Subject: Prialt (ziconotide intrathecal infusion)	**Original Effective Date:** 12/9/2020
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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. 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 (i.e., 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 document and provide the directive for all Medicare members.

RECOMMENDATIONS

This policy addresses Prialt (ziconotide intrathecal infusion) for the 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).

Intrathecal medication for pain management is an alternative for cancer patients and other severe, chronic, and intractable pain sufferers whose pain is not relieved by conventional drugs or other methods of opiate delivery. It may also serve as an alternative for patients who cannot tolerate the side effects of systemic administration of opioids in the doses needed for adequate pain management. Molina Healthcare may authorize an intrathecal infusion pumps when used to administer ziconotide intrathecally for members who have proven unresponsive to less invasive medical therapy and meets the criteria as outlined in this policy.

Intrathecal administration (or other routes of administration) of ziconotide for other indications is experimental and investigational because its effectiveness for these indications has not been established.

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Ziconotide intrathecal infusion

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)

- A synthetic equivalent of a naturally occurring conopeptide (venom) found in the piscivorous marine snail. 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.
- **Does not bind to the opioid receptors nor is it antagonized by opioid antagonists**
  Advantages over morphine in that it has no interaction with the opioid receptors. As a result, it can be demonstrated that there are none of the 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.

Clinical Studies

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 (IT) 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).

Summary of Evidence

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.

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.

FDA Indications

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)

Available as: INJ, solution, as acetate [preservative free]: 500 mcg/20 mL (20 mL); 100 mcg/mL (1 mL); 500 mcg/5 mL (5 mL)

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)

FDA Approved: December 23, 2004

Black Box Warnings: 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.

PHARMACOLOGIC CATEGORY: Analgesic, Nonopioid; Calcium Channel Blocker, N-Type

COVERAGE CRITERIA FOR INITIAL AUTHORIZATION

Prialt (ziconotide intrathecal infusion) for the management of severe chronic pain may be authorized for members who meet **ALL** the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❒ Prescribed by, or member is 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

2. Diagnosis/Indication [ALL]

Documentation of ALL the following criteria are required. May include chart notes from the member's medical records, relevant labs and/or tests, and other relevant clinical information supporting the diagnosis

- ❒ Diagnosis of severe, chronic pain for which intrathecal therapy is warranted

- ❒ 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
  - **Contraindication and Black Box Warnings*
  - *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.

- ❒ Prescriber attestation that member has been counseled and acknowledges understanding of the potential risk of psychosis or neurological impairment, and wishes to proceed with treatment

3. Age/Gender/Restrictions [ALL]

- ❒ 18 years of age or older
  - *Safety and efficacy have not been established in children*

- ❒ 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.

4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]

- ❒ 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: [ALL]

  - ❍ Non-opioid medications, including ALL the following: NSAIDs, acetaminophen, gabapentin, amitriptyline, topical lidocaine, carbamazepine, duloxetine, fluoxetine

  - ❍ Two (2) short-acting and/or long-acting opioids

  - ❍ Intrathecal (IT) morphine

- ❒ Member does **not** have an infection at the injection site, uncontrolled bleeding, or spinal canal obstruction that impairs CSF circulation (**Contraindication of intrathecal administration*)

- ❒ **Not prescribed, or intended for concurrent use with, ANY of the following.** Prescriber to submit treatment plan, including planned therapy modification or clinical rationale for maintaining treatment for review if member is currently on ANY of the following medications: [ANY]

  - ❍ 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.

  - ❍ 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.

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

  NOTE: MOLINA MEDICAL/PHARMACY REVIEWER to verify per member's claims, chart notes, and prescribing physician notes/attestation

- ❒ Prescriber agrees to monitor member's response to treatment throughout therapy, including improvements to pain severity AND neurological or psychiatric signs or symptoms

5. Contraindications*/Exclusions/Discontinuations

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to ziconotide or any component of the formulation
- ❒ Pre-existing history of psychosis
- ❒ A contraindication to the use of Intrathecal analgesia including:
  - ❍ The presence of infection at the microinfusion injection site
  - ❍ Uncontrolled bleeding diathesis
  - ❍ Spinal canal obstruction that impairs circulation of cerebrospinal fluid

Exclusions

- ❒ IV administration
- ❒ 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)
- ❒ 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].
  FOR EXCEPTION: Prescriber submit documentation of chart notes and treatment plan for review, if applicable.
- ❒ 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

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: *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.*

REAUTHORIZATION /CONTINUATION OF THERAPY

Continuation of therapy with Prialt (ziconotide intrathecal infusion) may be authorized for members who meet **ALL** the following criteria **[ALL]**

1. Initial Coverage Criteria

- ❒ Member currently meets initial coverage criteria appropriate for continuation of treatment

2. Adherence to Therapy/Compliance

N/A

3. Labs/Reports/Documentation required [ALL]

- ❒ Documentation of continued need for intrathecal (IT) therapy and evidence of pain control
- ❒ Member has received ongoing monitoring for neurological or psychiatric signs or symptoms throughout therapy

