

# ZICONOTIDE FOR CHRONIC SEVERE PAIN

The emerging use of Ziconotide shows potential of becoming a powerful non-opioid analgesic in the pain physician's armamentarium.

By Lynn R. Webster, MD and Keri L. Fakata, PharmD

Ziconotide intrathecal [IT] infusion represents a novel breakthrough in combatting intractable pain. It is a synthetic derivative (*w*-conotoxin) of a toxin isolated from the Magician's cone snail, *Conus magus* (formerly known as SNX-111) and has shown to be a powerful non-opioid analgesic. Its conception began in the early 1970s in the Philippines when, due to lack of resources, native scientist Baldomero Olivera abandoned his work on enzymes involved in DNA synthesis in favor of his passion for shell collecting, preferably the species *Conus magus*. In 1978, he returned to the United States and took a position with the University of Utah with plans to resume his DNA research; however, his focus changed after an inquisitive undergraduate student rotating through his lab performed some crude basic science on Olivera's isolated conopeptides. The astonishing results made Olivera once again abandon his DNA research and form a collaboration with biochemist George Miljanich from the University of Southern California, who had received funding from the National Institutes of Health (NIH) to research conopeptides and their effects on various molecular pathways. Miljanich went on to join a small biotech company and to proceed with the development of SNX-111.<sup>1</sup>

After three decades of trial and error and extensive clinical research, including three double-blind, placebo-controlled multi-center studies and four open-label long-term studies, ziconotide is now the first new FDA-approved IT analgesic since morphine was approved by the FDA over 20 years ago. Ziconotide is one of the most extensively studied new medications prior to FDA approval with experience in over 1,200 patients.

## Mechanism of Action

Ziconotide represents a new class of potent analgesics called neuronal calcium channel blockers (NCCBs). Its exact mechanism of action has not been established in humans; however, animal studies confirm its specificity for N-type voltage-sensitive calcium channels (N-VSCC) found throughout the nervous system and concentrated in the spine on the presynaptic terminals of primary nociceptors. Ziconotide blocks the N-VSCC and prevents release of the excitatory amino acid, glutamate, from the presynaptic terminal, thereby reducing the amount of stimulation at the dorsal horn neurons (see Figure 1).<sup>2</sup> N-VSCC are not affected by dihydropyridine calcium channel blockers, which are commonly used to treat headaches and cardiovascular disease and are known to block L-type calcium channels.<sup>3,4</sup>

Ziconotide does not interact with opioid receptors and, therefore, will not prevent withdrawal symptoms from opioids. Also, tolerance does not develop as seen with opioids.<sup>3,4</sup> Clinicians must be careful to titrate downward other IT medications if their intention is to withdraw the patient from current IT therapy before starting monotherapy with ziconotide.

## Pharmacokinetic Considerations

Ziconotide is a hydrophilic peptide, and its membrane permeability is low thus necessitating direct delivery to the site of action. The elimination half-life of ziconotide is 4.5 hours which is approximately equal to the turnover rate of the cerebral spinal fluid (CSF). Its volume of distribution of 140 ml is also equal to that of CSF, which indicates that it is eliminated by the turnover

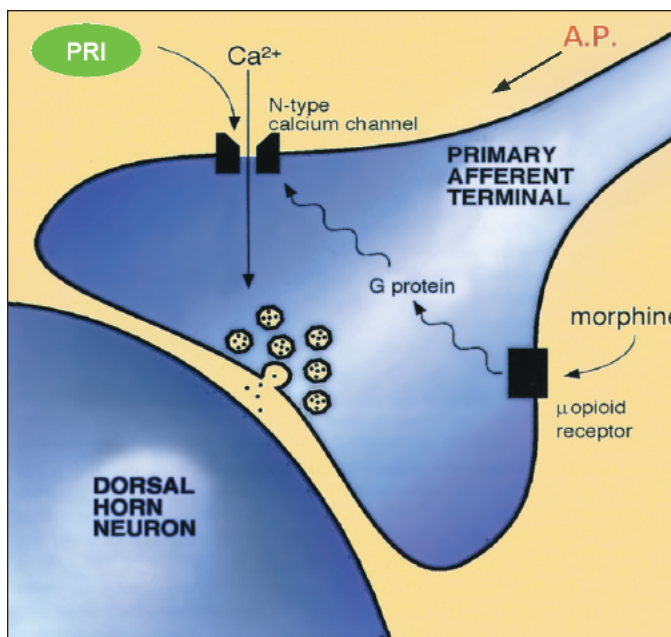


FIGURE 1. Ziconotide Mechanism of Action<sup>2</sup>

of CSF. With continuous IT infusion, once ziconotide reaches systemic circulation, it is expected to be rapidly cleaved by peptidases and proteases present in most organs. The half-life in the systemic circulation is approximately 1.5 hours.<sup>5</sup>

### Indication

Ziconotide is indicated for the management of severe chronic pain in patients for whom IT therapy is warranted and who are intolerant of, or refractory to, other treatments such as systemic analgesics, adjunctive therapies or IT morphine. Ziconotide is approved as a monotherapy.<sup>5</sup> Formal studies with ziconotide in combination with other IT pump medications are now being conducted.

