Molina Clinical Policy
Prialt (ziconotide intrathecal infusion): Policy No. 387

Last Approval: 12/9/2021
Next Review Due By: 12/2022

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Prialt (ziconotide intrathecal infusion) is indicated for the management of severe chronic pain in patients requiring intrathecal therapy and who are intolerant or refractory to other therapies (e.g., systemic analgesics, adjunctive therapies, intrathecal morphine). Ziconotide is a synthetic equivalent of a naturally occurring conopeptide (venom) found in the piscivorous marine snail. It acts by blocking calcium from binding to calcium channels involved with nociceptive processing and is thought to exhibit its pharmacological effects by blocking neurotransmitter release preventing pain signals from reaching the brain. Ziconotide does not bind to the opioid receptors nor is it antagonized by opioid antagonists. Ziconotide is advantageous over morphine in that it has no interaction with the opioid receptors. As a result, there are no endocrine side effects common with morphine administration and tolerance does not occur (Ver Donck 2008; Wallace et al. 2008). Tolerance does not develop to the analgesia induced by intrathecal ziconotide in animal experiments and clinical trials (Smith HS, 2009). Key ziconotide-related adverse events are neuropsychiatric, including depression, cognitive impairment, and hallucinations; depressed levels of consciousness; and elevation of creatine kinase levels. Ziconotide is also associated with a risk of meningitis due to possible contamination of the microinfusion device.

The efficacy and safety profiles of ziconotide have been assessed in three double-blind, placebo-controlled trials of 457 patients, and safety has been assessed in 1,254 patients overall, with severe chronic cancer, noncancer, and acquired immunodeficiency syndrome pain types.

The safety and efficacy of intrathecal ziconotide in the management of severe chronic pain were evaluated in 3 double-blind, placebo-controlled, multicenter studies in a total of 457 patients (268 ziconotide, 189 placebo). These studies used 2 different titration schedules: a slow schedule with dosage increased 2 to 3 times per week to a maximum of 19.2 mcg/day (0.8 mcg/h) at 21 days, and a fast schedule using daily dose increases up to a maximum of 57.6 mcg/day (2.4 mcg/h) in 5 to 6 days. Efficacy was assessed using the Visual Analog Scale of Pain Intensity (VASPI) score (a 100 mm visual analog scale where 0 mm = no pain and 100 mm = worst possible pain).

Ziconotide is a therapeutic option for treatment of severe chronic pain in patients who have exhausted all other agents, including intrathecal morphine, and for whom the potential benefit outweighs the risks of serious neuropsychiatric adverse effects and of having an implanted device. Ziconotide provides pain specialists with an alternative to morphine, to avoid opioid-related respiratory depression in patients with lung disease/compromised respiratory reserve or peripheral edema, and in patients with opioid resistance who require high doses or rapidly escalating doses, or who develop opioid-induced hyperalgesia. Unlike morphine and other opioids, ziconotide is not associated with issues of tolerance, withdrawal effects with abrupt cessation, or granulomas, which can have major deleterious effects (Deer TR et al. 2012). However, due to its narrow therapeutic window, ziconotide requires careful dose-titration. (Smith et al. 2009). Systemic toxicity is decreased by administration of smaller doses of ziconotide intrathecally. Long-term administration of intrathecal ziconotide does not appear to lead to tolerance and does not influence the response to morphine analgesia or tolerance to opiate-analgesia. However, due to the potential for serious neurologic and psychiatric side effects, its use should be limited to only those patients not responding to other therapies and it is recommended that ziconotide should only be used by clinicians and physicians experienced in intrathecal use.

The evidence evaluated for the FDA approval suggests an overall benefit for ziconotide intrathecal administration for patients who are intolerant of or refractory to other pain treatments. Despite the adverse events experienced by patients, the benefit of ziconotide IT treatment for chronic severe pain noted in the FDA approved indications outweighs the negative patient experience. Expert consensus of the behavioral algorithm for considering patients for IT pain therapy includes failure of conservative therapies, psychological evaluation, medical history evaluation, and an IT screening trial [Polyanalgesic Consensus Conference (PACC)]. Further studies are needed to determine the comparative efficacy of ziconotide and other pain therapies.

