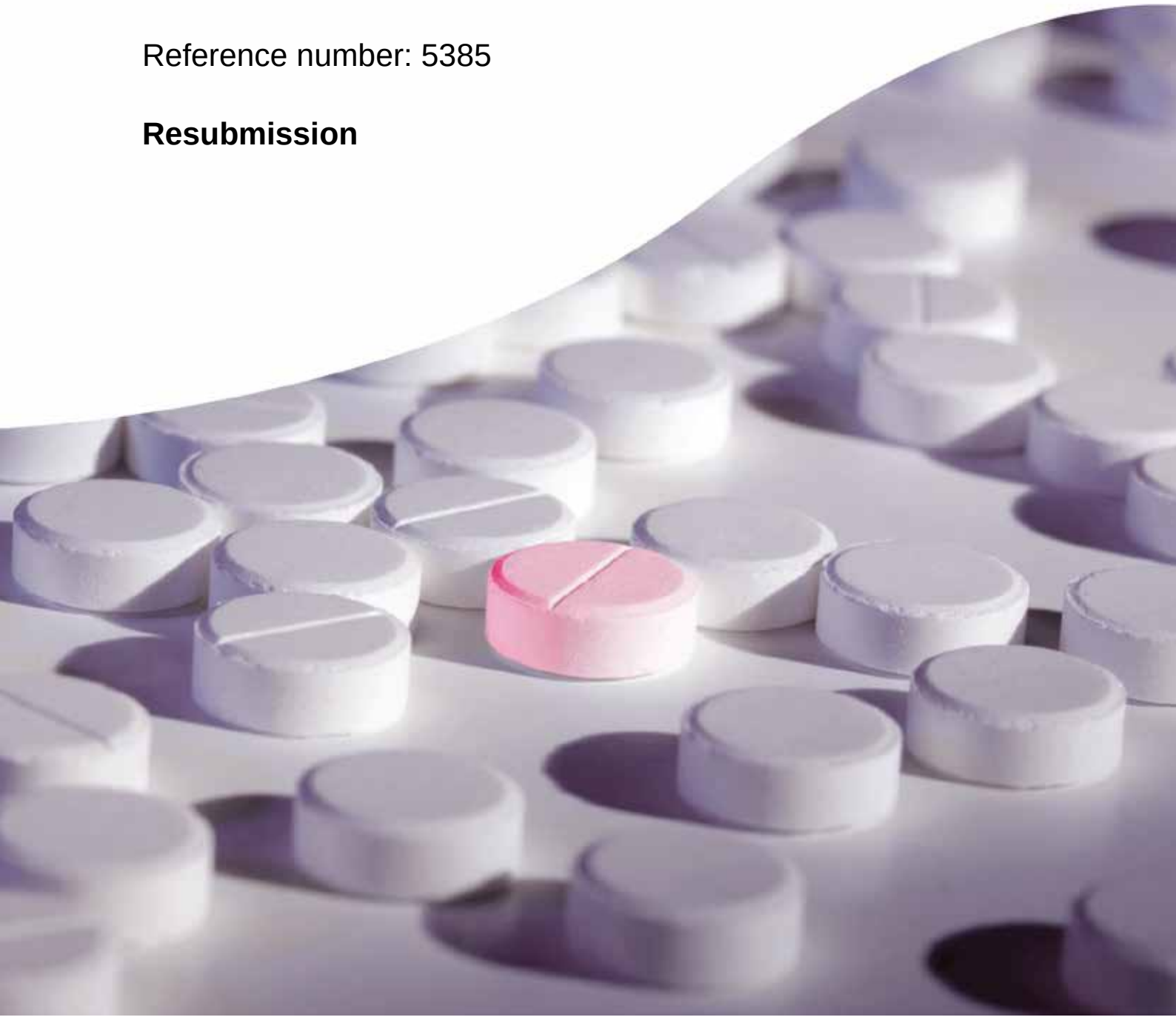
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG Secretariat Assessment Report

Ziconotide (Prialt®)
100 micrograms/ml solution for intrathecal infusion

Reference number: 5385

Resubmission



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

AWMSG Secretariat Assessment Report
100 micrograms/ml solution for intrathecal infusion

1.0 Key facts

Assessment details	Ziconotide (Prialt®) for the treatment of severe chronic pain in adults who require intrathecal analgesia. This is a resubmission, after a non-recommendation by AWMSG in July 2008, when the case for cost-effectiveness was not proven. The resubmission considers the use of a lower dose of ziconotide with a slower titration rate, as recommended by clinical guidelines, and has an approved patient access scheme discount.
Current clinical practice	Patients with severe chronic pain who need intrathecal analgesia are usually given off-label morphine. The British Pain Society and The Polyanalgesic Consensus Conference (PACC) recommend intrathecal delivery of ziconotide as an option for the first-line treatment of chronic malignant or non-malignant pain. Clinicians in Wales have raised an unmet need for a treatment for patients who have pain that is not controlled with intrathecal morphine or cannot tolerate the side effects of morphine.
Clinical effectiveness	Ziconotide reduced pain scores in three short pivotal studies comparing it with placebo (a large, randomised controlled trial [RCT] and two smaller supportive RCTs), and in several long-term studies, including studies of lower doses.
Cost effectiveness	A cost-utility analysis (CUA) compares ziconotide monotherapy with ziconotide in combination with morphine and with morphine monotherapy, in adult patients with chronic pain that is refractory, or minimally responsive to opioid analgesics. The company base case comparing ziconotide monotherapy to morphine monotherapy suggests an incremental cost-effectiveness ratio (ICER) of [commercial in confidence figure removed] per quality-adjusted life-year (QALY) gained and net health benefit ranging between [commercial in confidence figures removed] when values of £20,000 and £30,000 are placed on a QALY gain. AWTTC considers the most plausible ICER, given a comparator of morphine monotherapy, to be [commercial

