National PBM Drug Monograph

Ziconotide for Intrathecal Infusion (Prialt®)

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VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary

Ziconotide, a potent synthetic neuroactive peptide equivalent of an omega conotoxin derived from the venom of a marine snail, is the first N-type calcium channel blocker and nonopioid analgesic developed for intrathecal (IT) treatment of patients with severe, refractory chronic pain.

Pharmacokinetics

- When ziconotide was administered intrathecally, the mean CSF volume of distribution of IT ziconotide approximated the estimated CSF volume and the mean clearance of ziconotide from cerebrospinal fluid (CSF) closely approximated adult CSF turnover rates.
- After IT administration of ziconotide at doses of 0.1 to 7.0 mcg/h for 5 to 6 days, 56% of patients had nondetectable plasma concentrations of ziconotide.
- In the systemic circulation, ziconotide is expected to be rapidly cleaved to peptide fragments by ubiquitous peptidases and proteases.
- Therapeutic and adverse effects may be delayed in onset and offset.

FDA-appoved Indications

- Management of severe chronic pain in patients for whom IT therapy is warranted and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies, or IT morphine.
- Ziconotide must be administered intrathecally via an implanted Medtronic SynchroMed® EL or SynchroMed® II Infusion System, or Simms Deltec CADD Micro® External Microinfusion Device and Catheter.

Efficacy

- There are no head-to-head or active-control trials, effectiveness studies, or controlled trials longer than 3 weeks.
- Using fast dosage titration regimens (which were not approved by the FDA), the mean percentage decrease in pain was 53.1% on ziconotide (35.0% placebo-adjusted) in patients with severe chronic cancer or AIDS pain and 30.7% on ziconotide (24.8% placebo-adjusted) in patients with severe chronic noncancer pain.
- In a single trial that evaluated IT ziconotide using the FDA-recommended slow dosage titration regimen in treatment-refractory patients with severe chronic pain, the mean percentage decrease in pain was relatively small (14.7% on ziconotide; 7.5% placebo-adjusted; $p = 0.04$).
- IT ziconotide was remarkable for being efficacious in individuals with pain refractory to IT or systemic opioids and for achieving complete pain relief in some individuals who had previously not responded to other therapies.

- The efficacy of IT ziconotide seems to be similar in opioid-naïve and experienced patients.

Safety

- IT ziconotide has a narrow therapeutic margin. It produces dose-related adverse events that are primarily cerebellar, cognitive, and neuropsychiatric in nature.
- The recommended slow dosage titration regimen seemed to reduce the risk of serious adverse events and withdrawals due to adverse events that were seen in the previous two faster dosage titration trials. At the slower infusion rates, the most common adverse events were dizziness, nausea, asthenia, somnolence, diarrhea, confusion, ataxia, headache, vomiting, and abnormal gait. Urinary retention may also occur during IT ziconotide treatment.
- At the higher doses, some of the cognitive and neuropsychiatric effects were delayed, unpredictable, persistent, necessitated patient hospitalization, and could not be ruled out as causative or contributing factors in 3 deaths. The protracted time course of some of the serious cognitive and neuropsychiatric adverse events raised concern that ziconotide may produce irreversible central nervous system (CNS) injury, although preclinical studies did not demonstrate persistent CNS toxicity.
- Because of the potential severity of psychiatric symptoms and neurologic effects, IT ziconotide is contraindicated in patients with a history of psychosis.
- Potential risk factors for cognitive and neuropsychiatric adverse events include fast dosage titration, older age (≥ 65 years old), other CNS-depressant drugs; preexisting psychiatric disorders; and concomitant therapy with antiepileptics, neuroleptics, sedatives, or diuretics.
- Increased serum creatine kinase muscle isoenzyme (CK-MM) ≥ 3 times the upper limit of normal was observed in 11% of patients during clinical studies. Serum CK should be monitored periodically (e.g., every 2 weeks for first month and monthly as appropriate thereafter) during ziconotide treatment and as clinically indicated (e.g., new neuromuscular symptoms) or in the setting of reduced physical activity.
- Combination therapy with IT ziconotide and either IT opioids or IT chemotherapy is not recommended at this time. There is no data available on admixing ziconotide and other IT drug preparations.

Conclusions

Ziconotide is the first non-opioid IT treatment alternative for the management of patients with refractory chronic pain and only the fourth analgesic agent used intrathecally that is actually available in a formulation FDA-approved for IT administration. It has arguably undergone the best quality and most extensive efficacy and safety evaluations of any IT analgesic or anesthetic available. There are no pharmacologic treatment alternatives that are approved for IT administration on the VA National Formulary.

Ziconotide has a narrow therapeutic margin. In patients with refractory chronic pain, the average magnitude of reduction in pain intensity obtained during ziconotide therapy is relatively small, mainly because of limited tolerability due to adverse events. Ziconotide has been shown to be efficacious for various types of pain and there may be substantial benefits at the individual level. A small subgroup of patients refractory to standard treatments may experience complete pain relief and improved quality of life after IT ziconotide therapy. Although it has been shown to be efficacious relative to placebo in opioid-refractory pain, its efficacy relative to active agents and its effectiveness in actual clinical practice (with less intensive monitoring than those in clinical trials) have not been evaluated.

IT ziconotide may have some advantages over opioids. Its main advantage is that tolerance does not develop during long-term therapy, although this is based on limited long-term data. Ziconotide is not associated with addiction and lethal overdose, and vomiting and constipation were not commonly reported. Periodic apnea has been reported at toxic doses, but ziconotide is not considered to be a respiratory depressant. Long-term studies are needed to confirm that IT ziconotide is not associated with cardiac toxicity, endocrine effects, and spinal catheter-tip inflammatory masses / granulomas (seen with higher doses of IT morphine and IT hydromorphone).

There are important and uncertain trade offs associated with IT ziconotide therapy. The risks of serious adverse events in any individual are unpredictable, and in some patients, ziconotide therapy may result in more harm than benefit. Neuropsychiatric adverse events are usually manageable but may take weeks to months to resolve and, in some instances, may require prolonged hospitalization and intensive care monitoring. The long-term safety of ziconotide is unclear because of extremely limited experience with extended use.

Ziconotide requires specialized administration techniques, specific external or implantable infusion devices, and is best suited for patients who can be carefully followed by trained personnel and who have convenient access to medical facilities.

Further studies are needed to verify the recommended slow dosage titration method as the optimal dosing regimen in actual clinical practice; confirm a lack of tolerance to the analgesic effects; identify subgroups of patients who have higher benefit-to-risk ratios; characterize the long-term benefits and risks of IT ziconotide therapy; expand the efficacy and safety database on elderly patients, minority races, and patients with cancer; and evaluate the efficacy and safety of combination therapy with ziconotide and other IT analgesics.

Recommendations

Although IT ziconotide may offer some advantages over IT opioids, it is recommended that ziconotide be made available only to individuals who require IT therapy for chronic pain refractory to multiple forms of pain management. In addition, patients receiving ziconotide must be under the care of a VA pain specialist or anesthesiologist, who can explain and help the patient understand the potential benefits and harms of IT ziconotide therapy. Because long term safety and efficacy data are limited, IT ziconotide should not be added to the VA National Formulary.

IT ziconotide dosage titration should be slow and individualized to patient response (pain relief and functional ability) and tolerability. Clinicians should exercise caution when using ziconotide in patients 65 years of age and older.

Proposed Inclusion Criteria

Facilities should consider using a review committee to evaluate requests to prescribe intrathecal ziconotide.

Patients who meet ALL of the following criteria may receive IT ziconotide:

- Patient is under the care of a pain specialist or anesthesiologist who has experience in the management of polypharmacy with IT pain medications and has the resources to provide 24/7 care for problem management.
- Patient has chronic cancer or noncancer pain
- Patient has had documented inadequate response, intolerable adverse effects, or contraindication to
  systemic opioids plus adjuvant agents (e.g., antidepressants and/or antiepileptics) OR IT morphine (maximum tolerated dose not exceeding 15 mg/d) OR off-label IT hydromorphone

(maximum tolerated dose not exceeding 10 mg/d)[2] (in IT or epidural screening or treatment)
AND
IT clonidine, IT bupivacaine, AND a combination of IT analgesics.

- Patient has or will have an implanted Medtronic SynchroMed® EL or SynchroMed® II Infusion System, or Simms Deltec CADD Micro® External Microinfusion Device and Catheter.
- For noncancer pain, patient has received psychological evaluation (to help promote good therapeutic outcomes from IT therapy).