COVERAGE POLICY

Prialt (ziconotide intrathecal infusion) for the management of severe chronic pain **may be considered medically necessary** when **ALL** of the following clinical criteria are met:

1. Prescribed by, or under the supervision of, a pain management specialist (e.g., neurologist, anesthesiologist) experienced in the technique of intrathecal administration and familiar with the drug and device labeling; **AND**

2. Diagnosis of severe, chronic pain for which intrathecal therapy is warranted; **AND**

3. Evaluation by a licensed behavioral and/or medical health care provider to rule out pre-existing history of psychosis, current psychiatric symptoms or neurological impairment AND the absence of untreated, underlying mental health conditions/issues (e.g., depression, drug, alcohol abuse) as a major contributor to chronic pain;

   Informational Note: The behavioral algorithm for considering patients for IT pain therapy includes failure of conservative therapies, psychological evaluation, medical history evaluation, and an IT screening trial [Polyanalgesic Consensus Conference (PACC)].

   EXCEPTION: For members receiving palliative or end-of-life care where psychological and cognitive symptoms or psychiatric illnesses are commonly exacerbated or experienced. Documentation or attestation of palliative or end-of-life care required. **Recommendation:** The palliative care physician should assess for optimal psychological treatment or intervention for individuals with terminal illness which may include collaboration with psychiatrists or mental health resources.

AND

4. Member is age 18 or older
   Safety and efficacy have not been established in adolescents, children, infants, or neonates.

AND

5. Member has had a preliminary trial with a temporary intrathecal/epidural catheter to assess pain relief, degree of side effects and patient tolerability. Documentation of medication response and tolerance, including assessment in reduction of pain, increase in function and effects on the activities of daily living required for review.

   Refer to 'MCP-160: Implanted Intrathecal (Intraspinal) Infusion Therapy for Chronic Pain' for coverage policy of a temporary trial.

AND

6. Documentation of treatment failure at therapeutic or maximally tolerated doses for at least 3 weeks (verified via pharmacy claims if applicable), intolerance or contraindication to ALL the following:
   a. Non-opioid medications, including ALL the following: NSAIDs, acetaminophen, gabapentin, amitriptyline, topical lidocaine, carbamazepine, duloxetine, fluoxetine; **AND**
   b. TWO short-acting and/or long-acting opioids; **AND**
   c. Intrathecal morphine.

AND

7. Member does not have an infection at the injection site, uncontrolled bleeding, or spinal canal obstruction that impairs CSF circulation [Contraindicated in intrathecal administration]

AND

8. Not prescribed for, or intended for concurrent use with, **ANY** of the following:
   Treatment plan, including planned therapy modification or clinical rationale for maintaining treatment is required if member is currently on ANY of the following medications.

   a. Avoid Combination Use (may enhance the CNS depressant effect): azelastine (nasal), bromperidol, thalidomide, paraldehyde, orphenadrine, oxomemazine.

   MOLINA MEDICAL/PHARMACY REVIEWER: Verify member's claims history, chart notes, and prescribing physician notes/attestation. Authorization is not recommended if member is on any of these medications.

   b. Consider Therapy Modification: Oxycodone, Buprenorphine Benzodiazepines or other CNS depressants (i.e., chlormethiazole, droperidol, flunitrazepam, zolpidem, suvorexant, perampanel, opioid agonists)

   MOLINA MEDICAL/PHARMACY REVIEWER: Verify member's claims history, chart notes, and prescribing physician notes/attestation. Pharmacy/Medical Director to review treatment plan submitted and may request additional information or peer-to-peer with Prescriber if necessary.

   c. Other intrathecal medication(s) *Due to the lack of safety, efficacy, and long-term drug product stability.*

   MOLINA MEDICAL/PHARMACY REVIEWER: Verify the above per member's claims, chart notes, and prescribing physician notes and relevant documentation.

AND

9. Attestation of the following:
   a. Member has been counseled and acknowledges understanding of the potential risk of psychosis or neurological impairment and wishes to proceed with treatment; **AND**
   b. Prescriber will monitor member's response to treatment, including improvements to pain severity AND neurological or psychiatric signs or symptoms for duration of therapy.