It is important to note that concomitant use of oral opioid analgesics and adjunctive therapies are not contraindicated with ziconotide. The 1,254 clinical trial patients received several non-IT medications with 98% of patients remaining on their oral opioids, 66% on anxiolytics, 52% on anticonvulsants, 47% on neuroleptics and 34% of patients on sedatives for pain management and symptom control. Patients on several central nervous system (CNS) depressant medications are at higher risk of having confusion and dizziness or an altered level of consciousness.<sup>5</sup>

### Boxed Warning

Ziconotide has a black box warning stating that a patient with a pre-existing history of psychosis should not be treated with ziconotide due to the risk of severe psychiatric symptoms and neurological impairment that may occur during therapy. It advises that all patients should be monitored for cognitive impairment, hallucinations or changes in mood and consciousness that would be consistent with serious psychiatric conditions or neurological impairment.<sup>5</sup>

At this time, there is no antidote or antagonist for the reversal of adverse events related to ziconotide. If adverse events are severe or intolerable, ziconotide may be immediately removed

from the pump without precipitating withdrawal effects. Ziconotide may worsen depression, including the risk of suicidal ideations. The appropriateness of using ziconotide in patients with psychiatric comorbidities should be left to the judgment of treating physicians.

### Who are candidates?

Potential candidates for ziconotide are patients with severe pain in which IT pump therapy is warranted. Based on the authors' clinical experience, ziconotide appears to be as effective with nociceptive and visceral pain as with neuropathic pain, but prospective studies are needed to determine if there is a difference in efficacy among pain types or pain mechanisms. Ziconotide should not be used with patients who have a known hypersensitivity to ziconotide or L- methionine, an antioxidant in the formulation.

Patients who have a history of pre-existing psychosis or a high baseline of cognitive impairment that occurs with severe dementia or advanced Alzheimer's disease should probably not receive the drug unless the risk/benefit has been fully considered and the family informed of the potential for the underlying mental disease to be worsened. However, a chronic pain patient that is being treated for mild-to-moderate depression and is currently well controlled on an antidepressant may be considered a candidate for ziconotide.

### Administration

Ziconotide is intended for IT pump delivery only; it is not approved for epidural use. Ziconotide is a large peptide that will achieve limited permeability through the dura; therefore it will not likely be effective when administered epidurally. It has been studied in the SynchroMed EL and SynchroMed II Medtronic infusion systems as well as CADD-External Micro Infusion System by Smith Medical MD. Due to the charged nature of the peptide, it is estimated that approximately 17 mcg of ziconotide will adsorb to the titanium walls of the 20 ml SynchroMed EL and 20 ml SynchroMed II pump and an estimated 28-30 mcgs in the 40 ml Synchro Med II pump. This is thought to be a stable binding, and subsequent loss will not occur with each refill. To address this issue, ziconotide prescribing information, included in the manufacturer's package insert, recommends including three (2 ml) rinses with 25mcg/ml (undiluted) ziconotide in a pump that has never had ziconotide. After each 2 ml has been administered into the pump and withdrawn, the pump can be filled with the drug.<sup>5</sup>

The package insert also recommends that providers use the undiluted (25 mcg/ml) formulation for the first pump fill. This formulation comes in only a 20 ml single-use vial. The estimated cost of the 20 ml of 25 mcg/ml is \$3,500. It recommends that the pump be emptied and refilled in 14 days. After the first 14 days, the pump could be refilled with ziconotide at a desired concentration utilizing a stock concentration of 100 mcg/ml and diluting with preservative-free normal saline under aseptic technique. The 100 mcg/ml formulation is available in either a 1 ml or a 5 ml vial. The estimated cost of a 1 ml (100 mcg/ml) vial is \$700, and the cost of a 5 ml (100 mcg/ml) vial is estimated at \$3,500 (see Table 1). All formulations come in single-use vials and are billed as such. Medicare is billed for an entire vial for the patient. Any unused portion of the vial must be discarded.