Proposed Exclusion Criteria

Patients who meet any of the following criteria should NOT receive IT ziconotide:

- Contraindication to IT ziconotide therapy:
    - Previous history of psychosis.
    - Any other concomitant treatment or medical condition that would render IT administration hazardous (e.g., infection at the microinfusion injection site, uncontrolled bleeding diathesis, spinal canal obstruction that impairs circulation of CSF).
    - Concomitant IT chemotherapy.
    - Hypersensitivity to ziconotide or formulation components.
- Active suicidal or homicidal behavior, major uncontrolled depression or anxiety, or serious cognitive deficits.

Discontinuation Criteria

- NO improvement in either pain or functional ability during the first 3 weeks of IT ziconotide therapy.

Weigh Risks Versus Benefits

- Patients with refractory pain will very likely require concomitant therapy with systemic or IT analgesics. Weigh the potential risks and benefits before deciding to use IT ziconotide concomitantly with IT opioids or other IT agents, such as bupivacaine, clonidine, and baclofen. The stability of these analgesics in admixtures is unknown. The efficacy and safety of only ziconotide monotherapy has been evaluated in clinical trials.
- Consider potential risks versus benefits of using IT ziconotide in patients who do not have timely access to medical facilities, lack family or social support to assist with patient monitoring at home, and would have difficulty adhering to follow-up visits.

Introduction

Ziconotide, a nonaddictive analgesic 100 to 1000 times more potent than morphine, is the first intrathecally administered non-opioid agent to be FDA-approved for the management of severe, refractory chronic pain in patients who require intrathecal (IT) analgesic therapy.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating intrathecal (IT) ziconotide for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology and Pharmacokinetics

Mechanism of Action

The first drug to be FDA-approved in a new class designated the N-type calcium channel blockers (NCCBs), ziconotide (formerly, SNX-III) has a unique mechanism of action that produces strong antinociceptive effects in animal models of pain and in patients with chronic refractory pain that show poor response to morphine. Ziconotide is a potent synthetic neuroactive peptide equivalent of omega conotoxin MVIIA, a constituent of the venom of the fish-hunting marine snail, *Conus magus*. Animal studies suggest that ziconotide selectively and reversibly blocks the presynaptic neuronal N-type voltage-sensitive calcium channels, which are located throughout the central nervous system and concentrated on A-δ and C type primary afferent nociceptive nerves in the superficial layers of the dorsal horn of the spinal cord. By blocking calcium influx, it is believed to inhibit release of norepinephrine and excitatory neurotransmitters, reduce neuronal excitability, block synaptic transmission from nociceptive sensory neurons to dorsal horn neurons, and disrupt central sensitization (pathologic hypersensitivity) processes that perpetuate chronic pain states after removal of the initiating nociceptive stimulus.

Ziconotide does not bind to opioid receptors, is not blocked by opioid antagonists, and will not prevent withdrawal symptoms resulting from discontinuation of opioids. Ziconotide is nonaddicting and, unlike IT morphine and baclofen, does not produce tolerance.

Preliminary studies suggest that combined therapy with ziconotide and opioids may produce additive analgesia. In animal studies, the effects of ziconotide are additive with those of opioids. In a pilot clinical trial, morphine requirements have been shown to decrease with concomitant postoperative IT administration of ziconotide (7 mcg/h).[3]

When administered intravenously, ziconotide has poor penetration across the blood brain barrier and produces profound sympatholytic effects that result in hypotension.

Pharmacokinetics

The pharmacokinetic characteristics of ziconotide are summarized in Table 1.

Table 1 Pharmacokinetics of ziconotide (Mean ± SD)

	CSF	**Plasma**
	1–10 mcg IT x 1 h	0.3–10 mcg/kg/d IV
Parameter	Chronic pain (N = 23)	Population NR (N = 21)
Volume of distribution (ml)	155 ± 263	30,460 ± 6366
Protein binding (%)	NR	50
Cmax (ng/ml)	16.4–132	NR
AUC (ng·h/ml)	83.6–608	NR
Clearance (ml/min)	0.38 ± 0.56	270 ± 44
Half-life (h)	4.6 ± 0.9	1.3 ± 0.3

Source: PRIALT (ziconotide intrathecal infusion) Product Information[4]
NR, Not reported

Plasma concentrations of ziconotide were below quantitation limits (0.04 ng/ml) in 56% of patients at IT infusion rates ranging from 0.1 to 7.0 mcg/h for 5 to 6 days. Higher infusion rates were more likely to produce quantifiable plasma concentrations. Detectable ziconotide plasma concentrations remain constant after 9 months of IT infusion.

The mean CSF volume of distribution of IT ziconotide approximates the estimated CSF volume (140 ml) and the mean clearance of ziconotide from cerebrospinal fluid (CSF) closely approximates adult CSF turnover rates (0.3 to 0.4 ml/min).

The ziconotide molecule is cleaved at multiple sites by endopeptidases and exopeptidases. In the systemic circulation, ziconotide is expected to be rapidly cleaved to peptide fragments by multiple peptidases and proteases present in most organs. The biological activity of the proteolytic degradation products has not been evaluated.

After intravenous administration of ziconotide, less than 1% of the drug is eliminated in human urine.

There is some disparity between the pharmacokinetic characteristics and pharmacodynamic effects of the drug, in some cases, resulting in delayed and prolonged effects that occur beyond what would be expected based on the pharmacokinetic properties of ziconotide. Presumably, ziconotide may take time to distribute to distal areas of the spinal cord and reach its target site of action (the spinal dorsal horn) because it is a relatively large molecule as compared with morphine (31 versus 0.4 kDA).[5] It may also have delayed uptake and prolonged binding by tissues or produce delayed neuronal changes in the central nervous system. The onset of significant pain relief may be delayed 2 to 4 hours and maximum effects generally occur after 8 to 12 hours.[6] Offset of analgesic effects may follow a lag period of 24 to 48 hours.

Adverse events also may have delayed onset and offset. In one clinical trial, most adverse event symptoms occurred 2 to 3 days after initiation of ziconotide.[7] Central nervous system adverse events resolved 4 days (range, 0 to 58 days) after discontinuation of ziconotide. In one case report, ziconotide-associated delirium and agitation were reported to persist for several weeks; however, causality to the drug was confounded by a childhood history of hallucinations and a history of postoperative meperidine-related hallucinations and delirium.[8]

FDA-approved Indication(s) and Off-label Uses

FDA-approved Indication

Management of severe chronic pain in patients for whom intrathecal (IT) therapy is warranted, and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies, or IT morphine.

Off-Label Uses

Spasticity due to spinal cord injury (SCI). IT ziconotide (20 to 70 mcg/d and 7.2 to 144 mcg/d, higher than the eventual recommended maximal dose) was at least partially effective in relieving spasticity and pain in 2 patients who had post-SCI spasticity that was refractory to multiple oral medications and that became tolerant to IT morphine and IT baclofen.[9] Ziconotide was continued at 60 to 70 mcg/d for 7 months in one patient. In the other patient, ziconotide was discontinued after the patient experienced inadequate pain relief and neurologic adverse events. IT ziconotide therapy was attempted for spasticity after investigators in neuropathic pain trials observed that the drug diminished upper and lower extremity reflexes in some patients. The role of calcium channel blockers in spasticity has not been studied.

Acute postoperative pain. One randomized double-blind placebo-controlled pilot Phase II trial (N = 30) showed that a postoperative 48- to 72-hour continuous IT infusion of ziconotide (7 and

0.7 mcg/h) decreased morphine equivalent consumption and pain intensity; however, the treatment difference relative to placebo in terms of morphine equivalent consumption was statistically significant for only the higher dose.[3] Six patients in the high-dose group withdrew due to adverse events primarily involving the nervous system.

Uses Not Supported by Current Evidence

Neuroprotection. Phase III trials evaluating the neuroprotective effects of ziconotide following ischemic and traumatic brain injury were stopped because of blood pressure-lowering effects.

Other Routes of Administration. Epidural administration resulted in high plasma concentrations of ziconotide and a low cerebrospinal bioavailability of less than 1%, and was clinically ineffective. *Intravenous administration* resulted in profound sympatholytic effects and unacceptably high incidence of hypotension, somnolence, dizziness, dry mouth, and rhinitis.