4. Discontinuation of Treatment

- ❒ Unacceptable adverse effects or complications from ziconotide therapy, such as psychiatric symptoms and neurological impairment
- ❒ Contraindications/Exclusions to therapy [ANY]
  Authorization will not be granted if ANY of the following conditions apply [ANY]
  - ❍ Non-FDA approved indications
  - ❍ Hypersensitivity to ziconotide or any component of the formulation
  - ❍ Pre-existing history of psychosis
  - ❍ A contraindication to the use of Intrathecal analgesia including:
    - The presence of infection at the microinfusion injection site
    - Uncontrolled bleeding diathesis
    - Spinal canal obstruction that impairs circulation of cerebrospinal fluid
- ❒ Exclusions
  - ❍ IV administration
  - ❍ Concomitant treatment or medical condition that would render Intrathecal administration hazardous
  - ❍ 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].
    FOR EXCEPTION: Prescriber submit documentation of chart notes and treatment plan for review, if applicable.
  - ❍ 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

5. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: *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.*

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. **Recommended Dosage [ALL]**

Chronic pain (intolerant or refractory to other therapies)

- ❒ Intrathecal: Initial dose: ≤ 2.4 mcg/day (≤ 0.1 mcg/hour)

  NOTE: Initiating with more conservative dosing (see Alternate initial dosing) is preferred due to improved tolerability (McDowell 2016; Prager 2014)

- ❒ Alternate initial dosing (Off-label): Initial: 0.5 to 1.2 mcg/day (0.02 to 0.05 mcg/hour) (McDowell 2016). Initiating with no more than 0.5 mcg/day (0.02 mcg/hour) may be preferred (Prager 2014)

- ❒ 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 (ziconotide intrathecal infusion) is 19.2 mcg/day, to which the initiation dose of 2.4 mcg/day is titrated by day 21

2. **Authorization Limit [ALL]**

- ❒ Quantity limit: Dose does not exceed 19.2 mcg/day (0.8 mcg/hour)

- ❒ Duration of therapy [AS APPLICABLE]

  - ❍ Initial Therapy: May authorize up to 3 months of initial therapy

  - ❍ Continuation of therapy: May be authorized for up to 6 months year. Subsequent approval will be based on continuous progress notes from the Prescriber documenting improvement from baseline.

3. **Route of Administration [ALL]**

- ❒ Not for IV administration. For intrathecal administration only using Medtronic SynchroMed II Infusion System, or CADD-Micro ambulatory infusion pump

- ❒ Refer to Specialty Medication Administration Site of Care Policy P&P: MHI Pharm 11

- ❒ 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.

COVERAGE EXCLUSIONS

This policy addresses Prialt (ziconotide intrathecal infusion) for 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).

All other uses of Prialt (ziconotide intrathecal infusion) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy is considered experimental/investigational, and therefore will not be authorized, as the safety and effectiveness cannot be established by review of the available published peer-reviewed This is subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

SUMMARY OF EVIDENCE

Ziconotide 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 RL and colleagues (2006) assessed the slow titration schedule in 220 patients with severe chronic pain in a randomized, double-blind, placebo controlled. Patients were randomized 1:1 between ziconotide (n=112) and placebo (n=108). 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. 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).

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.)

Practice Guidelines and Position Statements

Polyanalgesic Consensus Conference (PACC)

The is comprised of a group of physicians and other clinicians in the field of IT therapy that was formed in 2000 to review the published literature and evidence pertaining to the efficacy and safety of IT therapies and provide published guidelines regarding their use. The panel develop an IT 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 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.

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.

The guidelines noted that if patients proceeding to the implantation of an IT 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 that patients are at increased risk of death immediately after reinitiating IT 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 undergo more frequent and vigilant monitoring.

Definitions

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.

Appendix

N/A

Coding Information: The codes listed in this clinical policy are for informational purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered. Coverage is determined by the benefit document. This list of codes may not be all inclusive and Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

CPT	Description

HCPCS	Description
J2278	Injection, ziconotide, 1 mcg

REFERENCES

Package Insert, FDA, Drug Compendia

Prialt (ziconotide) [prescribing information]. Lake Forest, IL: TerSera Therapeutics LLC; May 2019.

SynchroMed II Drug Infusion Pump. Medtronic website. Available at: https://www.medtronic.com/us-en/healthcare-professionals/products/neurological/drug-infusion-systems/synchromed-ii.html

Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2020. Available at www.clinicalpharmacology.com. Accessed October 2020 [Available with subscription]

US Food and Drug Administration (FDA)

- Ziconotide. Product Label and Approval History (2005). U.S. Food and Drug Administration. Available at http://www.accessdata.fda.gov. Accessed on September 2020

Clinical Trials, Definitions, Peer-Reviewed Publications

Atanassoff PG, Hartmannsgruber MW, Thrasher J, et al. Ziconotide, a new N-type calcium channel blocker, administered intrathecally for acute postoperative pain. *Reg Anesth Pain Med*. 2000;25:274-278.[PubMed 10834782]

Deer TR, Pope JE, Hanes MC, McDowell GC. Intrathecal Therapy for Chronic Pain: A Review of Morphine and Ziconotide as Firstline Options. *Pain Med*. 2019;20(4):784-798. doi:10.1093/pm/pny132

McDowell GC 2nd, Pope JE. Intrathecal ziconotide: dosing and administration strategies in patients with refractory chronic pain. Neuromodulation. 2016;19(5):522-532.[PubMed 26856969]10.1111/ner.12392.