### Stability, Compatibility and Storage Requirements

Ziconotide concentration can be reduced by two direct (thermal and oxidation) and one indirect (dilution) mechanisms. Ziconotide degrades in the pump over time due to exposure to body temperature around 37° C. It is also sensitive to pH changes and requires a pH around 5.0. Ziconotide is preservative-free but is formulated with free L-methionine, which is used to protect ziconotide from possible degradation due to oxidation. Dissolved oxygen in the IT reservoir chamber could subject ziconotide to oxidation. As a peptide, its degradation products are inactive and non-toxic amino acids. Ziconotide concentration may also become unstable when diluted to working concentrations for the pump. For example, when ziconotide is diluted from 100 mcg/ml 1ml formulation to 10 mcg/ml, this dilutes out the protection from oxidation afforded by methionine by a factor of 10 fold. Currently, there is no custom diluent available for diluting ziconotide to working concentrations, and diluting from the 25mcg/ml formulated vial is not cost effective. Ziconotide concentration can also be effected on initial pump fill; also the dead space or residual volume of the SynchroMed EL and SynchroMed II pumps needs to be considered. The maximum deadspace (residual) volume for the SynchroMed EL is 2.4 ml and 1.4 ml of both the 20 and 40 ml SynchroMed II pumps.<sup>6</sup> This dilution factor is one reason why an initial rinse with ziconotide is recommended.

Ziconotide is stable in excess of 10 years when stored in its lyophilized form at -20°; once formulated it has a shelf life of at least 39 months at 2-8°C. Ziconotide IT infusion requires refrigeration in transit and needs to be stored at temperatures of 2°C to 8°C ( 36° F- 46°F). The ziconotide formulation should not be frozen, and prolonged exposure to light should be avoided.<sup>4,5</sup> Ziconotide must be used within 24 hours once contents are removed from the vial. This is based on United States pharmacopeia standards for IT medications to maintain the quality and sterility of the product.

According to the package insert, IT pumps previously exposed to undiluted ziconotide (25 mcg/ml) formulation is stable in the pump for at least 60 days, whereas diluted ziconotide (100mcg/ml diluted with preservative-free saline to

ZICONOTIDE Vial Size	Content	Acquisition Cost	Actual Wholesale Price (AWP)
25 mcg/cc ( 20 cc)	500 mcg	\$3,040	~ \$3,650
100 mcg/cc (1 cc)	100 mcg	\$608	~\$730
100 mcg/cc (5 cc)	500mcg	\$3,040	~\$3,650

**TABLE 1.** Formulations of Ziconotide.

25mcg/ml) is stable in the pump for up to 40 days.<sup>5</sup> This information was determined from a stability/time curve and is based upon the amount of time it takes ziconotide to lose 10% of its original concentration.

According to abstracts accepted by the 7th Congress of the International Neuro-modulation Meeting in Rome, Italy, on June 10-13 2005, ziconotide (25 mcg/ml) under simulated clinical conditions (SynchroMed II placed in incubator at 37°C) appears to be reasonably stable with 35mg/ml hydromorphone, retaining 88% of its initial concentration up to 25 days with no appreciable changes in hydromorphone concentration. However, it is less stable with 35 mg/ml of morphine, maintaining only 70% of its concentration at 22 days.<sup>7,8</sup> Ziconotide (25 mcg/ml) appears to be stable with 2 mg/ml clonidine with neither compound demonstrating degradation at 28 days.<sup>9</sup> When 25mcg/ml of ziconotide is combined with 5 mg/ml of bupivacaine, it maintains 90% of its initial concentration for 22 days with no appreciable change in bupivacaine concentration.<sup>10</sup> The stability of 25 mcg/ml of ziconotide with 1.5 mg/ml of baclofen was also evaluated, demonstrating that at least 90% of initial ziconotide concentration was maintained for 12 days and 80% for 29 days, again demonstrating no noticeable effect on initial concentration of baclofen.<sup>11</sup> The clinical impact of the described thresholds of stability above is yet to be defined. Stability tests need to be completed on lower, clinically relevant concentrations on both ziconotide and other IT medications when used in combination.

Formal studies have not been published confirming the stability of ziconotide when used in combination with any of the commonly used IT medications. However, a paucity of data exist for other IT medications commonly used in combination as well. One in vitro study evaluates the stability of 50mg/ml of morphine, 25mg/ml of bupivacaine and 2 mg/ml of clonidine under simulated clinic conditions in the Synchro Med device at 37° C

for 90 days.<sup>12</sup> Although it is indicated for monotherapy, the use of ziconotide in combination with other IT medications would not appear to be practicing a different standard than is currently being applied to other IT medications used in combinations. If considering using ziconotide in combination with other IT medications, contact Elan Pain Information Center at 1-888-774-2581 for stability and compatibility information that may be available.

### Dosage and Titration

The package insert recommends that the beginning dose be less than or equal to 2.4 mcg/day and titrated to the patient's response. It further recommends that the dose not be increased by more than 2.4 mcg/day at intervals of no more than two to three times a week. The maximum recommended dose is 19.2 mcg/day. Note that the guidelines allow for a much slower titration than 2.4 mcg/day.