	in confidence figure removed], and the most plausible net health benefit to be [commercial in confidence figures removed] when values of £20,000 and £30,000 are placed on a QALY gain. Clinical experts have advised that ziconotide monotherapy would not be used instead of intrathecal morphine monotherapy but only used when intrathecal morphine monotherapy is not an option. Therefore the most appropriate comparator for ziconotide monotherapy, based on clinical expert advice, would be best supportive care. Use of an incorrect comparator limits the applicability of the health economic analysis. The cost-utility analysis presented does not reflect the decision problem being considered. The CUA submitted, which compares ziconotide monotherapy with morphine monotherapy, lacks comparative clinical effectiveness and treatment discontinuation evidence. A key cost-effectiveness driver, relative treatment discontinuation rate for morphine, is assumption based. Mortality is assumed to be equal to the general population.
Budget impact	The company estimates that three patients will receive treatment with ziconotide in Wales in Year 1, increasing to seven patients in Year 5. The company base case suggests an additional medicine acquisition cost of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. The base case also predicts additional NHS resource costs of [commercial in confidence figure removed] in Year 1 decreasing to [commercial in confidence figure removed] in Year 5. The additional resource costs are primarily a consequence of fewer ziconotide monotherapy patients discontinuing therapy compared to morphine monotherapy patients. The budget impact analysis assumes 40% of current treatment is displaced, which AWTTC considers to be plausible.
Additional factors to consider	The company and AWTTC consider ziconotide should be considered under the AWMSG's criteria for appraising medicines for severe conditions.

This assessment report is based on evidence submitted by Esteve Pharmaceuticals Ltd. and an evidence search conducted by AWTTC on 17, 28 and 30 October 2024.

2.0 Background

2.1 Condition and clinical practice

The National Institute for Health and Care Excellence (NICE) defines chronic pain as pain that persists or recurs for more than three months[1]. Pain could be due to an underlying condition, such as arthritis or cancer, or caused by a neurological condition[2]. Chronic cancer pain is moderate to severe, and lasts for longer than 6 to 12 months; it can severely affect patients' quality of life[3].

Pain that persists can be difficult to treat[2]. Sometimes oral and intravenous analgesics will not provide sufficient pain relief or they are not tolerated because of adverse side effects[4], and increasingly invasive strategies to treat pain can be used[3]. These include nerve blocks, surgery or the injection of a medicine such as morphine, hydromorphone, fentanyl, clonidine or local anaesthetics into the intrathecal space (the space surrounding the spinal cord)[3]. Intrathecal injection allows rapid absorption into the cerebrospinal fluid, allowing enhanced therapeutic effects, and can be an effective method of pain control[5].

The British Pain Society recommends intrathecal drug delivery for the treatment of chronic non-malignant pain, pain associated with cancer, and spasticity[5]. The British Pain Society's recommended medicines for first-line single-agent therapy to manage pain using intrathecal drug delivery devices (ITTD) are: preservative-free morphine; hydromorphone; or ziconotide[5].

The 2017 Polyanalgesic Consensus Conference (PACC) Recommendations for Intrathecal Drug Delivery: Guidance for Improving Safety and Mitigating Risks, highly recommended (defined as having good evidence that the measure is effective and benefits outweigh the harms) intrathecal ziconotide for the first-line treatment of cancer pain or other terminal conditions with nociceptive or neuropathic pain[6]. Ziconotide evidence was given a higher rating than intrathecal morphine which was recommended (defined as at least moderate evidence that the measure is effective and benefits exceed harms). The 2024 PACC guidance, Intrathecal Drug Delivery Guidance on Safety and Therapy Optimization When Treating Chronic Noncancer Pain, recommends starting ziconotide at a lower treatment dose than the licensed dose[7].

Intrathecal ziconotide is an alternative to morphine for patients who cannot tolerate opioids or whose pain is refractory to first-line therapies including morphine[3]. Clinical experts in Wales have indicated they would use ziconotide as a second-line agent and not instead of morphine intrathecally unless a patient was not suitable for intrathecal morphine.

2.2 Medicine

Ziconotide is a synthetic analogue of an omega-conopeptide found in the venom of the marine snail *Conus magus*[8]. It is an N-type calcium channel blocker, which binds to the N-type calcium channels on neurones in the spinal cord to inhibit the voltage sensitive calcium current and prevent the release of pain relevant neurotransmitters; thus preventing the spinal signalling of pain[8].