CONTINUATION OF THERAPY

1. Member continues to meet initial coverage criteria appropriate for continuation of treatment; **AND**
2. Documentation of continued need for intrathecal therapy and evidence of pain control**; AND**
3. Member has received ongoing monitoring for neurological or psychiatric signs or symptoms throughout therapy**; AND**
4. No evidence of unacceptable adverse effects or complications from ziconotide therapy, such as psychiatric symptoms and neurological impairment

LIMITATIONS AND EXCLUSIONS

1. Known allergy or hypersensitivity to ziconotide or any component of the formulation
2. Pre-existing history of psychosis
3. Other concomitant treatment(s) or medical condition(s) that would render intrathecal administration hazardous (e.g., infection at the injection site, *uncontrolled hematological disease (bleeding diathesis), spinal cord compression or any spinal canal obstruction that impairs circulation of cerebrospinal fluid)
   **Patients with clinically significant thrombocytopenia or bleeding problems such as coagulopathy, hemophilia, or von Willebrand's disease may not be appropriate candidates for ziconotide receipt.*
4. IV administration
5. Concomitant treatment or medical condition that would render intrathecal administration hazardous such as the presence of infection at the microinfusion injection site, uncontrolled bleeding diathesis, and spinal canal obstruction that impairs circulation of cerebrospinal fluid (CSF)
6. High risk of bleeding (e.g., history of bleeding tendency, concurrent uses of other anticoagulants/antiplatelets, liver cirrhosis or advanced liver disease, and advanced renal disease) **NOTE:** Treatment should be managed in accordance to current accepted guidelines [e.g., American Society of Interventional Pain Physicians (ASIPP 2019) Guidelines].

EXCEPTION: Prescriber submit documentation of chart notes and treatment plan for review, if applicable.

7. Requested dose and frequency is not in accordance with FDA-approved labeling, nationally recognized compendia, and/or evidence-based practice guidelines. **NOTE:** Doses above 19.2 µg/day (0.8 µg/hr.) will not be authorized

The following are considered **experimental, investigational and unproven** based on insufficient evidence:

1. Any indication other than those listed above

Based on the peer-reviewed medical literature the safety and effectiveness for indications other than the medically necessary indication listed above has not been established.

DURATION OF APPROVAL AND QUANTITY LIMITATIONS:

1. Dose does not exceed 19.2 mcg/day (0.8 mcg/hour)
2. Initial Therapy: May authorize up to 3 months of initial therapy
3. Continuation of therapy: May be authorized up to 6 months. Subsequent approval will be based on continuous progress notes from the Prescriber documenting improvement from baseline.

ADMINISTRATION:

1. Not for intravenous administration or epidural administration. For intrathecal administration only using Medtronic SynchroMed II Infusion System, or CADD-Micro ambulatory infusion pump.
2. Refer to Specialty Medication Administration Site of Care Policy P&P: MHI Pharm 11.
3. If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare.

DOSING CONSIDERATIONS:

Chronic pain (intolerant or refractory to other therapies)

- Initial dose: ≤ 2.4 mcg/day (≤ 0.1 mcg/hour). Initiating with more conservative dosing is preferred due to improved tolerability
  McDowell 2016; Prager 2014

  Alternate initial dosing (Off-label): 0.5 to 1.2 mcg/day (0.02 to 0.05 mcg/hour). Initiating with no more than 0.5 mcg/day (0.02 mcg/hour) may be preferred.

- Dosage titration: According to the manufacturer, dose may be titrated by ≤ 2.4 mcg/day (≤ 0.1 mcg/hour) at intervals ≤ 2 to 3 times/week to a maximum dose of 19.2 mcg/day (0.8 mcg/hour) by day 21; average dose at day 21: 6.9 mcg/day (0.29 mcg/hour). However, expert consensus recommends upward titration (based on analgesia and tolerability) in increments of no more than 0.5 mcg/day (≤0.02 mcg/hour) and not more often than once weekly (McDowell 2016; Prager 2014). A faster titration should be used only if the urgent need for analgesia outweighs the possible risk to patient safety.

Off-Label: Expert consensus recommends upward titration (based on analgesia and tolerability) in increments of ≤0.5 mcg/day (≤0.02 mcg/hour) and not more often than once weekly

- Maximum dose of Prialt is 19.2 mcg/day, to which the initiation dose of 2.4 mcg/day is titrated by day 21

MONITORING PARAMETERS: Psychiatric or neurological impairment; signs and symptoms of meningitis or other infection; serum CPK (every other week for first month then monthly); pain relief.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DRUG INFORMATION

ROUTE OF ADMINISTRATION: For intrathecal administration only using programmable implanted variable-rate microinfusion device (Medtronic SynchroMed EL or SynchroMed II) or external microinfusion device and catheter (CADD-Micro ambulatory infusion pump)

DRUG CLASS: Analgesic, Nonopioid; Calcium Channel Blocker, N-Type

FDA-APPROVED USES: Chronic pain
Management of severe chronic pain in patients for whom intrathecal therapy is warranted and who are intolerant of, or refractory to, other treatment (e.g., systemic analgesics, adjunctive therapies, intrathecal morphine)

NOTE: Dosage should be titrated according to the pain severity, patient response, and adverse event occurrence. Reduced initial dosages should be considered for elderly patients and for patients receiving CNS depressants.