Clinical investigators, with years of experience with ziconotide, have come to realize that the above recommendation of the maximum initial dosage of 2.4 mcg/day is a relatively high starting point. If an inexperienced clinician is to initiate ziconotide at the dose of 2.4 mcg/day and increase it by 2.4 mcg/day two to three times a week, the risk is great for overshooting the narrow therapeutic window of this medication. This rate is associated with a high incidence of severe adverse events and a high rate of discontinuation of ziconotide by the patient due to intolerance. Ziconotide is associated with adverse events such as nausea/vomiting, dizziness, abnormal gait, abnormal vision and confusion that may present themselves within the first few days of therapy if one was to start at the maximum 2.4mcg/day recommendation in the package insert. Cognitive effects such as memory loss, confusion and psychosis tend to have a later onset of approximately three weeks at an approximate median dose of 4.8 mcg/day. Therefore, to be safe and to not overshoot the therapeutic window, it is advisable to titrate no more often than

	Prescribing Information Recommendations	Practical Use Recommendations
Pump Rinsing	3 (2ml) 25mcg/ml undiluted ~\$1,095	3 (2ml) 8.33 mcg/ml diluted ~ \$365
Initial Fill	25 mcg/ml (14 ml) ~\$2,555	10 mcg/ml (5 ml) ~\$365
14 Day Refill ( refill with 30 day supply)	100 mcg/ml diluted ~\$730	100 mcg/ml diluted (~\$730)
Total Cost for up to 45 Days of Therapy	~\$4,380 (~\$3,650 w/o 14 day refill)	\$1,460 (~\$730 w/o 14 day refill)

**TABLE 2.** *Prescribing Information vs. Practical Use: Cost of initial 45 days of therapy*

weekly — once a month may be preferable. If adverse events do occur, they usually resolve after a dose reduction. Early onset adverse events usually will resolve in a few days whereas it may take up to three additional weeks to resolve late onset adverse events.

Overzealous titration would ultimately result in the failure of this valuable medication in an already heightened state of awareness of the FDA regarding drug adverse events. Experienced investigators are advocating start low and titrate slow to eliminate dose-related adverse events, to prevent overshooting the therapeutic window, and to provide overall greater pain relief and patient satisfaction with ziconotide.<sup>13</sup>

### Practical Considerations in Dosing and Titration

The administration guidelines set forth in the ziconotide-prescribing information sheet are likely to present a barrier to initiation of therapy. The actual wholesale price of the drug at approximately \$7.00/mcg makes the described flushing process impractical. The cost of flushing and refilling the pump in two weeks — according to the package insert — may be cost prohibitive. Therefore, an alternative process for initiation of ziconotide in new IT pumps and existing IT pumps is described below and in an algorithm presented in Figure 2 which may be more practical and affordable. It is important to note that these recommendation have not been studied; therefore, they are not recommended by the package insert. Table 2 demonstrates a cost comparison of package-insert recommendation vs. the off-label, practical-use recommendations presented in this article for the first 45 days of therapy.

### Trialing with Ziconotide

Before discussing initiation of ziconotide in a new IT pump, it is important to address the issue of trialing a pump. It is the standard of practice that candidates for a new IT pump are trialed with an IT med-

ication before a decision to implant a pump is made. Some reduction in pain is expected during the trial to justify proceeding with the implant. However, ziconotide is difficult to trial because of the need for slow titration to avoid undesirable adverse events. If ziconotide is to be trialed in an external system, it would probably require several weeks of a low infusion rate to obtain benefit. Infection risk, including meningitis, directly relate to length of trials with external systems. The risk vs. benefit of prolonged external trials would be difficult to justify in most cases due to the infection risk. Therefore, trialing patients to determine if they are candidates for an IT system will still likely require opioids in most instances. Once an IT delivery system is implanted, a small amount of ziconotide can be added in combination with an opioid or other medications.

Ziconotide is likely to make its place in pain therapeutics by being utilized in combination with other IT medication as opposed to monotherapy. Animal studies have shown that ziconotide is additive to possibly synergistic when combined with morphine and clonidine in different pain models.<sup>4</sup> Monotherapy with ziconotide could be considered if the patient is intolerant to IT opioids or other common pump medications.

### New IT Pump Patients

Initiating ziconotide with a first pump fill in a newly implanted system could be with ziconotide alone or in combination with an opioid. Ziconotide's use in combination therapy has not been FDA approved, and only a paucity of clinical studies exist on other IT combination therapies. However, it is a common practice in pain management to use various IT combinations: opioids, baclofen, clonidine or bupivacaine. Using the best medical evidence available, the Polyanalgesic Consensus Conference 2003 developed clinical guidelines of what should be used first, second and third line, etc., for IT therapy.<sup>14</sup> Morphine or Hydromorphone are

considered first line, with the second line including the addition of clonidine or bupivacaine, and the third line uses the three in combination. If side effects with first line opioids are present, it recommends switching to fentanyl or sufentanyl which are listed as fourth line recommendations along with midazolam and baclofen. The actual algorithm has 6 lines of recommendations with the last two lines consisting of medications that are less commonly used in IT therapy and for which evidence is lacking. It was proposed that Ziconotide may take its place in one of the upper lines of therapy, possibly even first line. It is important to understand that none of these drugs has been FDA approved for combination therapy. Therefore, it could be argued that the use of ziconotide in combination will not deviate from the current standard of care. Whether ziconotide is used as monotherapy or in combination, the infusion rate should be started low and titrated up very slowly.