In February 2005, the UK's Medicines and Healthcare products Regulatory Agency granted marketing authorisation to ziconotide (100 micrograms/ml solution for

infusion) for the treatment of severe, chronic pain in adults who require intrathecal pain relief[4].

Ziconotide is administered as a continuous infusion through an intrathecal catheter, using an external or internally implanted mechanical infusion pump (the Medtronic SynchroMed® II Infusion System)[4,8].

In 2017 the PACC issued Recommendations for Intrathecal Drug Delivery: Guidance for Improving Safety and Mitigating Risks[6]. The PACC guidance recommends that intrathecal ziconotide should be considered for the first-line treatment of cancer-related or noncancer-related pain, in the absence of psychiatric comorbidity or significant baseline renal disease[6]. The recommendation was made with a level of evidence of I (based on at least one properly designed controlled and randomised clinical trial)[6]. PACC 2024 guidance recommends starting ziconotide at a lower treatment dose than the licensed dose[7].

The Summary of Product Characteristics (SmPC) for ziconotide gives a starting dose of not more than 2.4 micrograms/day, which can be titrated in dose increments of ≤ 2.4 micrograms/day for each patient, according to analgesic response and adverse effects[8]. The maximum daily dose is 21.6 micrograms/day (0.9 micrograms/hour). The minimal interval between dose increases is 24 hours; the recommended interval between doses is 48 hours or more, for safety reasons. The SmPC also states that to limit the occurrence of serious adverse reactions, patients whose pain responds to ziconotide may require a smaller daily dose of around 3.0 to 4.5 micrograms/day or lower. Treatment should be discontinued in cases of a lack of, or insufficient, efficacy, defined as a pain reduction of < 20% at the maximum tolerated dose. The physician should always evaluate the benefit/risk on an individual basis[8].

However, clinical experts recommend a much lower starting dose, at ≤ 0.5 micrograms/day, and a slower increase by ≤ 0.5 micrograms no more than once per week[9]. The PACC 2024 recommends a starting infusion dose range for ziconotide of 0.5–2.4 micrograms/day; and when titrating ziconotide, an increase of ≤ 0.5 micrograms/day with weekly assessment is warranted[7]. If side effects occur, and depending on their severity, PACC recommends reducing the dose to a previously tolerated level that gave pain relief without the side effect[7]. These recommendations for a lower start dose and slower dose increase have the potential to increase the safety profile of ziconotide[5].

In July 2008 the All Wales Medicines Strategy Group (AWMSG) appraised ziconotide by intrathecal administration for the treatment of severe chronic pain, and issued a non-recommendation because the case for cost effectiveness was not proven. This resubmission has an approved patient access scheme (PAS) and proposes using a dose of ziconotide that is lower than the licensed dose with a slower rate of titration, as recommended by clinical guidelines.

2.3 Comparators

The comparators included in the company's submission are opioids, such as morphine. There are no other medicines licensed in the UK for use in intrathecal analgesia. Morphine is the most common analgesic used for intrathecal analgesia in the UK, although its use is off-label.

2.4 Guidance and related advice

- The Polyanalgesic Consensus Conference (PACC): Intrathecal Drug Delivery Guidance on Safety and Therapy Optimization When Treating Chronic Noncancer Pain. 2024[7]
- The British Pain Society: Intrathecal drug delivery for the management of pain and spasticity in adults: British Pain Society's recommendations for best clinical practice. 2024[5]
- All Wales Medicines Strategy Group: All Wales Pharmacological Management of Pain Guidance. 2022 (updated 2023)[2]
- The Polyanalgesic Consensus Conference (PACC): Recommendations for Intrathecal Drug Delivery: Guidance for Improving Safety and Mitigating Risks. 2017[6].

In 2008, the All Wales Medicines Strategy Group (AWMSG) issued a non-recommendation for ziconotide to treat severe chronic pain in adults who require intrathecal anaesthesia[10.]

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, ziconotide (Prialt®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

3.0 Clinical effectiveness

The Form B submitted includes evidence from several clinical studies of ziconotide therapy for chronic malignant pain and for chronic non-malignant pain. The studies include three pivotal studies, published during 2004–2006, comparing ziconotide with placebo: a large RCT and two small supportive RCTs. Longer term studies, studies of combination therapy and studies of lower doses of ziconotide were also included. Most of the studies are described below. The four studies of ziconotide used in combination therapy with other medicines are not described below as the clinical experts have advised that ziconotide will be used as monotherapy.

The three pivotal RCTs had follow-up periods that ranged from 10 days to three weeks[4]. In all of them the primary efficacy outcome measure was the mean percentage change from baseline to the end of the initial titration phase in the Visual Analogue Scale of Pain Intensity (VASPI). This is a 100 mm visual analogue scale where 0 mm = no pain, and 100 mm = worst pain imaginable. Responders were defined as those who experienced a 30% or greater decrease in mean VASPI score compared to baseline, without any increase in concomitant opioid therapy or change in opioid type[11-13]. Each RCT is described below.

