexed by reduced PCA morphine equivalent consumption and lower VASPI scores. Because of a favorable trend of decreased morphine consumption with an acceptable side effect profile in the 0.7 ug/hr-dose ziconotide group, the lower dosage may be closer to the ideal dose than the higher dosage. Large-scale studies are needed to clarify this issue.

In a multi-center, double-blind, placebo-controlled study, Staats and associates (2004) evaluated the safety and effectiveness of ziconotide in patients with pain that is refractory to conventional treatment (n = 111). Patients were individuals aged 24 to 85 years with cancer or AIDS and a mean VASPI score of 50 mm or greater. Subjects were randomly assigned in a 2:1 ratio to receive ziconotide or placebo treatment. Intrathecal ziconotide was titrated over 5 to 6 days, followed by a 5-day maintenance phase for responders and crossover of non-responders to the opposite treatment group. The main outcome measure was mean percentage change in VASPI score from baseline to the end of the initial titration period. Of the evaluable population, 67 (98.5 %) of 68 patients receiving ziconotide and 38 (95 %) of 40 patients receiving placebo were taking opioids at baseline (median morphine equivalent dosage of 300 mg/day for the ziconotide group and 600 mg/day for the placebo group; p = 0.63, based on mean values), and 36 had used intrathecal morphine. Mean VASPI scores were 73.6 mm in the ziconotide group and 77.9 mm in the placebo group (p = 0.18). Mean VASPI scores improved 53.1 % (95 % confidence interval [CI]: 44.0 to 62.2 %) in the ziconotide group and 18.1 % (95 % CI: 4.8 to 31.4 %) in the placebo group (p < 0.001), with no loss of effectiveness of ziconotide in the maintenance phase. Pain relief was moderate to complete in 52.9 % of patients in the ziconotide group compared with 17.5 % in the placebo group (p < 0.001). Five patients receiving ziconotide achieved complete pain relief, and 50.0 % of patients receiving ziconotide responded to therapy compared with 17.5 % of those receiving placebo (p = 0.001). The authors concluded that intrathecal ziconotide provided clinically and statistically significant analgesia in patients with pain from cancer or AIDS.
According to the manufacturer, the safety of Prialt administered as a continuous infusion has been examined in 1,254 patients with acute or chronic pain. The duration of treatment has ranged from a 1-hr intrathecal infusion to treatment lasting for over 7.5 years. The mean duration of treatment was 193 days with 173 patients (14 %) treated for at least 1 year. The average final dose was 17 ug/day (0.73 ug/hr). The most common side effects associated with the use of ziconotide are dizziness, nausea, confusion and headache. Prialt carries a black box warning that severe psychiatric symptoms and neurological impairment may occur during treatment. Patients with a pre-existing history of psychosis should not be treated with Prialt.

In a case-series study, Saulino et al (2009) reported the findings of intrathecal (IT) ziconotide and baclofen in 7 patients with neuropathic pain and spasticity; 5 of the 7 adult patients were receiving IT baclofen treatment when ziconotide was initiated. All 5 patients had experienced at least one previous failed IT treatment regimen. Pain intensity scores improved by a mean of 50.3 % with the use of ziconotide-baclofen therapy. Mean time to onset of pain relief was 15 weeks, at a mean ziconotide dose of 3.7 mcg/day. Within this group of patients, adverse events were observed in 1 patient, but they were not considered to be ziconotide-related and subsequently resolved. The remaining 2 patients were receiving ziconotide treatment when baclofen was initiated. Pain intensity scores improved by 75 % and 30 %, respectively. Pain relief was evident at 2 weeks and 1 week, with corresponding ziconotide doses of 2.4 mcg/day and 14.4 mcg/day, respectively. One patient in this group reported adverse events, but all resolved during continued treatment with the study drugs. Treatment regimens varied between patients in these case series; each regimen used a different titration strategy and different concentrations of ziconotide and baclofen. The authors concluded that combination IT ziconotide and baclofen therapy may be a treatment option for patients with neuropathic pain and spasticity. Moreover, they stated that future studies are needed to determine the optimal dosing and titration schedules for ziconotide-baclofen usage.

Yamamoto and Takahara (2009) noted that a blockade of N-VSCCs has been suggested for reducing the neuronal injury occurring from ischemia/reperfusion events. Thus, many efforts have been made to develop systemically available small-molecule N-type calcium channel blockers. These researchers reviewed the latest updates concerning small-molecule N-type calcium channel blockers as potential candidates for the next generation of therapeutics for neuropathic pain and ischemic stroke.

Kress and associates (2009) noted that although morphine and ziconotide are the only intrathecal analgesics currently approved by regulatory authorities in the United States (FDA) and Europe (national-level approval by individual countries for morphine and European Agency for the Evaluation of Medicinal Products approval for ziconotide), a wide variety of opioid and non-opioid drugs are being used in this way. There is no official guidance concerning the selection of these drugs or their use in combinations and a paucity of safety and effectiveness data from randomized controlled trials (RCTs).