COMPENDIAL APPROVED OFF-LABELED USES: For spasticity associated with spinal cord injury
Receipt of 9.6-70 mcg/day (0.4-2.9 mcg/hour) via intrathecal infusion over 7 months reduced spasticity from severe to mild or nonexistent for a woman with C5 quadriplegia. Also, a woman with complete paraplegia following a T8 burst fracture had her moderate to severe spasticity become mild with 7.2 mcg/day (0.3 mcg/hour) via intrathecal infusion. Both patient's intractable spasticity was unresponsive to intrathecal baclofen and morphine (Clinical Pharmacology; reference cited: Ridgeway 2000)

RISK EVALUATION AND MITIGATION STRATEGY (REMS): N/A

BOXED WARNING: Severe psychiatric symptoms and neurological impairment may occur during treatment with ziconotide. Do not treat patients with a preexisting history of psychosis with ziconotide. Monitor all patients frequently for evidence of cognitive impairment, hallucinations, or changes in mood or consciousness. Ziconotide therapy can be interrupted or discontinued abruptly without evidence of withdrawal effects in the event of serious neurological or psychiatric signs or symptoms.

SUMMARY OF MEDICAL EVIDENCE

Prialt (ziconotide intrathecal infusion) has been evaluated for treatment of chronic pain caused by malignant or non-malignant conditions in 3 randomized, double-blind, placebo-controlled clinical studies enrolling a total of 457 patients (268 ziconotide and 189 placebo). These studies used 2 different titration schedules: a slow schedule with dosage increased 2 to 3 times per week to a maximum of 19.2 mcg/day (0.8 mcg/h) at 21 days, and a fast schedule using daily dose increases up to a maximum of 57.6 mcg/day (2.4 mcg/h) in 5 to 6 days. Efficacy was assessed using the Visual Analog Scale of Pain Intensity (VASPI) score (a 100 mm visual analog scale where 0 mm = no pain and 100 mm = worst possible pain) (Rauck RL, et al. 2006; Staats PS, et al. 2004; Wallace MS, et al. 2006).

Rauck et al. (2006), in an attempt to reduce side effects and increase tolerability, conducted a double-blind, placebo-controlled study using a slower titration schedule and lower maximum dose than previous studies in 220 patients with chronic, noncancer refractory to conventional treatment. 220 patients with severe chronic pain were randomized to ziconotide (n=112) and placebo (n=108). Dosing with ziconotide was started at 2.4 mcg/day (0.1 mcg/hr) and the dose could be increased by 2.4 mcg/day (0.1 mcg/hr) two to three times/week (minimum titration interval 24 hours) to a maximum dose of 19.2 mcg/day (0.8 mcg/hr). The final mean dose at the end of the trial at 21 days was 6.9 mcg/day (0.29 mcg/hr). At baseline, 97% of these patients reported that their pain was refractory to treatment including IT morphine, IT bupivacaine (an off-label use for this drug) and/or IT clonidine (an off-label use for this drug) in addition to their systemic analgesics and adjunctive therapy. All IT medications were discontinued over a one- to three-week period and patients were maintained on a stable regimen of non-IT analgesics including opiates, for at least seven days prior to randomization. This period was successfully completed by 93% of the patients screened. Significant AEs reported in the ziconotide group were dizziness, confusion, ataxia, abnormal gait, and memory impairment. Discontinuation rates for AEs and serious AEs were comparable for both groups. Slow titration of ziconotide, a nonopioid analgesic, to a low maximum dose resulted in significant improvement in pain and was better tolerated than in two previous controlled trials that used a faster titration to a higher mean dose. Results from the MMSE indicated no substantial changes in mental status and no significant differences between the ziconotide and placebo groups. However, no occurrences of respiratory depression, drug dependence, or withdrawal symptoms (potential hazards of

opioid administration) were reported during this study, and there was no evidence of tolerance to ziconotide or of granuloma formation at the tip of the IT catheter (as is observed rarely during IT opioid treatment in association with neurological sequelae).Overall, the results of this study suggest that IT ziconotide infusion therapy is an option for patients with severe, refractory chronic pain. Efficacy data from this study should be interpreted with caution, as there was no comparator group in the study. An important limitation of this study is that it is unlikely that rare AEs would have been detected.