3.1 Study 95-001 in patients with chronic malignant pain

This study enrolled 111 patients (mean age 55.5 years; range 24–85 years) with chronic, severe, malignant, intractable pain associated with cancer (87%) or AIDS (12%)[4,12]. Patients' average pain score was equal to, or more than, 50 mm on the VASPI score during the three days before enrolment. Patients were randomly assigned to receive ziconotide (n = 71) or placebo (n = 40) in a ratio of 2:1 and were discontinued of all intrathecal medication three days before study enrolment. However, oral analgesic treatment could be continued[12].

Treatment consisted of an initial titration phase of five days, with a maintenance phase of five to six days[12]. At the end of the titration phase, non-responders crossed over to receive the alternative blinded treatment. The mean baseline opioid usage was very high, at 5.4 g/day of oral morphine equivalents. 67 (98.5%) of 68 patients randomised to ziconotide and 38 (95%) of 40 patients randomised to placebo were receiving opioids at baseline. The median morphine dosage for ziconotide patients was 300 mg daily and for placebo was 600 mg daily. An average of 32% (n = 36) of patients across both arms had received prior intrathecal morphine[12].

The initial dosing of ziconotide was 5 nanograms/kg/h, then 0.4 micrograms/h with incremental adjustments every 12 hours to ≤ 0.1 microgram/h, with incremental adjustments once every 24 hours up to a maximum dose of 2.4 micrograms/h[4,12].

The primary efficacy endpoint in the 111 intent-to-treat (ITT) population showed a greater change in VASPI score from baseline to end of the study of 51.4% for the ziconotide arm, versus 18.1% for the placebo arm ($p < 0.001$)[12]. Mean VASPI scores were 73.6 mm (SD 1.8 mm) and 77.9 mm (SD 2.3 mm) at baseline; these were reduced by 51.4% (95% confidence interval [CI] 44–62.2) in the ziconotide group and 18.1% (95% CI 17.3–49.4) in the placebo group ($p < 0.001$)[4,12].

3.2 Study 96–002 in patients with severe, chronic, non-malignant pain

This study enrolled 257 patients (mean age 52 years) with chronic, severe non-malignant pain, of whom 76% had neuropathic pain[13]. The patients' mean baseline opioid use was 528 milligrams/day oral morphine equivalents. 58% of patients had previously been treated with intrathecal morphine and 98% of patients had pain of greater than one year's duration[13].

Patients were randomised to receive ziconotide (n = 170) or placebo (n = 87) in a ratio of 2:1[13]. The hourly infusion rate ranged from 0.1 to 7.0 micrograms/hour, with upward titration until intolerable related adverse events or satisfactory analgesia and a 24-hourly titration interval. The upper dose limit was then reduced to 0.4 to 3.9 micrograms/hour. Finally, dose range was reduced to 0.1 to 2.4 micrograms/hour with an upward titration until satisfactory analgesia or a related adverse event occurred. Non-responders to initial therapy were crossed over to the alternative blinded treatment at the end of the initial titration phase[13].

Of the 169 patients receiving initial ziconotide, 40 patients discontinued during initial titration and eight withdrew during the maintenance phase with ziconotide[13]. Forty eight patients (28.2%) completed initial titration and did not enter the second phase and 82 patients (48.2%) entered the second phase. In the placebo group, seven patients discontinued during initial titration and no patients discontinued during the maintenance phase; 18 patients discontinued during the crossover phase with ziconotide[13].

There was a significant improvement in mean percentage change in VASPI score from baseline to end of titration phase (six days) for ziconotide (31.2%) (95% confidence interval (CI): 24.6 to 36.9%) compared to placebo (6.0%) (95% CI: 0 to 11.9%) in the ITT population ($p \leq 0.001$)[13]. Mean VASPI scores were 80.1 mm (± 15.1 mm) and 76.9 mm (± 14.58 mm) at baseline and were reduced to 54.4 mm (± 29.3 mm) and 71.9 mm (± 30.93 mm) after six days with ziconotide and placebo, respectively[13].

Use of concomitant opiate treatment did not change significantly for either treatment group during the titration phase[13].

3.3 Study 301 in patients with severe chronic pain

This study enrolled 220 patients (mean age 52 years) with chronic severe intractable pain of any aetiology[11]. The mean duration of pain was 14 to 15 years. Most patients (97%) were considered refractory to treatment by their physicians and 90% had already been treated with intrathecal morphine. All patients already had implanted pumps and more than one intrathecal medicine had already been used by 58% of the patients before their enrolment. 96% of patients had non-malignant pain and 98.6% had tried oral opioids before enrolment. 74% of patients had neuropathic pain. Failed back surgery was the most common pain aetiology, reported for 60.7% of patients in the ziconotide group and 55.6% of patients in the placebo group. At baseline, the mean VASPI score was 80.7 mm (± 14.98 mm) in the ziconotide group and 80.7 mm (±14.91 mm) in the placebo group at baseline[4,11].