Example: One vial of the 1ml size of 100 mcg/ml can be utilized to rinse and fill the pump. This will require the compounding of two syringes from the same vial: 50 mcg/0.5 ml diluted to final volume 6 ml ( 8.33 mcg/ml) of preservative-free normal saline for 3 (2ml) rinses and 50 mcg/0.5 ml diluted to final volume of 5 ml to final concentration of 10 mcg/ml for pump refill. If the addition of an opioid such as hydromorphone is desired, 10 mcg/ml of ziconotide and 10mg/ml of hydromorphone in a final volume of 5 ml would be appropriate. An initial starting rate for a new patient could be 0.5 mcg/day of ziconotide and 0.5 mg/day of hydromorphone. This may be titrated to a maximum of 1 mcg/day of ziconotide and 1 mg/day of hydromorphone as tolerated within the first month of therapy. A refill (30 day supply) should occur in 14 days utilizing the same concentrations in order to maintain the desired concentration of ziconotide at, or above, 90%. If choosing to refill at 14 days, the dose should not be titrated until one week after

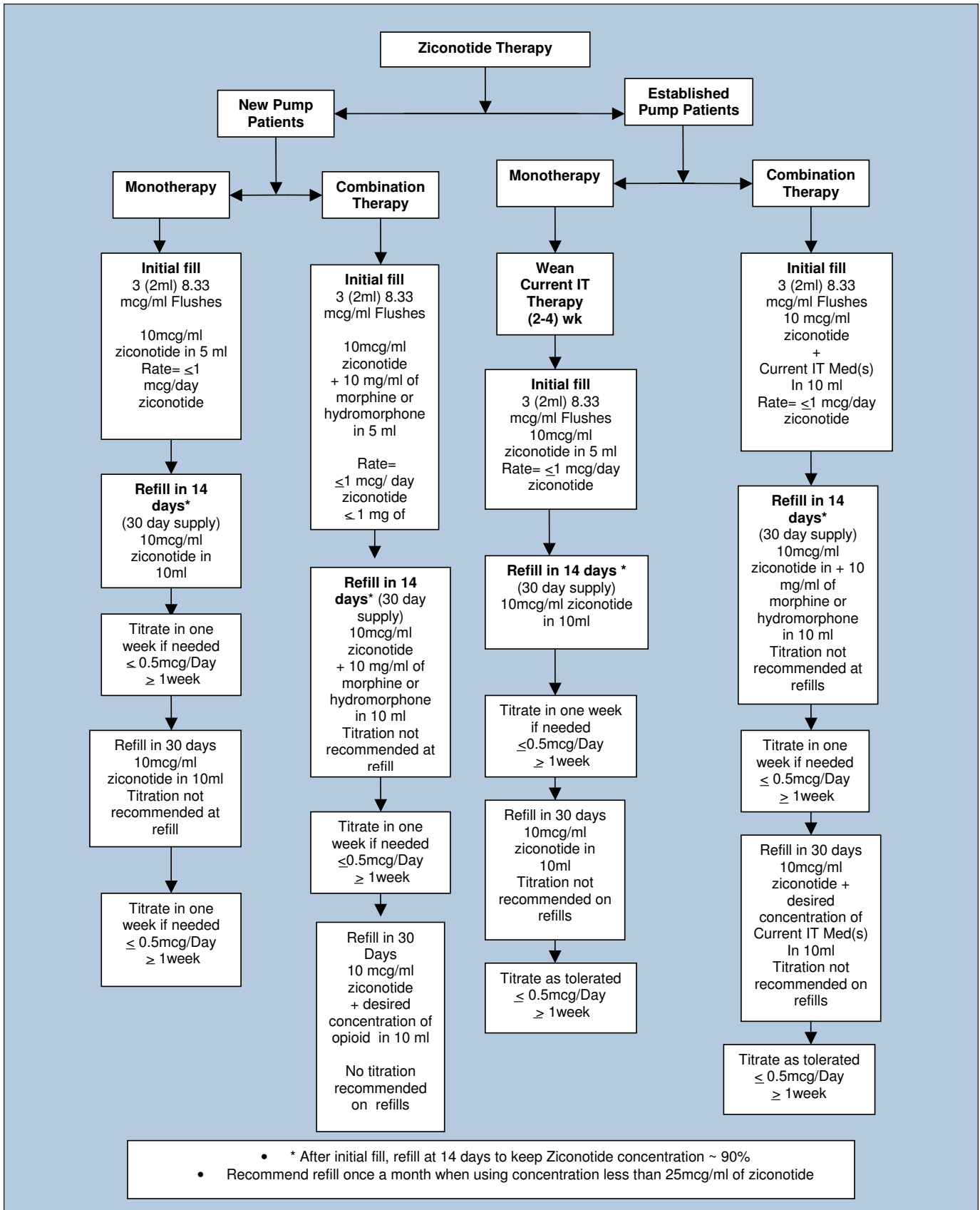
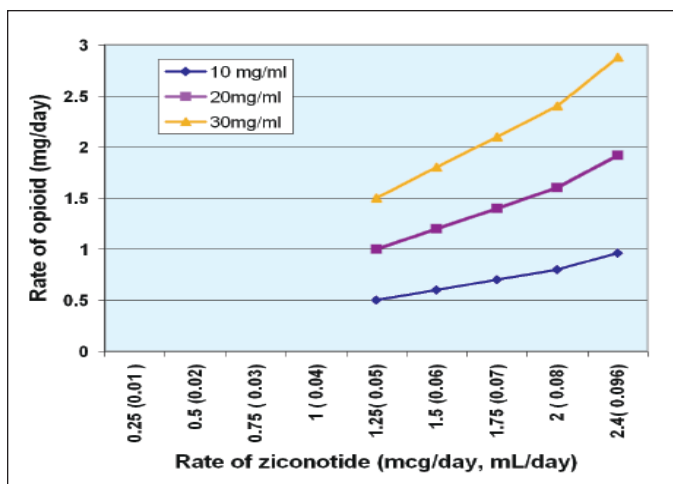