Staats et al. (2004) evaluated the safety and effectiveness of ziconotide in patients with pain that is refractory to conventional treatment in a multi-center, double-blind, placebo-controlled, randomized study in 111 patients (n = 111) with cancer or AIDS. Patients were individuals aged 24 to 85 years with cancer or AIDS and a mean VASPI score of 50 mm or greater despite therapy with a regimen of systemic or intrathecal analgesics. Subjects were randomly assigned in a 2:1 ratio to receive ziconotide or placebo treatment. Patients were assigned to receive ziconotide (n=71) or placebo (n=40). Intrathecal ziconotide was titrated over 5 to 6 days, followed by a 5-day maintenance phase for responders. Non-responders were crossed over to the alternative treatment. At baseline, 67 of 68 (98.5%) evaluable patients in the ziconotide group and 38 of 40 (95%) in the placebo group were taking opioids (median morphine equivalent dosage of 300 mg/day in the ziconotide group and 600 mg/day in the placebo group). Mean VASPI scores at baseline were 73.6 mm in the ziconotide group and 77.9 mm in the placebo group. Mean VASPI scores improved 53.1% (95% CI, 44% to 62.2%) in the ziconotide group and 18.1% (95% CI, 4.8% to 31.4%) in the placebo group ($P < 0.001$). Efficacy did not decline in the ziconotide group during the maintenance phase. Pain relief was moderate to complete in 52.9% of ziconotide-treated patients compared with 17.5% of patients in the placebo group ($P < 0.001$). Five patients in the ziconotide group experienced complete pain relief. Opioid use decreased by 9.9% in the ziconotide group and increased 5.1% in the placebo group. Twenty-six patients in the placebo group crossed over to ziconotide therapy and experienced a 44.9% mean reduction in VASPI score at the end of the crossover phase. The researchers concluded that intrathecal ziconotide provided clinically and statistically significant analgesia in patients with pain from cancer or AIDS. (Staats PS, et al. 2004)

Wallace et al. (2006) assessed ziconotide in a double-blind placebo-controlled study enrolling 257 patients with refractory, intractable, nonmalignant pain. Patients were treated with intrathecal ziconotide (n=170) or placebo (n=87). Pain was classified as both neuropathic and nociceptive of a chronic nonmalignant etiology. Mean percent VAS improvement was 31.2% for ziconotide versus 6.0% for placebo ($p \leq 0.001$) with 33.7% of ziconotide patients reported as responders versus 12.8% for placebo ($p < 0.001$). Lastly, 43.8% of ziconotide patients had moderate or better pain relief with 8.9% of patients reporting complete pain relief versus only 17.4% of placebo reporting moderate or greater pain relief without any patients reporting complete pain relief. The first 28% of patients enrolled received an initial infusion rate of 0.4 mcg/h with the dosage titrated to a maximum of 7 mcg/h; however, poor tolerability prompted a revision in the dosing regimen. Therapy was initiated at a dosage of 0.1 mcg/h in 72% of patients and titrated as needed every 24 hours over 5 to 6 days to a maximum dosage of 2.4 mcg/h. Baseline VASPI score was 80.2 mm in the ziconotide group and 76.8 mm in the placebo group. With the lower-dosage regimen, the mean VASPI improvement was 31.8% in the ziconotide group and 6.6% in the placebo group ($P = 0.002$). Most of the AEs were related to the nervous system, including dizziness, confusion, urinary retention, nausea, vomiting, and amblyopia