Current VA National Formulary Alternatives

There are few FDA-approved and evidence-supported options available for patients with refractory chronic pain, and IT therapy is often among the last line of analgesic alternatives in the treatment of chronic pain. Some experts feel that there will be limited benefit from intraspinal morphine after other routes of morphine administration have been ineffective, particularly in treating neuropathic pain.[2]

Recommended first-line IT analgesic therapies are morphine for intrathecal injection and off-label IT injection of hydromorphone[2]; both of these preparations are nonformulary. Second-line IT therapies (alone or in combination with first-line opioids) are spinal bupivacaine and off-label IT use of epidural clonidine; these are also nonformulary. Off-label IT use of fentanyl, sufentanil, and midazolam, or intraspinal baclofen (FDA-approved for spasticity only) are third-line alternatives. There are no other NCCBs available.

Access

Elan distributes ziconotide exclusively through TheraCom, a specialized pharmacy distributor. Address: 9177 Key West Avenue, Rockville, MD 20850. Phone: 1-888-PRIALT-1.

Dosage and Administration

Ziconotide is available as a sterile, preservative-free solution for intrathecal (IT) administration in 20-ml single-use vials at a concentration of 25 mcg/ml to be used undiluted, and 1-, 2-, or 5-ml single-use vials each at a concentration of 100 mcg/ml to be used undiluted or diluted to the appropriate concentration with preservative-free 0.9% sodium chloride for injection. Only the undiluted 25 mcg/ml formulation should be used for naïve (initial) pump priming.

Ziconotide should be administered only via the Medtronic SynchroMed® EL or SynchroMed® II Infusion System or Simms Deltec CADD Micro® External Microinfusion Device and Catheter by or under the direction of a physician who is experienced in IT administration techniques and familiar with ziconotide and device labelling. Refer to the product information and device manufacturer's manuals for instructions on reservoir rinsing, initial filling, reservoir refilling, and programming the implantable and external infusion systems.

> The frequency of severe adverse events during ziconotide therapy is dose-related. Therefore, to improve the safety and tolerability of ziconotide, the initial dosage rate should not exceed 2.4 mcg/d (0.1 mcg/h). Infusion rate increments should not exceed 2.4 mcg/d (0.1 mcg/h) and should not be made more frequently than 2 to 3 times per week. The maximum recommended dose in the U.S. is 19.2 mcg/d (0.8 mcg/h) by day 21. Smaller initial doses (e.g., 1.2 mcg/d or

0.05 mcg/h) and smaller, less frequent increments (e.g., 1.2 mcg/d or 0.05 mcg/h once weekly) may be necessary.

Faster dosage titration schedules increase the risk of serious adverse events and withdrawals due to adverse events; therefore, they should only be used if there is an urgent need for analgesia that outweighs the potential risks to the patient.

Dosing in Special Populations

No studies in patients with hepatic or renal dysfunction have been performed.

Data in elderly patients is limited. In clinical studies, 22% of patients were ≥ 65 years of age and 7% were ≥ 75. The risk of confusion was higher in the subgroup of patients ≥ 65 years old (42%) than in the younger subgroup of patients < 65 years old (29%). There were no other age-related differences in clinical response. Dosing in elderly patients should be cautious, starting at the low end of the dosing range for ziconotide.

Storage

Ziconotide should be refrigerated during transit. Store undiluted and diluted ziconotide at 2°C to 8°C (36°Fto 46°F). Do NOT freeze ziconotide. Protect from light.

Efficacy

There are no head-to-head or active-control trials, effectiveness studies, or controlled trials longer than 3 weeks. Limited data is available from observational safety studies extending beyond 1 year. There were no trials comparing ziconotide with active intrathecal agents such as opioids, bupivacaine, or clonidine.

Efficacy Measures

Visual Analogue Scale of Pain Intensity (VASPI). This is a 100-mm scale commonly used in pain trials (0 mm = No Pain, 100 mm = Worst Pain Imaginable).

Responder rate. Responders were patients who obtained at least 30% improvement in VASPI scores (VASPI-30, Study 301) or at least 30% improvement in VASPI scores without opioid change; i.e., increase in dose or change in concomitant opioid (VASPI-30 WOC). Although the VASPI scores correlate with 11-point numerical rating scale (NRS) scores, it should be noted that minimal clinically important changes in chronic pain scores were shown to be at least 30% improvement on the NRS (NRS-30),[10] and therefore, the VASPI-30 may not be directly comparable to NRS-30 responder rates.

Summary of efficacy findings

Three major efficacy trials compared ziconotide against placebo, two using a fast titration schedule (Studies 95-001 and 96-002) and one using a slow titration schedule (Study 301), in a total of 457 patients (268 ziconotide, 189 placebo) with severe chronic cancer or noncancer pain, of whom 20% had exclusively non-neuropathic pain. Treatment duration was no longer than 3 weeks in controlled trials. Dosing titration schedules are shown in Table 2.

Table 2 Dosage titration schedules in clinical trials

Parameter	Slow Titration (Study 301)	Fast Titration (Studies 95-001, 96-002)
Initial dose, mcg/d	2.4	9.6[†]
Dosage increments, mcg/d	1.2–2.4	Not reported
Rate of dosage increases, times/wk	2–3	7–14
Protocolled (Actual) maximum dose, mcg/d	21.6 (19.2)[‡]	57.6
Time to maximum dose, d	21	5–6

[†] Modified protocol in Study 95-001
[†] Note that the protocolled maximum dose in Study 301, and the maximum dose recommended by the European Medicines Agency (EMEA), is 21.6 mcg/d. The actual maximum dose used in the clinical trial, and the FDA-recommended maximum dose, is 19.2 mcg/d.

Ziconotide at the higher infusion rates (Studies 95-001 and 96-002) showed significant efficacy compared with placebo; the placebo-adjusted mean percentage decrease in VASPI scores from baseline to day 5–6 (end of initial titration) were 35.0% in Study 95-001 (patients with severe chronic cancer pain and AIDS pain) and 24.8% in Study 96-002 (patients with severe noncancer pain) (see Appendix Table 1). At the fast dosage titration regimens used in these studies, many patients developed serious adverse events (SAEs), including neuropsychiatric SAEs that could not be excluded as being causally related to several deaths. Multiple protocol modifications were needed to find safer and more tolerable doses. In Study 95-001, there were an insufficient number of patients treated with the revised and proposed dosing schedule to adequately assess efficacy and safety of that regimen, and data integrity was challenged after patients at one site became unblinded because of study misconduct.

The manufacturer then performed Study 301 using a slower dosage titration schedule in a highly treatment-refractory patient population with severe chronic cancer or noncancer pain of mostly neuropathic origin. The main efficacy findings of the slow titration trial are summarized in Table 3.

Table 3 Results of major efficacy trial evaluating slow dosage titration of ziconotide (Study 301)

Outcome Measure	Ziconotide N = 112	Placebo N = 108	Difference (95% CI)	P-value
% ↓ in VASPI, mean	12%	5%	7% (0.4 to 13)	0.04
Responder Rate (VASPI-30, % of patients)	16%	12%	4% (–0.05 to 0.13[‡])	0.50[‡]
Responder Rate (VASPI-50, % of patients)[†]	8%	2%	6% (0.01 to 0.12[‡])	0.07[‡]
↓ Use of non-IT opioids (% of patients)	24%	17%	7% (NR)	NR

↓, Decrease; IT, Intrathecal; VASPI, 100-mm Visual Analogue Scale of Pain Intensity; VASPI-30 or -50, At least 30% or 50% reduction, respectively, in VASPI score from baseline to week 3
[†] Estimated from Figure 1 of Prialt (ziconotide intrathecal infusion) product information[4]
[‡] Calculated value

Ziconotide produced a significant, small decrease in VASPI scores as compared with placebo ($p = 0.04$). The treatment differences in VASPI-30 and -50 responder rates did not reach the level of statistical significance. Ziconotide was noted to produce complete (100%) relief of neuropathic pain in a small subset of these otherwise treatment-refractory patients (ziconotide 2% versus placebo 1%).

According to the EMEA Scientific Discussion,[11] long-term data from only 31 patients, in whom dosage requirements remained stable (mean, 0.4 to 0.6 mcg/h) over 1 year, suggested a lack of tolerance to the analgesic effects of ziconotide over time.

The EMEA reviewer noted that a high rate of confusion and other AEs seemed to affect the evaluation of efficacy since there was a greater reduction in mean VASPI scores in confusion-affected versus unaffected ziconotide subgroups across the three major efficacy trials. However, a

greater treatment effect was consistently seen in unaffected ziconotide patients than unaffected placebo patients, suggesting that the VASPI results were adequate to demonstrate efficacy despite confounding by patient confusion and other adverse events.