Patients had a three-week weaning period to discontinue intrathecal therapy, followed by a one-week stabilisation period without intrathecal medicines[11]. Patients were randomised to placebo (n = 108) or ziconotide (n = 112), receiving a starting dose of 0.1 microgram/h intrathecally with titration in dose increments of 0.05 microgram/h to 0.1 microgram/h at 24-hour intervals to a maximum dose of 0.9 microgram/h. Treatment was for three weeks with a mean dose at study end of 0.29 microgram/hour (6.96 micrograms/day)[11].

There was a significantly greater mean percentage change in VASPI score from baseline to Week 3, using the last observation carried forward (LOCF) method to impute missing data, for ziconotide (14.7%) compared to placebo (7.2%) ($p = 0.036$)[4,11].

Response to treatment was a secondary endpoint and was defined as a decrease in VASPI score of greater than or equal to 30%[11].The proportion of treatment responders did not differ significantly between groups (16.1% for ziconotide, 12.0% for placebo [$p = 0.39$]) at Week 3[11].

There was a 23.7% mean decrease in weekly opioid use from the pre-treatment stabilisation period to Week 3 in the ziconotide group, compared to a 17.3% decrease in the placebo group ($p = 0.44$, non-significant)[11].

There was no significant difference in quality of life scores between the ziconotide and placebo groups at Week 3, when assessed with the Treatment Outcomes in Pain instrument[11]. There was also no significant difference in five of the six subscales of the Brief Pain Inventory tool. However, a company-defined sleep questionnaire showed improvements in sleep duration and quality, and the Global McGill Pain Relief total score was improved for ziconotide compared with placebo[11].

3.4 Lower dose ziconotide – a retrospective review

A retrospective review was conducted of low-dose ziconotide as first-line intrathecal monotherapy[14]. In total 15 consecutive patients (aged 43–80 years; mean age 57.3 years) who were implanted and treated with intrathecal ziconotide, and who had complete data sets at three months, were reviewed. Patients were included in the

study if they had a clinically successful single bolus trial before implant of a test dose between 1 microgram and 5 microgram ziconotide. Six patients had neuropathic pain, six had failed back surgery syndrome and three had complex regional pain syndrome type 1; seven patients had received high-dose opioids. Data were collected on ziconotide dose, oral pain medicines taken, pain relief measured by the numerical pain rating scale (NRS), activities of daily living (ADL) and adverse events[14].

At 69 days (±10 days) eight patients (53%) had responded to treatment, shown by a ≥ 30%improvement in NRS scores (seven patients), ADL scores (seven patients) or both (six patients)[14]. These eight patients had NRS scores of 8.4 ± 0.7 (mean ± standard error mean [SEM]) at baseline, which reduced to 2.4 ± 1.0 after initial dosing at 2.6 ± 0.3 months after implant, and 4.0 ± 1.3 after a mean of 12.9 ± 5.9 months[14].

The initial dose in 12 patients was 1.2 micrograms/day; three patients had initial doses between 0.6 micrograms/day to 1.4 micrograms/day[14]. Visits were at 2–4 week intervals, with mean titration doses between 1.4 micrograms/day (Visit 1) and 2.8 micrograms/day (Visit 5)[14].

Adverse events attributed to ziconotide were reported in three patients[14]. These were symptoms of dizziness in two patients, which resolved with decrease of ziconotide dose to previous dosage; and one patient had transient urinary retention that resolved without intervention. No patients had withdrawal symptoms, and no patients had discontinued ziconotide at three-month follow-up[14].

3.5 Patient Registry of Intrathecal Ziconotide Management (PRIZM)

The Patient Registry of Intrathecal Ziconotide Management (PRIZM) was an open-label, long-term, multicentre, observational study of adult patients with severe chronic pain[15]. An interim analysis of PRIZM data was conducted in July 2015, which included 93 patients (mean 56.3 years) at 23 centres in the USA.

The most common prespecified primary diagnoses (≥ 5% of patients) in 51 patients who had ziconotide as the first intrathecal medicine were: failed back surgery syndrome (16.7%), central pain syndrome (10.4%), complex regional pain syndrome (8.3%), low back pain (8.3%), and diabetic neuropathy (6.3%). For patients who had had prior intrathecal therapy with other medicines, 41% had failed back surgery syndrome, 29.3% had low back pain and 7.3% had cancer pain[15].

The mean initial ziconotide dose in the overall patient population was 1.6 micrograms/day, which was titrated to 3.2 micrograms/day at Week 12 (n = 59); 3.0 micrograms/day at Month 6 (n = 46); 2.4 micrograms/day at Month 9 (n = 30); and 1.9 micrograms/day at Month 12 (n = 21)[15].

The primary efficacy outcome was “average pain for the past 24 hours” rated by patients on an 11-point Numeric Pain Rating Scale (NPRS; ranging from 0 [no pain] to 10 [pain as bad as the patient can imagine]) at Week 12. The NPRS was assessed at every clinic visit. Treatment response was defined as a ≥ 30% reduction from the baseline NPRS score.