FIGURE 2. Ziconotide Therapy



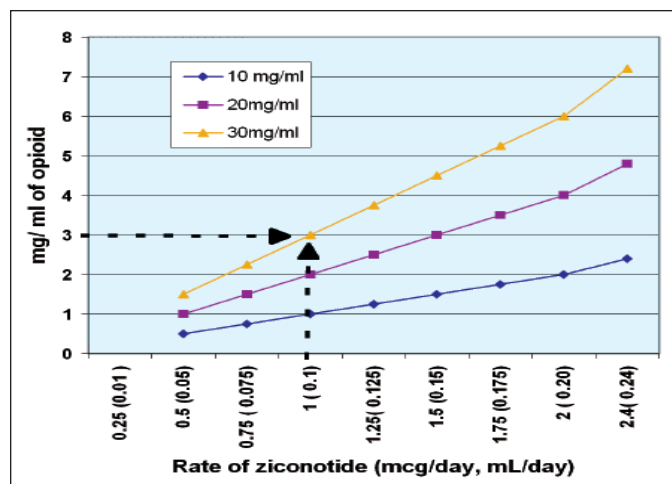
**FIGURE 3.** Maximum Daily Rate of Opioid (Morphine or Hydromorphone) in Combination with 25mcg/ ml of Ziconotide

the 14 day refill until a more stable concentration can be achieved in the pump. After the 14 day refill, an increase of the infusion rate every three to seven days would be reasonable based upon the low concentration of ziconotide and hydromorphone. However, limiting the daily infusion rate of ziconotide to no more than 1mcg/day for the first 30 to 45 days will reduce the risk of unpleasant adverse events. After 45 days, which includes the 14 day refill, the pump can be refilled and the ratio of ziconotide to opioid may be adjusted at this time if more opioid is desired. Some might consider this an extremely slow titration rate; however, the slow development of analgesia is preferable to producing early toxicity. Avoid any dosage changes for Ziconotide on refill days, patient may return to clinic in 1 to 2 weeks after refill for titration of dose. The patient will inherently get a dose increase on each refill due to degradation of Ziconotide that occurs in the pump over time. Refills should occur monthly for concentrations below 25 mcg/ml.

The first month's cost for this example, assuming the 14 day refill is completed, is approximately \$1,400 for ziconotide. This is in contrast to the package insert recommendation of an initial flush (6 ml) and pump fill with 25 mcg/ml (14-40 ml) followed by a refill in 14 days (20-40 ml) with a total cost of at least \$4,000 for the first month (see Table 2).

**Established Pump Patients**

The decision with established pump patients is to either wean IT therapy and convert to ziconotide alone or add ziconotide to the existing IT therapy. There are challenges to weaning IT therapy for ziconotide monotherapy. Providing the patient with alternative analgesia during the weaning process may not be easy. This process could take several weeks in order to avoid withdrawal from the existing IT medications. Using a slow upward titration of ziconotide could result in unacceptable delay in adequate analgesia. Exceptions to this slow titration may be in patients with malignancies in whom opioid or combination therapy has been inadequate and life expectancy is short.<sup>15</sup> In such cases, the risk/benefit profile may justify a more rapid titration not to exceed package-insert instructions. Adding ziconotide to the existing IT therapy may avoid the risk of withdrawal and the delay in providing potential analgesia associated with the wean-



**FIGURE 4.** Maximum Daily Rate of Opioid (Morphine or Hydromorphone) in Combination with 10 mcg/ ml of Ziconotide

ing process. However, patients on moderate doses of IT opioids present a challenge when trying to maintain the daily opioid dose and initiating ziconotide at ≤1 mcg/day.