Subgroup analyses, which should be interpreted with caution, suggested the following:

- A better response in patients with cancer pain than noncancer pain (responder rates 47.9% versus 33.7%).
- Efficacy in both neuropathic (N = 314) and nonneuropathic (N = 82) pain, with a possibly better response in neuropathic pain (placebo-adjusted mean percentage change in VASPI scores from baseline, EMEA meta-analysis: 16.8% and 7.9%, respectively).
- Similar mean improvements in VASPI scores in ziconotide-treated patients who were IT morphine-naïve versus experienced patients (post-hoc analyses, Studies 95-001 and 96-002). The mean percentage decrease in VASPI scores in IT morphine-naïve and experienced ziconotide-treated subgroups were 29.6% and 33.2%, respectively, in Study 96-002 (data not reported for Study 95-001). According to the EMEA Scientific Discussion,[11] these results strongly suggested that mandatory prior (first-line) IT morphine use should not be required in all situations. Based on the results of Study 301 (which found small benefit and a nonsignificant difference in responder rates in a relatively more selective study population), it is possible that ziconotide may be less efficacious in patients who do not respond to or are intolerant to systemic morphine.

Differences in therapeutic effect across trials (95-001, 96-002, and 301) existed, possibly due to differences in patient populations, dose regimens, treatment durations, and study design. The study evaluating short-term (5- to 6-day) therapy with ziconotide in malignant pain (95-001) showed the greatest benefit with ziconotide relative to placebo (placebo-adjusted mean percentage decrease in VASPI from baseline to 5–6 days, 35.0%; adjusted rate of VASPI-30 responders who did not have an increase in dose or change in type of concomitant opioid, 32.5%). The slow titration trial (Study 301) evaluating 3-week therapy with ziconotide in the most refractory patients (most had failed IT combination therapy) showed the smallest therapeutic effect (placebo-adjusted mean percentage decrease in VASPI from baseline to day 21, 7.5% and adjusted VASPI-30 responder rate [not further specified], 4.1%).

According to the EMEA Scientific Discussion, "The requirement for intrathecal analgesic therapy, whether in cancer or non-cancer pain, is a clinically valid parameter to define the target population."[11]

For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials* (page 19).

In summary, IT ziconotide has shown to be effective for various types of pain and there may be substantial benefits at the individual level. A small subgroup of patients may experience complete pain relief and improved quality of life. Although it has been shown to be efficacious relative to placebo in opioid-refractory pain, its efficacy relative to active agents and its effectiveness in actual clinical practice (with less intensive monitoring than those in clinical trials) have not been evaluated.

Adverse Events (Safety Data)

Safety data on IT ziconotide are based on 1254 patients with acute or severe chronic pain who were treated with ziconotide for widely varying durations, ranging from 1 hour to more than 7.5 years (mean, 193 days). The safety database includes the results of four long-term, open-label

extension studies (977 patients). Ziconotide was given to 173 patients (14%), almost all of whom had noncancer pain, for at least 1 year. The mean final dose was 17.6 mcg/day (0.73 mcg/h).

N-type voltage-sensitive calcium channels are present in brain tissue and are concentrated in the cerebellum; therefore, many of the neurologic adverse events associated with ziconotide reflect altered cerebellar function or blockade of spinocerebellar pathways and/or basal ganglia (e.g., dizziness, nystagmus, gait abnormalities, ataxia). Ziconotide may also inhibit central autonomic pathways, resulting in nausea, vomiting, urinary retention, amblyopia, and hypotension.

In general, the adverse effects of ziconotide using faster dosage titration regimens seem to be more severe and unpredictable than those observed with opioids.[12] In some cases, severe nervous system adverse events were persistent. The slower dosage titration regimen seemed to reduce the incidence and severity of adverse events and substantially decreased the risk of confusion.

Ziconotide will not prevent withdrawal symptoms related to weaning opioid therapy.

Contraindications

Previous history of psychosis.

Any other concomitant treatment or medical condition that would render IT administration hazardous (e.g., infection at the microinfusion injection site, uncontrolled bleeding diathesis, spinal canal obstruction that impairs circulation of CSF).

Concomitant IT chemotherapy (see Drug Interactions, page 14).

Hypersensitivity to ziconotide or formulation components.

Warnings

Severe psychiatric symptoms and neurologic impairment. Monitor patients frequently for hallucinations, cognitive impairment, mood changes, and altered consciousness. Ziconotide may be interrupted or discontinued abruptly without risk of inducing withdrawal symptoms. Patients should be advised against engaging in hazardous activity requiring mental alertness or motor coordination. There may be additive effects with other CNS-depressant drugs; ziconotide dosage may need to be decreased.

Precautions

Meningitis and Other Infections. Meningitis occurred in 3% (40 cases) of the ziconotide group and 1% (1 case) in the placebo group. Of the 41 cases of meningitis, 37 occurred during ziconotide and 1 during placebo treatment (total, 38 [93%]) using external infusion systems. Treatment of meningitis usually involves removal of the ziconotide microinfusion device.

Cognitive and Neuropsychiatric Adverse Events. Various neuropsychiatric adverse events were reported during ziconotide treatment (Table 4). Cognitive impairment may be slow to develop (several weeks) and to resolve after discontinuation of ziconotide infusion (3 to 15 days). Elderly patients (≥ 65 years of age) may have a greater risk of confusion. Ziconotide may cause or worsen depression. The incidence of suicide, suicide attempts, and suicide ideations was higher on ziconotide (0.27/patient year, 3 cases) than placebo treatment (0.10/patient year, 1 case). Acute psychiatric events were reported in ziconotide-treated patients (Table 4). Patients with preexisting psychiatric disorders may be at higher risk.

Table 4 Cognitive and Neuropsychiatric Adverse Events (% of patients)

Adverse Events	Ziconotide N = 1254 662 patient-years
CNS and Cognitive Symptoms	
Confusion	33.0%
Memory impairment	22.0%
Speech disorder	14.0%
Aphasia	12.0%
Thinking abnormal	8.0%
Amnesia	1.0%
Suicide	0.2%
Acute Psychiatric Disturbances	
Hallucinations	12.0%
Paranoid reactions	3.0%
Hostility	2.0%
Delirium	2.0%
Psychosis	1.0%
Manic reactions	0.4%

Reduced Level of Consciousness. Unresponsiveness or stupor, without respiratory depression, occurred in 2% of patients. Concomitant treatment with antiepileptics, neuroleptics, sedatives, or diuretics may increase the risk of depressed levels of consciousness.

Increased Serum Creatine Kinase (Muscle Isoenzyme, CK-MM). Increased serum creatine kinase (CK) concentrations above the upper limit of normal (ULN) occurred in 40% of patients and CK concentrations ≥ 3 times the ULN was observed in 11% of patients during (mostly open-label) clinical studies. Symptomatic myopathy with electromyographic findings (1 case) and acute renal failure with rhabdomyolysis and severe CK elevations (17,000 to 27,000 IU/l; 2 cases) occurred. Most cases occurred within 2 months of starting treatment, although time to occurrence was variable. Serum CK should be monitored periodically (e.g., every 2 weeks for first month and monthly as appropriate thereafter) during ziconotide treatment and as clinically indicated (e.g., new neuromuscular symptoms) or in the setting of reduced physical activity.

Pregnancy Category C. Continuous intravenous infusion of ziconotide was embryolethal but not teratogenic in rats. No well-designed studies have been conducted in pregnant women. Consider the potential benefits versus risks before considering IT ziconotide therapy.

Serious Adverse Events

In the slow titration clinical trial, the incidence of any serious adverse event (SAE) was 11.6% on ziconotide (13/112) and 9.3% (10/108) on placebo (difference, 2.3%), and 1.8% and 1.9% of patients were considered to have treatment-related SAEs. Nervous system SAEs occurred in 4.5% (5/112) and 1.9% (2/108) of ziconotide and placebo patients, respectively. One placebo patient died. These results contrasted with the initial safety database from the faster dosage titration trials (Studies 95-001 and 96-002), in which 38.1% of all patients (many with comorbid conditions) developed SAEs, 14% were considered treatment-related, and 76 deaths— including 3 in which ziconotide could not be ruled out as a causative/contributing factor (2 aspiration pneumonia, 1 suicide)—occurred among ziconotide-treated patients.