In a retrospective, observational study, Deer and colleagues (2009) evaluated the safety and tolerability of ziconotide combination therapy. Patients with severe
chronic pain of non-cancer origin who were receiving inadequate analgesia with intrathecal opioid therapy (with or without intrathecal adjuvants) and who had ziconotide added to their intrathecal regimens were included. Patient characteristics, intrathecal ziconotide doses, concomitant intrathecal and systemic drug use, VAS pain scores, Oswestry Disability Index scores, mini-mental status examination scores, neurological examination results, clinical observations (including adverse event reports), and equipment complications were reviewed for 12 weeks after ziconotide initiation. A total of 16 patients were identified. Ziconotide was initiated at a dose of 0.5 mcg/day and titrated to a mean dose of 2.64 mcg/day at week 12. Intrathecal opioids were fentanyl (n = 3), hydromorphone (n = 7), morphine (n = 5), and sufentanil (n = 1). Adverse events were noted in 1 patient, who reported increased depression and pain during combination therapy; ziconotide treatment was discontinued, and all adverse events resolved over a 4-week period. Substantial pain relief (greater than or equal to 4-point decrease in VAS score) was reported in 3 of 15 patients (20.0 %) and increased functional capacity was evident in 3 of 15 patients (20.0 %). The drawbacks of this study were that it was a retrospective study with a limited number of patients from a single center. The authors concluded that results from this observational study suggest that combination intrathecal ziconotide and opioid therapy may be a safe and potentially effective treatment option for patients with refractory chronic pain. They stated that prospective RCTs are needed to evaluate ziconotide combination therapy.

Wallace and colleagues (2010) noted that there is a need for a critical assessment of the currently available published literature on ziconotide combination therapy. They summarized and evaluated the publications from pre-clinical and clinical peer-reviewed experiments that have examined the safety and effectiveness of ziconotide in combination with a variety of other drugs. A total of 11 relevant publications were identified through a systematic search of multiple databases. In pre-clinical studies, additive or synergistic anti-nociceptive effects were discovered when ziconotide was used in combination with baclofen, clonidine, or morphine; however, no additional anti-nociceptive effects were observed when bupivacaine was added to ziconotide therapy. Safety data from animal studies revealed that ziconotide did not exacerbate morphine-induced respiratory depression, or clonidine-induced hypotension or bradycardia; however, ziconotide did potentiate morphine-induced hypotension and inhibition of gastrointestinal tract motility. Results from 2 open-label trials indicated that combination ziconotide and morphine therapy produced greater analgesia than was produced by the use of either drug alone. Preliminary support for the use of ziconotide in combination with baclofen, morphine, or hydromorphone was provided by case studies. The authors concluded that although clinical and pre-clinical studies provide some support for the use of ziconotide in combination with baclofen, clonidine, morephine, or hydromorphone, strong evidence-based data are limited. They stated that RCTs with long-term outcomes are needed.

Andras et al (2011) stated that the Irukandji syndrome is caused by the sting of some small jellyfish species. The syndrome has severe life-threatening consequences. The exacerbating pain and cardiovascular symptoms (tachycardia and hypertension) are hard to control in many cases. These researchers proposed a new possible therapy for Irukandji syndrome -- intravenously administered ziconotide. The proposed experimental plasma
concentration of ziconotide for rats is in the range of 0 to 6 μg/ml. Based on a molecular biological scenario of the venom action mechanism at cellular level, these investigators suggested that the proposed method should be functional in re-establishing the normal cardiovascular parameters of the experimental animals and concomitantly it should abolish the severe pain caused by envenomation. The authors expected that positive experimental results in agreement with their theory will lead to the possibility of a new therapy for the Irukandji syndrome and possibly for other envenomations with similar etiology.

CPT Codes / HCPCS Codes / ICD-9 Codes

Other CPT codes related to the CPB:

- 62350
- 62351
- 62360
- 62362
- 99601
- 99602

HCPCS codes covered if selection criteria are met:

- J2278  Injection, ziconotide, 1 mcg

Other HCPCS codes related to the CPB:

- E0779  Ambulatory infusion pump, mechanical, reusable, for infusion 8 hours or greater
- E0780  Ambulatory infusion pump, mechanical, reusable, for infusion less than 8 hours
- E0781  Ambulatory infusion pump, single or multiple channels, electric or battery operated, with administrative equipment, worn by patient
- E0783  Infusion pump system, implantable, programmable (includes all components, e.g., pump, catheter, connectors, etc.)
- E0785  Implantable intraspinal (epidural/intrathecal) catheter used with implantable infusion pump, replacement
- E0786  Implantable programmable infusion pump, replacement (excludes implantable intraspinal catheter)
- J2270, J2271, J2275, S0093  Injection, morphine sulfate
- J2275, S0093

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):
Occlusion and stenosis of precerebral arteries, occlusion of cerebral arteries, transient cerebral ischemia, and acute but ill-defined, cerebrovascular disease

Other ICD-9 codes related to the CPB:

For pain - code by site or disease (too many to list)

V45.89 Other postprocedural status

The above policy is based on the following references:

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