The Patient Global Impression of Change (PGIC; a 7-point ordered categories of patient's rating of overall improvement: "very much better," "much better," slightly better," "no change," "slightly worse," "much worse," and "very much worse"), was a secondary efficacy outcome that was evaluated at Month 3 and then every three months[15]. Improvement in overall status, measured by the PGIC, was defined as a response of "very much better," "much better," or "slightly better." At every visit patients had safety assessments for adverse events and vital signs. Patients were followed for up to 18 months, as long as they continued to receive intrathecal ziconotide (monotherapy or in combination with other intrathecal medicines). 57% of patients still active in PRIZM at Month 12 and 69% of patients who remained in the Italian registry study longer than six months were receiving intrathecal ziconotide monotherapy[15].

Mean baseline NPRS score was 7.4 (standard deviation 1.9) in patients who received ziconotide as their first intrathecal medicine, and 7.9 (1.6) in patients who had prior intrathecal therapy with other medicines[15]. Mean (SEM) percentage changes in NPRS scores were −29.4% (5.5%) in patients on ziconotide as first therapy (n = 26) and +6.4% (7.7%) in patients who had had prior intrathecal therapy with other medicines (n = 17) at Month 6; and −34.4% (9.1%) in ziconotide-first patients (n = 14) and −3.4% (10.2%) in patients who had prior intrathecal medicines (n = 9) at Month 12. Improvement from baseline, measured by PGIC score, was reported in 69.2% of ziconotide-first patients (n = 26) and 35.7% of patients who had prior intrathecal medicines (n = 14) at Month 6; and 85.7% of ziconotide-first patients (n = 7) and 71.4% of patients who had prior intrathecal medicines (n = 7) at Month 12[15].

The most common adverse events overall (≥ 10% of patients) were: nausea (14.0%), confusional state (10.8%), and dizziness (10.8%)[15]. Adverse events led to study discontinuation in 16.1% of patients overall: 23.5% of patients treated with ziconotide first, and 7.1% of patients who had prior intrathecal medicines[15].

A subset of 28 patients remained on the study and completed 18 months of treatment[16]. In the final data analysis in January 2017, in the overall patient population, 17.4% had ≥ 30% pain reduction from baseline at Week 12, with a mean reduction in pain of 10.9%. At Month 18, 38.5% of patients had ≥ 30% pain reduction from baseline, with a mean pain reduction of 24.7%. Patient-rated improvement was reported in 67% of patients at Week 12 and in 71% at Month 18[16].

Almost all patients experienced adverse events, the most common of which were nausea (25.8%), confusional state (22.6%), and dizziness (20.4%)[16]. Treatment emergent adverse events led to treatment discontinuation in 30 patients (32%): 18 patients who received ziconotide as their first intrathecal medicine, and 12 patients who had received prior intrathecal medicines[16].

The study concluded that intrathecal ziconotide provided clinically meaningful pain relief in 17.4% and 38.5% of patients at Week 12 and Month 18, respectively[16].

3.6 Cohort study in spinal cord injury-related pain

A prospective cohort study assessed the responder rate and long-term efficacy of ziconotide in the treatment of pain related to spinal cord injury[17]. Twenty consecutive patients (aged 30–72 years) with chronic neuropathic pain related to spinal cord

lesions that was refractory to medical pain management were considered for inclusion. Patients were tested by lumbar puncture injection of ziconotide or continuous intrathecal infusion, and if they had a significant decrease in pain scores (> 40%) they were implanted with a continuous infusion pump. Pain scores were measured using the Visual Analogue Scale (VAS), which measures pain intensity using a visual analogue scale that consists of a 10 cm line, with two endpoints representing 0 ("no pain") and 10 ("pain as bad as it could possibly be") [17].

Fourteen patients had decreases of > 40% in VAS pain scores, but due to adverse effects and patient choice, only 11 were implanted with permanent pumps[17]. Patients were followed up for an average of 3.59 years, and in eight patients an above threshold considered a significant decrease in pain scores was maintained[17].

3.7 Study of the impact of ziconotide on patients' experience of neuropathic pain

A prospective study enrolled 14 patients with neuropathic pain who were eligible for implantation of an intrathecal analgesia programmable pump system using ziconotide[18]. Three patients were excluded from analysis because they withdrew from the study (one moved out of the area and two were unable to adhere to the programming regimen). The other 11 patients had a successful trial of bolus ziconotide, experiencing > 50% pain relief[18].

NRS scores were assessed at intervals to evaluate pain levels and guide dose titration[18]. Clinical responses were evaluated with the Pain Catastrophising Scale (PCS), Short-Form 36 (SF-36), Oswestry Disability Index (ODI) and Beck Depression Inventory (BDI) questionnaires, completed at baseline after surgery and at three, six and 12 months post-operatively[18].

Patients received an initial dose of 1.2 micrograms/day ziconotide and dosages were increased by 0.2 micrograms/day at 3-week and 6-week follow-up appointments, and by 0.4 micrograms/day at eight weeks, 10 weeks, three months and then monthly up to six months[18]. Dosage titration after six months was increased according to clinician discretion and patient needs.