A number of case reports document serious psychiatric adverse events particularly following initiation at high doses (0.2 to 0.4 mcg/h) and fast titration (increments made every 12 to 48 hours).[1,8] These serious events included prolonged delirium and agitation, unresponsiveness (even to sternal rub), nystagmus, ataxia, bradycardia, orthostatic hypotension, periods of apnea, and difficulty voiding/urinary retention. After resolution of symptoms weeks to months later, patients are amnestic to the adverse events. Pain was not always reduced despite the toxic doses. In one case, intractable *delirium and agitation* developed during ziconotide therapy (14.4 to 15.6 mcg/d) in a patient who had a childhood history of hallucinations and a history of postoperative meperidine-related delirium and hallucinations.[8] The patient was managed with physical restraint, pharmacologic paralysis, and artificial ventilation. The delirium resolved only after electroconvulsive therapy. The protracted time course of some of the SAEs raised concern that ziconotide may produce irreversible CNS injury, although preclinical studies did not demonstrate persistent CNS toxicity.

Common Adverse Events

The most common adverse events (≥ 25%) reported in all ziconotide clinical trials were dizziness, nausea, confusion, headache, somnolence, nystagmus, asthenia, and pain.

Shown in **Table 5** are the most frequently reported treatment-emergent adverse events that occurred more commonly during slowly titrated ziconotide than placebo (regardless of causality), including more frequent adverse events (≥ 10%) and adverse events reported on ziconotide but not on placebo.

Table 5 Incidence of Treatment-emergent Adverse Events Reported More Commonly on Ziconotide than Placebo in Slow Titration Clinical Trial

	Ziconotide N = 112	Placebo N = 108
Adverse Event	**% of patients**	
Reported in ≥ 10% of Patients in Either Treatment Group		
Any AE	93	82
Body as a Whole	*57*	*42*
Asthenia	22	12
Headache	15	12
Pain	11	7
Digestive	*60*	*51*
Nausea	41	31
Diarrhea	19	17
Vomiting	15	13
Anorexia	10	5
Nervous System	*81*	*51*
Dizziness	47	13
Somnolence	22	15
Confusion	18	5
Ataxia	16	2
Abnormal Gait	15	2
Memory Impairment	12	1
Hypertonia	11	5
Special Senses	*20*	*11*
Abnormal Vision	10	4
Urogenital	*22*	*12*
Reported on Ziconotide and Not on Placebo		
Urinary Retention	9	0
Nystagmus	8	0
Hallucinations	7	0
Vertigo	7	0

The incidence of pain as an adverse event was not statistically significantly different in the ziconotide and placebo groups. Nonetheless, in earlier trials (Studies 95-001 and 96-002), pain as an adverse event ("pain exacerbation") was more common on ziconotide than placebo. Paradoxical hyperalgesia cannot be excluded.

IT catheter complications and cutaneous surgical complications assessed by investigators as related to ziconotide therapy were each reported in ≥ 2% of patients during clinical studies.

Tolerability

Serious adverse events and withdrawals due to adverse events were less frequently reported when IT ziconotide was titrated slowly over 21 days rather than using a faster dosage titration schedule. In the slow titration trial, the adverse events that led to withdrawal of therapy were dizziness (2 cases), nausea, agitation, and tremor (1 case each). In the faster titration trials, 50.6% of ziconotide patients (N = 1048) and 6.6% of placebo patients (N = 151) withdrew due to an adverse event, most commonly confusion (11.7% of ziconotide and 0.7% of placebo patients).[11]

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials* (page 19).

Overdosage

Pump programming errors and incorrect drug concentrations may result in ziconotide overdoses. Patients who received higher than the maximum protocolled dose in clinical studies (912 mcg/d) developed exaggerated pharmacologic effects (e.g., ataxia, nystagmus, dizziness, stupor, unresponsiveness, spinal myoclonus, confusion, sedation, hypotension, word-finding difficulties, garbled speech, nausea, and vomiting). Symptoms resolved within 24 hours after temporary or permanent discontinuation of the IT ziconotide infusion (CSF half-life, 4.6 h; plasma half-life, 1.3 h). Unlike opioids, ziconotide was not associated with respiratory depression, although episodes of apnea associated with severe delirium, agitation, and unresponsiveness, were reported in a patient who developed toxicity after protocolled dosing of ziconotide.[1]

There is no known antidote for treating ziconotide toxicity as there is naloxone for reversing opioid overdose.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name ziconotide: Zidovudine (injectable)

LA/SA for trade name Prialt: Primabalt, Promit (both injectable)

Drug Interactions

Formal pharmacokinetic drug-drug interactions have not been performed. IT ziconotide is not expected to interact pharmacokinetically with other drugs because of low plasma drug concentrations, low (50%) plasma protein binding, and likely rapid and complete degradation by endopeptidases and exopeptidases present throughout the body. It is not metabolized by the cytochrome P450 system and other Phase I biotransformation processes.

Pharmacodynamic interactions are theoretically possible because N-type calcium channels are widely distributed, numerous drugs affect transcellular calcium movement, and other ion channels in the same nerve distribution may be affected by other drugs.

IT Opioids. Use of IT opioids in combination with ziconotide has not been assessed in clinical studies and is not recommended at this time. Systemic opioids were used concurrently in more than 90% of patients treated with IT ziconotide and in 98% of patients in the slow titration trial. Ongoing clinical trials are evaluating IT morphine plus ziconotide.

CNS Depressants (antiepileptics, neuroleptics, sedatives). Concomitant use of CNS depressants may increase the risk of CNS adverse events.

Diuretics. Diuretics may decrease CSF turnover. Although there is no consistent evidence suggesting that concomitant use of ziconotide and diuretics may increase the risk of adverse events,[11] the U.S. product information advises that patients taking diuretics may be at higher risk of depressed consciousness.

IT Chemotherapy. The EMEA Scientific Discussion advised that ziconotide is contraindicated in combination with IT chemotherapy because of increased risk of infection (due to multiple instrumentation of the subarachnoid space) and possibly unpredictable ziconotide CSF kinetics and effects (due to altered CSF flow dynamics from co-administering chemotherapy via an indwelling IT catheter).[11]

Stability and Compatibility of Combination IT Therapy

There is no available data on the stability and compatibility of admixtures containing ziconotide solution for IT injection and other drugs used intrathecally, such as opioids, bupivacaine, clonidine, and baclofen.

Acquisition Costs

The estimated annual drug cost per patient for IT ziconotide is about $14,779 to $17,859. These figures do not include the cost of the infusion devices.

Table 6 Drug costs of ziconotide

Drug	Volume (ml)	Cost	Cost / Day / Patient	Cost / Year / Patient
Ziconotide 25 mcg/ml	20	$2935.83	$48.93[†]	$17,859[†]
Ziconotide 100 mcg/ml	1	$587.16	$40.49[‡]	$14,779[‡]
Ziconotide 100 mcg/ml	5	$2935.83	$48.93[‡]	$17,859[‡]

[†] Calculated using a pump refill expiry of 60 d
[‡] Calculated using an average dose of 6.9 mcg/d and pump refill expiry of 60 d

Pharmacoeconomic Analysis

There are no cost-effectiveness pharmacoeconomic analyses on ziconotide.

In a model-based budget impact analysis performed by the manufacturer, 29 out of 1 million theoretical health care plan participants were estimated to be candidates for receiving ziconotide therapy (i.e., those who failed IT primary opioid monotherapy [morphine], failed morphine screening and passed ziconotide screening, or not IT opioid candidate and passed ziconotide screening). The model predicted that one year of ziconotide therapy in the 29 patients would result in a net increase in total costs (non-pump plus pump costs) by 8 cents per member per month and by $988,673 overall, at an average net cost per ziconotide-treated patient of $34,092.

Conclusions

Ziconotide is the first non-opioid IT treatment alternative for the management of patients with refractory chronic pain and only the fourth analgesic agent used intrathecally that is actually available in a formulation FDA-approved for IT administration. It has arguably undergone the best quality and most extensive efficacy and safety evaluations of any IT analgesic or anesthetic available. There are no pharmacologic treatment alternatives that are approved for IT administration on the VA National Formulary.

Ziconotide has a narrow therapeutic margin. In patients with refractory chronic pain, the average magnitude of reduction in pain intensity obtained during ziconotide therapy is relatively small, mainly because of limited tolerability due to adverse events. Ziconotide has been shown to be efficacious for various types of pain and there may be substantial benefits at the individual level. A small subgroup of patients refractory to standard treatments may experience complete pain relief and improved quality of life after IT ziconotide therapy. Although it has been shown to be efficacious relative to placebo in opioid-refractory pain, its efficacy relative to active agents and its effectiveness in actual clinical practice (with less intensive monitoring than those in clinical trials) have not been evaluated.