Deer et al. (2019) evaluated the evidence for morphine and ziconotide as 1st-line IT analgesia agents for patients with chronic pain. Medline was searched (through July 2017) for "ziconotide" or "morphine" and "intrathecal" and "chronic pain" with results limited to studies in human populations. The literature supports the use of morphine (based primarily on non-controlled, prospective, and retrospective studies) and ziconotide (based on RCTs and prospective observational studies) as 1st-choice IT therapies. The 2016 Polyanalgesic Consensus Conference (PACC) guidelines recommended both morphine and ziconotide as 1st-line IT monotherapy for localized and diffuse chronic pain of cancer-related and non-cancer-related etiologies; however, one consensus point emphasized ziconotide use, unless contraindicated, as 1st-line IT therapy in patients with chronic non-cancer-related pain. Initial IT therapy choice should take into consideration individual patient characteristics (e.g., pain location, response to previous therapies, co-morbid medical conditions, psychiatric history). **Trialing is recommended to assess medication efficacy and tolerability.** The PACC guidelines recommended conservative initial dosing strategies for both morphine and ziconotide. Due to its narrow therapeutic window, ziconotide requires careful dose-titration. Ziconotide is contraindicated in patients with a history of psychosis; IT morphine administration may be associated with serious side effects (e.g., respiratory depression, catheter tip granuloma), require dose increases, and cause dependence over time. **The authors concluded that based on the available evidence, morphine and ziconotide are recommended as 1st-line IT monotherapy for cancer-related and non-cancer-related pain. The choice of first-in-pump therapy should take into consideration patient characteristics and the advantages and disadvantages of each medication.**

These researchers noted that the interim analysis data of the US-based Patient Registry of Intrathecal Ziconotide Management (PRIZM) registry suggested sustained effectiveness when ziconotide is used as the 1st-line agent in the pump; however, increased patient numbers and additional analyses of these data will contribute to the knowledge of and comfort in using non-opioid IT analgesics. **Further investigation is needed to better understand the risks and benefits associated with the choice of initial IT medication (i.e., morphine or ziconotide) in diverse chronic pain populations.**

Safety. The safety of Prialt administered as a continuous infusion has been examined in 1,254 patients with acute or chronic pain. The duration of treatment has ranged from a 1-hr intrathecal infusion to treatment lasting for over 7.5 years. The mean duration of treatment was 193 days with 173 patients (14 %) treated for at least 1 year. The average final dose was 17 ug/day (0.73 ug/hr). The most common side effects associated with the use of ziconotide are dizziness, nausea, confusion and headache.

Surgical Procedures

Intrathecal ziconotide was evaluated in a double-blind pilot study enrolling 30 patients undergoing elective total abdominal hysterectomy, radical retropubic prostatectomy, or total hip replacement. After intrathecal injection of local anesthetic and before surgical incision, a continuous intrathecal infusion of either placebo or ziconotide 0.7 mcg/h or 7 mcg/h was initiated and continued for 48 to 72 hours postoperatively. Efficacy was evaluable in 26 patients. Seventeen patients (9 of 12 [75%] in the placebo group, 5 of 12 [42%] in the low-dose group, and 3 of 6 [50%] in the high-dose group) requested additional narcotics or ketorolac. Mean daily patient-controlled analgesia morphine equivalent consumption was lower in the ziconotide-treated patients (P = 0.04), although the greatest difference was observed in the high-dose group. Between 24 and 48 hours postoperatively, patients in the high-dose group received 6.6 mg of morphine equivalent, compared with 20.7 mg of morphine equivalent in the low-dose group. VASPI scores during the first 8 postoperative hours were much lower in the ziconotide-treated patients. More patients in the high dose ziconotide group experienced side effects requiring discontinuation of therapy. The investigators concluded that the high dose was associated with an unacceptable incidence of side effects, and the low dose was only marginally more effective than placebo; therefore, the optimal dose for postoperative pain may lie somewhere in between and closer to the lower dose (Atanassoff PG, et al.)

National and Specialty Organizations

American Society of Interventional Pain Physicians (ASIPP) issued an evidence-based practice guideline on interventional techniques in the management of chronic spinal pain (Manchikanti et al., 2013a; Manchikanti et al., 2013b). No randomized controlled trials for the treatment of chronic noncancer pain with intrathecal opioids was identified in the review. It was based on 7 observational studies, which concluded a long-term benefit from intrathecal infusion devices. ASIPP guidelines recommended the use of intrathecal infusion systems for recalcitrant noncancer pain although the evidence base was rated as “limited,”.