Of the 11 patients (mean age 55.36 years) who completed the study, seven patients responded to ziconotide treatment, based on numeric rating scale (NRS) (a tool used to measure pain intensity with a scale from 0 to 10, with 0 representing no pain and 10 representing the worst pain possible). The minimum clinically important difference is a ≥ 1.2-point reduction in NRS score[18].

At a mean follow-up of 10.91 months (± 0.70 months), significant improvements were recorded for the entire cohort in SF-36 emotional well-being (P = 0.04), SF-36 pain (P = 0.02), and ODI (P = 0.03) significantly improved for the entire cohort[18]. In the seven patients who were responders significant improvements were recorded in SF-36 emotional well-being (P = 0.01), SF-36 pain (P = 0.04), ODI (P = 0.02), PCS-Rumination (P = 0.02), PCS-Helplessness (P = 0.02) and PCS-Total (P = 0.003) scores improved significantly only for patients who were responders[18].

Eight adverse events occurred during the study[18]. Two patients reported transient hallucinations. Two patients experienced pump malfunctions, which required surgical repair. Neither of the two patients who required surgical revision experienced

withdrawal, but both had recurrence of their pain at the presentation of their malfunction. Other adverse effects that were reported but were of unclear cause included transient leg swelling, transient visual changes, and bilateral leg weakness[18].

3.9 Safety information

The SmPC for ziconotide states that ziconotide treatment should only be done by physicians experienced in intrathecal administration of medicines[8]. Patients should undergo a neuropsychiatric evaluation before, after starting and during intrathecal ziconotide and immediately when any depressive signs or symptoms appear[8].

The SmPC recommends that, to limit the occurrence of serious adverse reactions, patients who respond to ziconotide may need a daily dose of approximately 3.0–4.5 micrograms/day or lower, which is smaller than the doses used in clinical studies[8]. The dose of ziconotide should be adjusted according to the severity of pain, the patient's response to therapy and the occurrence of adverse reactions[8].

When side effects occur, the PACC intrathecal drug delivery guidance (2024) recommends to reduce the intrathecal infusion dose of ziconotide to the last tolerated level that relieved pain without side effects[7]. In the setting of severe side effects, PACC also recommends that ziconotide can be discontinued without the risk of withdrawal[7].

In clinical studies, 88% of patients reported adverse reactions. The most common adverse reactions in long-term studies were: dizziness (42%), nausea (30%), nystagmus (23%), confusional state (25%), abnormal gait (16%), memory impairment (13%), blurred vision (14%) headache (12%), asthenia (13%) vomiting (11%) and somnolence (10%)[8]. Serious but rare side effects include psychosis, suicide and rhabdomyolysis[5]. Ziconotide should only be used by clinicians experienced in the introduction and dose escalation of the drug as well as the diagnosis and management of its side effects. The recommendations for a lower start dose and slower dose increase have the potential to increase the safety profile of ziconotide[5].

3.10 AWTTC critique

- Ziconotide is the only medicine licensed for intrathecal analgesia. This resubmission highlights evidence of its efficacy in reducing pain scores when used as monotherapy, and when doses lower than stated in the SmPC are used.
- There is no treatment option available for patients with severe pain requiring intrathecal treatment in whom intrathecal morphine is not a suitable treatment. Severe pain is reported as impacting on patients' quality of life and for chronic pain patients this is over a prolonged period. Clinical experts in Wales have highlighted there is an unmet need for treatment for these patients. Clinical guidelines (British Pain Society and PACC) recommend intrathecal ziconotide, given at lower doses than recommended in the SmPC, for intrathecal analgesia.
- Most patients who responded to treatment with ziconotide had reductions in pain scores of over 30%, which is clinically significant for patients with severe pain.
- There are no direct comparator studies, and no licensed comparator medicines. Clinical experts in Wales have advised that ziconotide would not be

used instead of intrathecal morphine, but only used when intrathecal morphine is not an option. Therefore, the comparator based on clinical expert advice would be best supportive care.

- Ziconotide lacks the serious side effects of morphine of respiratory depression, tolerance, dependence, accidental overdose, decreased testosterone levels in men, and catheter tip granuloma formation, potentially leading to spinal cord compression [18].
- A risk-benefit evaluation conducted in 2024 concluded that, from analysis of the available literature, although the benefit/risk assessment of ziconotide in chronic pain appears favourable when used as monotherapy, specific long-term prospective, randomised studies are still lacking[19].
- The pivotal RCTs comparing ziconotide with placebo were conducted over very short timeframes (five days to three weeks), and only a small number of patients were treated. However, there is additional clinical evidence from prospective studies of the use of ziconotide for longer time periods, and of using smaller doses of ziconotide.

4.0 Cost-effectiveness

4.1 Context

The company's submission includes a cost-utility analysis (CUA) comparing ziconotide monotherapy with ziconotide in combination with morphine and with morphine monotherapy, in adult patients with chronic pain that is refractory, or minimally responsive to opioid analgesics. The medicines are delivered via an intrathecal pump. Ziconotide is delivered at a continuous daily dose of 3.5 micrograms, the daily dose of morphine is 12 mg, combination therapy is modelled as 50% of ziconotide and morphine doses.