IT ziconotide may have some advantages over opioids. Its main advantage is that tolerance does not develop during long-term therapy, although this is based on limited long-term data. Ziconotide is not associated with addiction and lethal overdose, and vomiting and constipation were not commonly reported. Periodic apnea has been reported at toxic doses,[1] but ziconotide is not considered to be a respiratory depressant. Long-term studies are needed to confirm that IT ziconotide is not associated with cardiac toxicity, endocrine effects, and spinal catheter-tip inflammatory masses / granulomas (seen with higher doses of IT morphine and IT hydromorphone[2]).

There are important and uncertain trade offs associated with IT ziconotide therapy. The risks of serious adverse events in any individual are unpredictable, and in some patients, ziconotide therapy may result in more harm than benefit. Neuropsychiatric adverse events are usually manageable but may take weeks to months to resolve and, in some instances, may require prolonged hospitalization and intensive care monitoring. The long-term safety of ziconotide is unclear because of extremely limited experience with extended use.

Ziconotide requires specialized administration techniques, specific external or implantable infusion devices, and is best suited for patients who can be carefully followed by trained personnel and who have convenient access to medical facilities.

Further studies are needed to verify the recommended slow dosage titration method as the optimal dosing regimen in actual clinical practice; confirm a lack of tolerance to the analgesic effects; identify subgroups of patients who have higher benefit-to-risk ratios; characterize the long-term benefits and risks of IT ziconotide therapy; expand the efficacy and safety database on elderly patients, non-Caucasian races, and patients with cancer; and evaluate the efficacy and safety of combination therapy with ziconotide and other IT analgesics.

Recommendations

Although IT ziconotide may offer some advantages over IT opioids, it is recommended that ziconotide be made available only to individuals who require IT therapy for chronic pain refractory to multiple forms of pain management. In addition, patients receiving ziconotide must be under the care of a VA pain specialist or anesthesiologist, who can explain and help the patient understand the potential benefits and harms of IT ziconotide therapy. Because long term safety and efficacy data are limited, IT ziconotide should not be added to the VA National Formulary.

IT ziconotide dosage titration should be slow and individualized to patient response (pain relief and functional ability) and tolerability. Clinicians should exercise caution when using ziconotide in patients 65 years of age and older.

Proposed Inclusion Criteria

Facilities should consider using a review committee to evaluate requests to prescribe intratehcal ziconotide.

Patients who meet ALL of the following criteria may receive IT ziconotide:

- Patient is under the care of a pain specialist or anesthesiologist who has experience in the management of polypharmacy with IT pain medications and has the resources to provide 24/7 care for problem management.
- Patient has chronic cancer or noncancer pain
- Patient has had documented inadequate response, intolerable adverse effects, or contraindication to
  systemic opioids plus adjuvant agents (e.g., antidepressants and/or antiepileptics) OR IT morphine (maximum tolerated dose not exceeding 15 mg/d) OR off-label IT hydromorphone (maximum tolerated dose not exceeding 10 mg/d)[2] (in IT or epidural screening or treatment) AND
  IT clonidine, IT bupivacaine, AND a combination of IT analgesics.
- Patient has or will have an implanted Medtronic SynchroMed® EL or SynchroMed® II Infusion System, or Simms Deltec CADD Micro® External Microinfusion Device and Catheter.
- For noncancer pain, patient has received psychological evaluation (to help promote good therapeutic outcomes from IT therapy).

Proposed Exclusion Criteria

Patients who meet any of the following criteria should NOT receive IT ziconotide:

- Contraindication to IT ziconotide therapy:
  - Previous history of psychosis.

  - Any other concomitant treatment or medical condition that would render IT administration hazardous (e.g., infection at the microinfusion injection site, uncontrolled bleeding diathesis, spinal canal obstruction that impairs circulation of CSF).
  - Concomitant IT chemotherapy.
  - Hypersensitivity to ziconotide or formulation components.
- Active suicidal or homicidal behavior, major uncontrolled depression or anxiety, or serious cognitive deficits.

Discontinuation Criteria

- NO improvement in either pain or functional ability during the first 3 weeks of IT ziconotide therapy.

Weigh Risks Versus Benefits

- Patients with refractory pain will very likely require concomitant therapy with systemic or IT analgesics. Weigh the potential risks and benefits before deciding to use IT ziconotide concomitantly with IT opioids or other IT agents, such as bupivacaine, clonidine, and baclofen. The stability of these analgesics in admixtures is unknown. The efficacy and safety of only ziconotide monotherapy has been evaluated in clinical trials.
- Consider potential risks versus benefits of using IT ziconotide in patients who do not have timely access to medical facilities, lack family or social support to assist with patient monitoring at home, and would have difficulty adhering to follow-up visits.

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Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to June 2006) and the OVID Cochrane Central Register of Controlled Trials using the search terms ziconotide and Prialt. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials and noncontrolled observational extension and safety studies were included in this section. Information on controlled trials reported in a review article were also included.[13]

Abbreviations Used in Appendix Tables

↓, Decrease or reduction
Δ, Change
BL, Baseline
BPI, Brief Pain Inventory
CPRS, Category Pain Relief Score (6-point scale)
CGIP-vg/ex, Clinical Global Impression Overall Pain Control-"very good" or "excellent"
CGIS-al/cs, Clinical Global Impression of Patient Satisfaction scale-"a lot" or "complete satisfaction" with therapy
CPRS, Categorical Pain Relief Scale
HAM-D, Hamilton Depression Scale
LO, Last observation
MTD, Maximum tolerated dose
MMSE, Mini Mental State Examination
N_A, Number analyzed
N_R, Number randomized
PI, Product Information
SAE, Serious adverse event
TOPS, Treatment Outcomes in Pain Survey
TRSAE, Treatment-related serious adverse event
ULN, Upper limit of normal
VASPI, 100-mm Visual Analog Scale for Pain Intensity
VASPI-30 or -50, 30% (or 50%) or greater improvement from baseline in VASPI
VASPI-30 WOC, VASPI-30 without opioid change (increase in dose or change in type of concomitant opioid therapy)
WD, Withdrawal
WDAE, Withdrawal due to adverse event.