American Society of Regional Anesthesia and Pain Medicine and American Society of Anesthesiologists (ASRA-ASA) issued practice guidelines addressing chronic pain management in 2010 to update a previous version of the guidelines from 1997. The guidelines noted that observational studies report that intrathecal opioid injections can provide effective pain relief for 1 to 12 months for patients with neuropathic pain. The recommendation is that intrathecal opioid administration may be used for patients with neuropathic pain. However, shared decision making regarding this procedure should involve a discussion of potential complications. In addition, a neuraxial opioid trial should be conducted prior to permanent implantation of intrathecal drug delivery systems (ASRA-ASA, 2010).

Polyanalgesic Consensus Conference (PACC) is comprised of a group of physicians and other clinicians in the field of intrathecal therapy that was formed in 2000 to review the published literature and evidence pertaining to the efficacy and safety of intrathecal therapies and provide published guidelines regarding their use. The panel develop an intrathecal drug selection algorithm based on evidence and expert opinion. The review and algorithm have been updated 3 times since then, most recently in 2017 and 2018 (Deer et al., 2017a; Deer et al., 2017b; Deer et al., 2019). The 2016 consensus conference, from which the updated guidelines were developed and published in 2017, did not delineate pain treatment recommendations by pain type (i.e., nociceptive, neuropathic) because many patients with chronic pain syndromes experience both nociceptive and neuropathic pain, but instead provided separate guidance for localized and diffuse pain.

- The 2016 PACC guidelines recommended both morphine and ziconotide as first-line intrathecal monotherapy for localized and diffuse chronic pain of cancer-related and non-cancer-related etiologies; however, one consensus point emphasized ziconotide use, unless contraindicated, as 1st-line IT therapy in patients with chronic non-cancer-related pain.
- The behavioral algorithm for considering patients for intrathecal pain therapy includes failure of conservative therapies, psychological evaluation, medical history evaluation, and an intrathecal screening trial.
- The guidelines noted that if patients proceeding to the implantation of an intrathecal drug delivery system, the medications recommended as first-line therapies for neuropathic pain are morphine, ziconotide, or morphine plus bupivacaine. For nociceptive pain, the recommended first-line medications are morphine, hydromorphone, ziconotide, and fentanyl.
- The recommended starting dose of ziconotide doses is 0.5 to 2.4 micrograms per day.
- Evidence of an increased risk of death immediately after reinitiating intrathecal opioids, or after performing a revision to the drug delivery system, was also noted. In particular, patients who have sleep apnea, psychiatric conditions, or are taking certain medications or supplements should be monitored more frequently and vigilantly.

SUPPLEMENTAL INFORMATION

Nociceptive pain: The most common type of pain and is caused by the detection of noxious or potentially harmful stimuli by the nociceptors around the body.

Neuropathic pain: Pain associated with damage to the neurons in the body, following an infection of injury to the area, resulting in messages of pain being sent to the central nervous system and brain regardless of noxious stimuli. This type of pain is often described as shooting pain, as it travels along the nerves in an abnormal manner causing abnormal sensations of pain. Neuropathic pain has been reported a constant sensation of pain and intermittent episodes, which may or may not be aggravated by stimuli or touch.

Visual Analogue Scale of Pain Intensity (VASPI; also known as VAS): A worldwide, validated, subjective measure for acute and chronic pain. A VAS score for pain is determined by using a horizontal line, 100-millimeter (mm) in length, anchored by word descriptors at each end; "no pain" (0 mm) on the left end and "worst imaginable pain" (100 mm) on the right end. The participant marks on the line the point that they feel represents their current state of pain.

CODING & BILLING INFORMATION

CPT Codes – N/A

HCPCS Code

HCPCS	Description
J2278	Injection, ziconotide, 1 mcg

AVAILABLE DOSAGE FORMS: Solution, Intrathecal, as acetate [preservative free]: Prialt: 500 mcg/20 mL (20 mL); 100 mcg/mL (1 mL); 500 mcg/5 mL (5 mL)

FDA Approved: December 23, 2004

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

12/8/2021	Policy reviewed and updated. No changes in coverage criteria; added relevant professional society guidelines (ASIPP; ASRA-ASA) and updated references.
9/2021	Policy converted to new template.
12/9/2020	New policy. IRO Peer Review: 10/9/2020. Practicing physician board certified in Physical Med & Rehab, Pain Management.

REFERENCES

Government Agency

1. Centers for Medicare and Medicaid Services (CMS). Medicare coverage database (no National Coverage Determination identified). Available from CMS.

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APPENDIX

Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*

Medicare National Coverage In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.