Pope JE, Deer TR, Bruel BM, et al. Clinical uses of intrathecal therapy and its placement in the pain care algorithm. Pain Pract. 2016; 8: 2-3.

Prager J, Deer T, Levy R, et al. Best practices for intrathecal drug delivery for pain. Neuromodulation. 2014;17(4):354-372; discussion 372.[PubMed 24446870]10.1111/ner.12146

Rauck RL, Wallace MS, Leong MS, et al. A randomized, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain. J Pain Symptom Manage. May 2006; 31(5):393-406. PMID 16716870

Saulino M, Kim PS, Shaw E, et al. Practical considerations and patient selection for intrathecal drug delivery in the management of chronic pain. J Pain Res. 2014; 7: 628-631.

Smith H.S., Deer T.R. Safety and efficacy of intrathecal ziconotide in the management of severe chronic pain. Ther. Clin. Risk Manag. 2009;5(3):521–534. Available at: http://dx.doi.org/10.2147/ TCRM.S4438

Staats PS, Yearwood T, Charapata SG, et al. Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS: a randomized controlled trial. JAMA. 2004;291:63-70.[PubMed 14709577]

Ver Donck A. An Open-Label, Multicenter Study of the Safety and Efficacy of Intrathecal Ziconotide for Severe Chronic Pain When Delivered via an External Pump. Neuromodulation. Technology at the Neural Interface. 2008;11(2):103–111. Available at: http://dx.doi.org/10.1111/j.1525-1403.2008.00150.x

Wallace M.S., Rauck R., Fisher R., Charapata S.G., Ellis D., Dissanayake S. Intrathecal ziconotide for severe chronic pain: safety and tolerability results of an open-label, long-term trial. Anesth. Analg. 2008;106(2):628–637. Available at: http://dx.doi.org/10.1213/ane.0b013e3181606fad

Wallace MS, Charapata SG, Fisher R, et al. Intrathecal ziconotide in the treatment of chronic nonmalignant pain: a randomized, double-blind, placebo-controlled clinical trial. Neuromodulation. Apr 2006; 9(2):75-86. PMID 22151630

Wallace MS, Rauck R, Fisher R, et al. Intrathecal ziconotide for severe chronic pain: safety and tolerability results of an open-label, long-term trial. Anesth Analg. Feb 2008; 106(2):628-37. PMID 18227325

Webster LR and Fakata KL. Ziconotide for chronic severe pain. Practical Pain Management. May 2005. 5(4): 47-56.

Professional Society Guidelines and Other Publications

American Society of Interventional Pain Physicians (ASIPP) Guidelines. Responsible, Safe, and Effective Use of Antithrombotics and Anticoagulants in Patients Undergoing Interventional Techniques: American Society of Interventional Pain Physicians (ASIPP) Guidelines. Pain Physician 2019; 22:S75-S128. Available at: https://www.painphysicianjournal.com/current/pdf?article=NjEwMw%3D%3D&journal=118

- Manchikanti L, et al. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) guidelines. Pain Physician 2017; 20: S3-S92.
- Navani A, et al. Responsible, safe, and effective use of biologics in management of low back pain: American Society of Interventional Pain Physicians' guidelines. Pain Physician 2018; in press.
- Manchikanti L, et al. An update of comprehensive evidence-based guidelines for interventional techniques of chronic spinal pain: Part II: Guidance and recommendations. Pain Physician 2013; 16:S49-S283

Deer TR, Pope JE, Hayek SM, et al. The Polyanalgesic Consensus Conference (PACC)

- Recommendations on intrathecal drug infusion systems best practices and guidelines. Neuromodulation. 2017a;20(2):96-132.
- Recommendations for intrathecal drug delivery: guidance for improving safety and mitigating risks. Neuromodulation. 2017b;20(2):155-176.

Deer TR, Prager J, Levy R, et al. Polyanalgesic Consensus Conference 2012: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. Neuromodulation. 2012;15(5):436-464; discussion 464-436.

Reviews, Revisions, and Approvals	Approval
Policy Developed Peer Review: AMR Peer Review Network. 10/9/2020. Practicing Physician. Board certified in Physical Med & Rehab, Pain Management.	MCPC 12/9/2020

**Policy Revisions: All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were reviewed and revised with the most recent medical literature and available evidence. Coverage criteria for Initial and Continuation of Therapy revised/updated as appropriate.*