Appendix Table 1 Placebo-controlled trials of IT ziconotide in chronic pain

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results	Author's conclusions *Critique*
Rauck (2006)[14]; Product Information[4,15] U.S. Trial #301 "Slow Titration Trial" MC (39) DB PC RCT ITT, LOCF, sensitivity analyses; post hoc BOCF by FDA N_R = 220 Outpatients	*Inclusion criteria:* *For screening*—Severe chronic pain inadequately controlled by systemic and/or IT analgesics; VASPI score ≥ 50 mm; pain of any etiology that warranted the use of IT therapy; programmable SynchroMed infusion system implanted prior to study. For randomization—VASPI ≥ 50 mm; successful discontinuation of all IT medications; stabilized regimen of systemic analgesics and other necessary medications. *Main Exclusion Criteria:* known sensitivity to ziconotide; contraindications to IT therapy; IT medications (these were discontinued before randomization)	Ziconotide IT 2.4 mcg/d (0.1 mcg/h), increased by 1.2–2.4 mcg/d (0.05–0.1mcg/h) 2–3 times/wk Min titration interval: 24 h Max allowable dose: 21.6 mcg/d (0.9 mcg/h); Max actual dose: 19.2 mcg/d (0.8 mcg/h) Final mean dose: 6.9 mcg/d (0.29 mcg/h) Duration: 21 d All IT medications were tapered off over 1 to 3 wk; patients were maintained on a stable regimen of non-IT analgesics, including opioids, for at least 7 d before randomization.	Ziconotide vs. Placebo Age, y, mean: 52.5 vs. 54.8 Sex, M/F, % of pts: 47.3/52.7 vs. 50.9/49.1 Race, Caucasian, % of pts: 95.5 vs. 91.7 Mean baseline VASPI score: 81 mm in both groups Neuropathic pain: 73.6% (Failed Back Surgery Syndrome, FBSS, 58%) Co-morbidities: NR Of 248 patients enrolled at screening, 198 (79.8%) were receiving IT morphine and/or other IT drugs and required weaning; weaning was successful in 92.9% of these patients. Refractory to treatment, including IT morphine, IT bupivacaine, and/or IT clonidine, as well as systemic analgesics and adjunctive therapy: 97% Previously treated with IT morphine (90%), > 1 IT drug (58%), oral opioids (99%), spinal cord stimulation (40%), spinal surgery (67%), neuroablation (10.5%), physical therapy (94%). Median IT opioid prior to dosing, expressed in oral morphine equivalents: 1200 mg/d (range, 13–51,000)	N_R = 220 Efficacy Results Outcome — ZCN N = 112 — PBO N = 108 — Diff (95% CL) Mean % ↓ in VASPI, BL to d 21 (PEV): 14.7 [12 in PI] — 7.2 [5 in PI] — 7.5* [7 (0.4, 13)] in PI] Mean % ↓ in VASPI, BL to end of initial titration: 14.7 — 7.2 — 7.5** (NR) VASPI-30 Responders, % (LOCF, BOCF): 16.1 — 12.0 — 4.1† (–6.0 to 14.1) VASPI-50 Responders, % (BOCF): 8 — 2 — 6 (NR) VASPI-100 Responders, % (BOCF): 2 — 1 — 1 (NR) CGIS-al/cs, %: 28 — 12 — 16 (NR) CGIP-vg/ex, %: 12 — 1 — 11 (NR) Use of non-IT opioids, %: –24 — –17 — –7† (NR) * p = 0.04 ** p = 0.036 † NSD Changes in VASPI using ITT with LOCF analyses were confirmed in analyses not using LOCF. Mean % change in VASPI: significant at Week 1 (p = 0.0026) but not at Week 2 (p = 0.12) Effect of ZCN on pain was variable over time in some patients (e.g., improved in VASPI score in first or second week but did not maintain pain relief in third week, or showed no early reduction in VASPI scores but improved by third week). Significant (p < 0.05) treatment difference seen in change in Global McGill Pain Relief total score; sleep pattern and sleep quality on a sponsor-defined sleep questionnaire; CPRS; and BPI enjoyment of life subscale. NSD between treatment groups: CPRS (p = 0.0596); quality of life on TOPS questionnaire; most of BPI subscales (sleep, relations, work, mood, walking) % of "Safe" doses (those not followed by dosage reduction): 59%	No deaths were reported during the study. (In the OL extension, 3 deaths were reported in the 120-day Safety Update; these deaths were considered unlikely to be related to ziconotide.) Outcome — ZCN N = 112 — PBO N = 108 — Diff (95% CL) Any WD, %: 8.0 — 7.4 — 0.6 (NR) WDAE, %: 5.4 — 4.6 — 0.8† (NR) SAE, %: 11.6 — 9.3 — 2.3† (NR) TRSAE, %: 1.8 — 1.9 — –0.1 (NR) ≥ 1 AE, %: 92.9 — 82.4 — 9* (NR) * p = 0.023 NSD between groups in WDAEs and SAEs. ZCN-related SAEs: chest pain, hypertension, ataxia, dizziness, and neuralgia The rate of SAEs (11.6% on ZCN) was much lower than the rate of 30.6% seen in a trial that used faster dosage titration (Staats, 2004). Most common AEs (≥ 10% of patients) on ZCN: abnormal gait, abnormal vision, anorexia, asthenia, ataxia, confusion, diarrhea, dizziness, headache, hypertonia, memory impairment, nausea, pain, somnolence, and vomiting. AEs rated mild or moderate: 83.6% vs. 83.8% Median onset of AEs: 3 to 9.5 d Time to resolution of AEs: Up to 2 wk NSD between treatments in changes from baseline to termination in total MMSE score and HAM-D total score. No changes in vital signs or ECG. Lab abnormalities: increased uric acid, lactate dehydrogenase, creatine kinase (CK). Two ZCN patients had CK levels > 3 times ULN at baseline (198 IU/l); these 2 patients plus an additional 3 patients had increases in CK > 3 times ULN at study end point. One of these 5 patients developed an SAE (hypokalemia, considered not related by investigator); and 4 developed muscular symptoms (myalgia, muscle cramps). Analysis of concomitant antidepressant or anxiolytic therapy revealed no trends in AEs.	Using the slow dose titration regimen, the degree of pain relief was less than that noted in two previous trials, but patient retention and safety profiles were better. *Treatment difference in VASPI score changes was relatively small and smaller than the previous inpatient trials. This may be due to lower doses, different setting, longer study duration, or greater number of refractory patients enrolled in this trial.* Despite high frequency of severe and SAEs, the majority of patients (91.1%) planned to participate in the OL extension study. *Fair quality* *External Validity: Applicable to selected group of outpatients with severe intractable pain requiring IT therapy; probably applicable to veterans; limited data in non-caucasians.*

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results	Author's conclusions *Critique*
Staats (2004)[7] Prialt Manufacturer Dossier, FDA Medical Review,[16] EMEA Scientific Discussion,[11] Mathur (2000)[13] Trial 95-001 U.S., Australia, Netherlands MC (32) DB PC RCT with partial CO; 2:1 randomization; stratification within center by cancer or AIDS diagnosis and by history of IT morphine use Evaluable and mITT analyses (N_R = 111; N_A = 108 for efficacy; N_A = 112 for safety, including 1 OL compassionate-use patient) Hospitalized patients	*Inclusion criteria:* Cancer or acquired immune deficiency and mean VASPI score ≥ 50 mm during the 3 d before enrollment *Exclusion criteria:* Pregnancy; sepsis; inadequately treated infection; dementia; untreated affective disorders; nonpatent spinal canal; severe asthma; cardiac facilutre; bradyarrhythmias; neurocardiogenic syncope	After a screening and preinfusion evaluation (1–7 d) and 5- or 6-day initial titration phase, VASPI-30 responders continued on therapy for 5–6 d. Nonresponders crossed over , re-titrated, and received opposite therapy for 5–6 d. Originally initiated ziconotide at 5 ng/kg/h; modified to 9.6 mcg/d (0.4 mcg/h), increased q12h to MTD (N = 48). Modified initial dose to ≤ 2.4 mcg/d (0.1 mcg/h), titrated increments q24h; max. 57.6 mcg/d (2.4 mcg/h) Mean final dose: 21.8 mcg/d (0.91 mcg/h)	Ziconotide vs. Placebo Age, y, mean: 55.3 vs. 56.6 Sex, M/F: 34/34 vs. 20/20 Race, Caucasian: 83.8% vs. 95% Systemic analgesics: 94.1% vs. 95% Cancer: 87% AIDS: 13% Mean BL VASPI: 75 mm	Efficacy Results, Evaluable Patients [mITT, if different from evaluable]] Outcome / ZCN N = 68 / PBO N = 40 / Diff (95% CL) Mean % ↓ in VASPI, BL to end of initial titration (PEV): 53.1 [51.4%] / 18.1 / 35.0* (NR) VASPI-30 WOC Responders, %: 50.0 [47.9] / 17.5 / 32.5 (NR) VASPI-50 Responders, % (post hoc): 42.3 / 17.5 / 24.8 (NR) VASPI-100 Responders, %: 7.4 / NR / — CPRS-M/C Responders, %: 53.0 / 17.5 / 35.5* (NR) Use of non-IT opioids, %: –9.9 / +5.1 / –15.0 * p < 0.001 Mean % reduction in VASPI score at the end of crossover phase was 44.9% among patients who crossed over from PBO to ZCN (N = 26) and 4.2% for those who crossed over from ZCN to PBO (p=0.005). p < 0.05: CPRS response rate NSD: WBPI subsets, linear correlation between % Δ in VASPI and % Δ in opioid use at end of initial titration period. % of "Safe" Doses (those not followed by dosage reduction): 5%	Deaths: 13, most related to patient's terminal illness. According to the FDA medical reviewer,[16] some deaths appeared to be causally related to neuropsychiatric AEs. Outcome / ZCN N = 71 / PBO N = 40 / Diff (95% CL) Any WD, %: 34.7 / 27.5 / 7.2 (NR) WDAE, %: NR / NR / NR SAE, %: 30.6 / 10.0 / 20.6 (NR) ≥ 1 AE, %: 97.2 / 72.5 / 24.7 Most common SAEs on ZCN during initial titration: confusion, somnolence, urinary retention Considered possibly related to ZCN: suicide (1 case) Considered probably related to ZCN: pneumonia (1 case) Meningitis: 5 cases on ZCN vs. 2 on PBO Most common AEs on ZCN vs. PBO: somnolence, confusion, abnormal gait, nausea and vomiting, fever, postural hypotension, urinary retention, dizziness, nystagmus. Lower initial dosage, smaller dose increments, and less frequent dose titrations tended to decrease the incidence of AEs.	Data integrity was called into question when FDA inspection of one site revealed that patients had been unblinded to study treatment due to study misconduct. There were also numerous protocol violations. Too few patients were treated with the revised and proposed dosing regimen to adequately assess efficacy and safety. *Poor quality (see above)* *External validity: Limited because of uncertainties about data integrity and benefit/risk assessments.*
Mathur (2000)[13] Trial 96-002	*Inclusion criteria:* Intractable	IT Ziconotide vs. Placebo	Age, y, mean: 52 Age, gender, race: similar	Efficacy Results, Evaluable Patients [mITT, if different from evaluable] ZCN / PBO / Diff		No power calculations