The Polyanalgesic Consensus Conference 2003 developed recommendations for maximum daily dose and concentration of IT pump medications in order to reduce the risk of inflammatory masses. Concentrations of morphine and hydromorphone in excess of 30mg/ml should be avoided. Figure 3 demonstrates the maximum daily rate of morphine or hydromorphone that can be achieved by utilizing package-insert recommendations of undiluted 25 mcg/ml formulation of ziconotide. The lowest daily dose that ziconotide can be initiated at is 1.25 mcg/day because both the SynchroMed EL and Synchro Med II require a minimal infusion of 0.048 mL/day. The X axis provides both the daily dose of ziconotide in mcg/day and volume per day in mL/day in parentheses. Therefore to initiate ziconotide using undiluted 25 mcg/ml formulation at 1.25 mcg/day, the maximum amount of hydromorphone or morphine the patient can receive is 1.5 mg/day.

Figure 4 demonstrates the maximum daily rate of morphine or hydromorphone that can be achieved by utilizing a ziconotide 100 mcg/ml (1 ml vial) formulation diluted to a concentration of 10 mcg/ml. Again, the X axis provides both the daily dose of ziconotide in mcg/day and volume per day in mL/day in parentheses. The maximum daily dose of morphine or hydromorphone that a patient can receive is 3 mg/day at 30 mg/ml of opioid if the patient is initiated at 1 mcg/day of ziconotide. Existing opioid doses that exceed this rate will require a greater dilution of ziconotide. Dilutions to ≤5 mcg/ml ziconotide are likely not stable out to one month, and refills may need to occur every two to three weeks until the patient is titrated up on ziconotide. Concentrations below 10 mcg/ml should be avoided.

The same procedure described for new IT pump patients could be utilized for the 3-(2ml- 8.33 mcg/ml) rinses. Ziconotide initial infusion rate could be 0.5 to 1 mcg/day. Changing the ratio of ziconotide to the other IT medications at pump refill times would allow for an adjustment of only the ziconotide infusion rate without affecting the infusion rates of the other IT medications. This obviously means that it will take several months for ziconotide to reach a therapeutic level in some pa-

tients, but that would be preferable to producing severe adverse events and losing the potential benefit from the drug. The alternative is to perform more pump refills, wasting considerable amounts of unused drug. This could be very expensive and should be avoided, if possible.

### Monitoring Considerations

Patients should be continually assessed for adverse events related to ziconotide. Ziconotide may be additive or synergistic in some combinations, which may allow downward titration of the concomitant IT medications. Instruct the patient to immediately notify clinic personnel or to seek emergency medical attention if experiencing any serious adverse events. Note that other systemic medications may also be reduced once efficacy is obtained. Based on the lead author's clinical experience, IT ziconotide has allowed some patients to be weaned off all oral opioids.

In clinical studies with ziconotide, a significantly elevated serum Creatinine Kinase muscle isoenzyme (CK-MM) was common in 40% of patients participating mostly in open label studies. Elevation CK-MM usually occurred within the first two months of therapy. Other isoenzymes were rarely affected. Risk factors for elevated CK-MM include male patients on concomitant antidepressants, anticonvulsants or IT morphine. In most cases, prolonged elevation had no limiting adverse events. Of all patients studied in clinical trials, one case of symptomatic myopathy occurred and two acute renal failures associated with rhabdomyolysis and extreme CK elevation (17,000-27,000 IU/L). The product insert recommends physicians monitor CK periodically: once every two weeks at initiation and monthly thereafter.<sup>5</sup>

A baseline CK should be obtained with another CK at two months. Thereafter, every six months may be acceptable. CKs should be obtained if the patient is exhibiting any new neuromuscular symptoms.

### Consent

Prior to initiation of therapy, new and existing patients should sign an informed written consent indicating the risks and benefits of using ziconotide in combination with other IT medications. The use of consents should occur when any IT medication is used as they are almost always used off label.

### Conclusion

Ziconotide has the potential of becoming an important analgesic in our armamentarium. It would be unfortunate if overzealous use and unrealistic expectations of this drug lead to dissatisfaction from adverse events. Managing expectations of the clinicians, the payers and the patients will be crucial in finding the most appropriate way to use this novel compound. Immediate pain relief should not be expected with the recommended slow titration. Treatment with ziconotide will need to be based on the individual's response but also on what is known about the drug. During the next year, much will be learned about how to improve successful use of this novel drug. The field of pain medicine is fortunate to have a new powerful non-opioid analgesic available for the thousands of patients who find the current treatments less than adequate. ■

*Dr. Webster is board certified in anesthesiology and pain management and is also certified in addiction medicine. In his private practice, he treats chronic-pain patients, many of whom have complex diagnoses. He also detoxes opioid-addicted patients. This dual role lends Dr. Webster a valuable perspective. He is dedicated to treating patients in pain while simultaneously working to minimize the potential for abuse and addiction.*

*His clinical research interests are diverse. They include pain and pain mechanisms, substance abuse and addiction, and cultural and political attitudes toward pain management. A primary focus is the development of novel agents to treat pain. Dr. Webster earned his doctorate of medicine from the University of Nebraska Medical Center and completed his residency in the University of Utah Medical Center's department of anesthesiology. He has authored numerous scientific abstracts and journal articles and lectures extensively. His contact information is: Lynn R. Webster, MD, FACP, FASAM, Medical Director, Lifetree Pain Clinic and Clinical Research; 3838 S 700 E, Suite 200, Salt Lake City, UT 84106; e-mail lynnw@lifetreepain.com*

*Dr. Fakata is a clinical pharmacy practitioner specializing in pain management and palliative care. An experienced clinical researcher, Dr. Fakata partners with the clinic's other physicians to provide patients access to investigational treatments for pain. Dr. Fakata received her doctorate in pharmacy from the University of Nebraska Medical Center and*

*completed her general pharmacy practice residency and pain management and palliative care postdoctoral fellowship at the University of Utah.*

*Dr. Fakata's research focus is how long term-opioid use affects the neuro-endocrine-immune systems. She has several peer-reviewed publications and book chapters in the area of pain management. Dr. Fakata awards include honors from NIH and the American Pain Society.*

### References

1. Stix G. A Toxin Against Pain. *Scientific American*. April 2005. 88-93
2. Mather et al. Neuronal N-type Calcium Channels: New Prospect in Pain Therapy. *Pharmaceutical News*. 1998 Vol. 5, No. 5.
3. Mathur VS. *Ziconotide: A New Pharmacological Class of Drug for the Management of Pain*. *Seminars in Anesthesia, Perioperative Medicine and Pain*. 2000., 19 (2): 67-75.
4. Miljanich GP. Ziconotide: Neuronal Calcium Channel Blocker for Treating Severe Chronic Pain. *Current Medicinal Chemistry*. 2004. 11: 3029-3040.
5. Ziconotide [prescribing information]. San Diego, CA: Elan Pharmaceuticals, Inc. 2004.
6. SynchroMed El/SynchroMed II Programmable Pump Comparison Chart. Medtronic, Inc. 2004.
7. Shields D and Montenegro R. The Chemical Stability of Admixtures Combining Ziconotide and Hydromorphone during Simulated Intrathecal Administration. (Abstract) *Neuromodulation*. 2005. Vol 8 (in press).
8. Shields D, Montenegro R, and Ragusa M. The Chemical Stability of Admixtures Combining Ziconotide and Morphine Sulfate during Simulated Intrathecal Administration. (Abstract) *Neuromodulation* 2005. Vol 8 (in press).
9. Shields D and Montenegro R. The Chemical Stability of Admixtures Combining Ziconotide and Clonidine during Simulated Intrathecal Administration. (Abstract) *Neuromodulation*. 2005. Vol 8 (in press).
10. Shields D, Montenegro R, Ragusa M. The Chemical Stability of Admixtures Combining Ziconotide and Bupivacaine during Simulated Intrathecal Administration. (Abstract). *Neuromodulation*. 2005. Vol 8 (in press).
11. Shields D, Montenegro R, and Ragusa M. The Chemical Stability of Admixtures Combining Ziconotide and Baclofen during Simulated Intrathecal Administration. (Abstract). *Neuromodulation*. 2005. Vol 8 (in press).
12. Classen AM, Wimbash GH, Kupiec TC. Stability of Admixture Containing Morphine Sulfate, Bupivacaine Hydrochloride, and Clonidine Hydrochloride in an Implantable Infusion System. *Journal of Pain and Symptom Management*. 2004. 28(6):603-611.
13. Willis KD, Fisher R, Hassenbusch S, et al. Giant Cone Snail: "Start Low and Go Slow" Caution recommendations regarding titration schedule for Ziconotide. *Neuromodulation*. 2005. (in press)
14. Hassenbusch SJ, Portenoy RK, Cousins MI, et al. Polyanalgesic Consensus Conference. 2003. An Update on the Management of Pain by Intraspinal Drug Delivery -Report of an Expert Panel. *Journal of Pain and Symptom Management*. 2004. 27(6):540-563.
15. Staats PS, Yearwood T, Charapata SG, et al. Intrathecal Ziconotide in the Treatment of Refractory Pain in Patients with Cancer or Aids. *JAMA*. 2004. 291(1) 63-70.