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results	Author's conclusions *Critique*
MC DB PC RCT mITT N = 257; N_A = 240 Hospitalized patients	chronic nonmalignant pain, VASPI ≥ 50 mm while on stable oral and systemic analgesics and who currently had an IT pump or clinical need for such a pump	Initial titration phase: 6 d Initial and max doses: Same as modified doses in Staats (2004) Mean final dose: 24.5 mcg/d (1.02 mcg/h) VASPI-30 responders who had no increase in concomitant opioid use and no change in type of opioid used were eligible to enroll into a long-term OL extension study	between treatment groups (no data provided) Mean oral morphine equivalents: 528 mg/d Previous IT morphine: 58% On opioids: > 70% On antidepressants: > 60% Neuropathic pain: 76% Ziconotide vs. Placebo Mean baseline VASPI score higher on ZCN: 80.2 vs. 76.9 mm "Neuropathic" pain: 77.8% vs. 77.3%	Outcome / ZCN N = 162 / PBO N = 78 / Diff (95% CL) Mean % ↓ in VASPI, BL to end of initial titration (PEV): 30.7 [31.2] / 5.9 / 24.8* (NR) VASPI-30 WOC Responders, %: 33.3 [33.7] / 13.9 [12.8] / 19.4** [20.9]** CPRS M/C Responders, %: 43 / 18 / 25** (NR) VASPI-50 Responders, % (post hoc): 28.4 / 7.0 / 21.4** (NR) * p = 0.0002 ** p ≤ 0.002 Mean % ↓ in VASPI among patients refractory to IT morphine (N = 66): ZCN –18.4 vs. PBO +6.4 (p = 0.027) Improved on WPBI subsets for mood, sleep, and enjoyment of life: % of patients higher on ZCN than PBO (no data provided) (p ≤0.01). Mean percent change in Global McGill pain scores: 23.6% vs. 9.2% (p = 0.014 in article / p = 0.028 by EMEA analysis). No significant linear correlation between % Δ in VASPI and % Δ in opioid use. % of "Safe" doses: 20%	Outcome / N=169 / N=86 / (95% CL) Any WD, %: 28.4 / 29.1 WDAE, %: NR / NR / NR SAE, %: NR / NR / NR ≥ 1 AE, %: NR / NR / NR AEs significantly (p < 0.05) more common on ZCN than PBO: vestibular effects (nystagmus, abnormal gait, dizziness), nausea and vomiting, amblyopia, and urinary retention	reported. *External validity: May be limited because numerous amendments to the dosing protocol were made, making interpretation of results difficult..*

Appendix Table 2 Pooled Analysis of Major Efficacy Trials (Studies 95-001 and 96-002)

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results	Author's conclusions *Critique*
EMEA Scientific Discussion[11] Pooled analysis mITT	See Studies 95-001 and 96-002	See Studies 95-001 and 96-002	See Studies 95-001 and 96-002	Outcome: Mean % ↓ in VASPI, BL to end of initial titration (PEV) — ZCN N = 162: 37.3; PBO N = 78: 9.8; Diff (95% CL): 27.5* (19.4–35.6) VASPI-30 WOC Responders, % — ZCN: NR; PBO: NR; Diff: NR p < 0.001 The difference in mean % improvement in VASPI score between ZCN and PBO was somewhat greater for cancer pain patients (Study 95-001) vs. noncancer pain patients (Study 96-002): 33.3% vs. 25.2%. The cumulative proportion of responders by dose level at end of initial titration showed that 92% of responders (in pooled ITT analysis of all dosing regimens) and 90% of responders (in pooled ITT of 0.1–2.4 mcg/h regimen) responded by a ZCN dose of 1.2 mcg/h.	NR	NR

Appendix Table 3 Long-term, open-label extension studies

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results	Author's conclusions *Critique*
FDA Medical Review[16] 14-month extension, Study 352, interim report (240 days) (ongoing) N=85 (37 who were on ziconotide and 48 placebo from Study 301)	Completed Study 301 or 302 and wished to be treated with ziconotide.	Ziconotide Gradual increments made over 14 mos.	NR	NR	NR	Most patients terminated ZCN therapy after a few months.
Staats (2004, abstract)[17] Study 95-002 MC OL extension study N_A = 145 of 155 enrolled	*Inclusion criteria:* Malignant or nonmalignant chronic pain; demonstrated analgesic response to ziconotide in previous placebo-controlled trials. Participated in Studies 95-001 and 96-002.	IT Ziconotide maintained at optimal dose established in previous trial for first 30 d (mean, 14.4 mcg/d or 0.6 mcg/h), then dosage adjustable at not more than twofold increase per 12-h period.	Age, y, mean: 55 (range, 24–85) Cancer pain, n: 48 Noncancer pain, n: 107	Days in study: mean, 288 d; median, 86 d. Treated for at least 360 d, n: 34 ZCN Tx Time Point 4 wk / 12 mo / LO Outcome: Mean % Δ in VASPI from BL N = 139 / N = 31 / N = 144 37.2* / 45.8* / 36.9* * p < 0.0001 vs. baseline The apparent increase in efficacy was considered to reflect selection bias (n decreased with time). Dosing was stable among patients who were treated for at least 12 mo (N = 31; mean dose at Month 12, 14.4 mcg/d or 0.6 mcg/h).	None	*External Validity: Results may apply to patients with intractable severe chronic cancer or noncancer pain*
EMEA Scientific Discussion[11] Study 302 MC 3-wk OL outpatient study with optional extension phase (ongoing) Planned N=150	IT-naïve patients with chronic, severe pain of either cancer or noncancer original; VASPI score ≥ 40 mm	Includes a treatment phase involving IT Ziconotide via external pump, uptitrated at ≤ 0.1 mcg/h NMT once every 24 h over 3 wk Cancer pain patients may be eligible to continued with external system for additional 6 mo. Noncancer pain patients who are suitable for implantable pump will terminate study and be enrolled in Study 352.	NR	NR	NR	—
EMEA Scientific Discussion[11] Study 351 OL long-term extension, longest exposure to ziconotide (ongoing) N=50 over 3 yr	Completed OL long-term studies 95-002 and 98-022	NR	NR	NR	NR	—

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results	Author's conclusions *Critique*
EMEA Scientific Discussion[11] Study 501, ZEST Study MC OL long-term, compassionate use (started January 2004 in U.S. under IND; ongoing)	NR	Ziconotide Initial dose: 0.1 mcg/h Increments: ≤ 0.1 mcg/h every 48 h Max dose: 0.9 mcg/h	NR	NR	NR	—

Appendix Table 4 Open-label observational safety studies

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results	Author's conclusions *Critique*
Ellis (2004, abstract)[18] Study 98-022 MC OL safety study Outpatient setting N_A = 643 of 644 enrolled	Chronic noncancer nociceptive and/or neuropathic pain requiring intraspinal analgesia; no minimum VASPI eligibility criterion	IT Ziconotide started at 2.4 mcg/d (0.1 mcg/h) and titrated over 1 mo to analgesic response; max. increments 0.1 mcg/h once in a 24-h period	"Almost all" previously failed to respond to aggressive conventional therapy for pain control. Most common pain etiologies: back pain, failed back surgery syndrome (FBSS),, complex regional pain syndrome (CRPS), trauma Noncancer pain: 97% Neuropathic pain: 79%	Days on ZCN: mean, 199 d; median, 67 d Treated for at least 360 d, n: 119 ZCN 1 mo Outcome — N = 643 Mean % ↓ in VASPI from BL Back pain — 58.3 FBSS — 50.0 CRPS — 68.2 Trauma — 43.9 Other — 62.0 VASPI-30 Responder, % — 15.9 **Outcome at 1 mo** / **All Pts N = 453** / **Pts with VASPI ≥ 50 mm† N = 394** Mean % ↓ in VASPI from BL: 7.2%* / 18.3** VASPI-30 Responder, %: 31% / — * p < 0.01 ** p < 0.0001 † Comparable population to major efficacy trials; post hoc analysis % of "Safe" doses (those not followed by dosage reduction): 46%		*External Validity: Results may apply to relatively short-term (1 mo) treatment of patients with severe chronic noncancer pain. Unable to assess applicability to veterans because of insufficient information.*