The CUA takes the form of a Markov model, comprising 7-day cycles. The model adopts a 40-year time horizon and an NHS Wales/Personal and Social Services perspective. Costs and outcomes are discounted at 3.5%. The submission incorporates a simple Wales Patient Access Scheme discount. The model is characterised by five health states: titration phase, response phase, non-response phase, best supportive care phase (BSC), and death. Patients may transition to death from any health state.

Patients begin the model in the titration phase receiving an initial dose of their first-line treatment, this is up-titrated weekly until the median daily dose is reached. The titration phase state is a tunnel state. Patients progress from the titration phase state to either the responder phase state or non-responder phase state. Patients remain on their first-line treatment in the responder state until response is lost, this is modelled as treatment discontinuation, they progress to the non-responder phase where they receive their second-line treatment. The second-line treatment for ziconotide monotherapy and for morphine monotherapy is ziconotide combination therapy, those on ziconotide combination therapy as a first-line therapy receive best supportive care as their second-line therapy.

There is no direct clinical evidence comparing ziconotide monotherapy with ziconotide combination therapy or morphine monotherapy and there is no network

meta-analysis included in the submission. The efficacy data used to inform the transition probabilities are derived from an RCT which focused on ziconotide versus placebo[11]. This trial defined treatment response as a ≥ 30% reduction in VASPI score from baseline to the end of the titration period, with treatment response rates of 16.1% reported for ziconotide compared to 12.0% for placebo, but this was not statistically significant (p = 0.39). The company assumes equivalence in efficacy across the three treatment options. A weekly probability of treatment response of 5.80% is applied for each of the three treatment options for the first three titration phase cycles.

Once titration is complete, responding patients remain in the response state until response is lost with treatment discontinuation rates applied to transition non-responding patients to the subsequent line of therapy or best supportive care. The median time on treatment duration of 2.55 years reported by Rauck et al., 2006[11] is converted to an annual rate of 27.19% and applied to ziconotide monotherapy and ziconotide combination therapy. It is assumed that a greater proportion of patients discontinue treatment with morphine (relative rate 1.42).

Mortality is applied equally across all states of the model. Adverse events are informed by Rauck et al., 2006[11] for both the titration phase and for subsequent treatment states. Adverse events are assumed to be equal for ziconotide and morphine, this is considered a conservative assumption. Eight adverse events are included in the analysis; these have been chosen from a complete list of 15 due to utility data availability.

Ziconotide monotherapy dosing is included at 3.5 micrograms daily with morphine at 12 mg daily based on the literature[11]. Combination therapy is assumed to comprise equal proportions of ziconotide and morphine. Best supportive care consists of the six most common medications reported in Rauck et al., 2006[11], the relative proportions are weighted to offer full coverage. Medicine acquisitions costs are sourced from the British National Formulary (BNF), the cost of ziconotide is based on the Wales PAS price. The model applies a vial sharing assumption for vials of ziconotide, however pack sharing is not applied for BSC. Administration and monitoring resource use is assumed. Adverse event costs are informed by Dewilde et al., 2009[20], with unit costs sourced from Personal Social Services Research Unit (PSSRU)[21] and the NHS reference costs[22]. All patients are modelled as having an intrathecal drug delivery device (ITDD) in situ at model entry, the amortised cost of insertion, removal and the pump device are applied according to a 6.5-year lifespan.

There are no clinical trials reporting health-related quality of life for this patient group that offer disaggregated figures for each of the health states. The CUA model uses VASPI scores for the population in conjunction with literature-based time trade-off utility scores from Eldabe et al., 2010[23] to inform the health state utility values. Patients in the responding phase state experience a utility value of 0.04, this is the highest utility value in the CUA model; the lowest health state utility value, excluding the additional impact of adverse events, is −0.15, this is for patients on best supportive care. Adverse event utility decrements are applied additively to health states. Negative utility values are seen as worse than death.

Deterministic and probabilistic sensitivity analyses and scenario analyses were conducted to test the influence of the uncertainty of individual parameters on the

model results. The parameters tested, among others, included: discontinuation factor, utility scores, monitoring costs and number of healthcare resources required.

4.2 Results

The results of the base case are detailed in Table 1. When compared with morphine monotherapy, the incremental cost-effectiveness ratio (ICER) generated is [commercial in confidence figure removed] per quality-adjusted life-year (QALY) gained. The main cost differences can be attributed to medicine acquisition costs. The incremental QALY gains are predominantly driven by avoidance of the best supportive care (BSC) state where utility values are negative. The company base case also generates net health benefit ranging between [commercial in confidence figures removed], when values of £20,000 and £30,000 are placed on a QALY gain.

When compared to ziconotide combination therapy, ziconotide monotherapy has an ICER of [commercial in confidence figure removed] per QALY gained. The cost differences can largely be attributed to the combination therapy arm spending more time in the BSC state and its associated higher monitoring costs. The incremental QALY gains are predominantly driven by avoidance of the BSC state for the monotherapy arm where utility figures are negative.

The fully incremental analysis shows that morphine monotherapy dominates ziconotide combination therapy; accordingly, subsequent reporting focuses on ziconotide monotherapy compared to morphine monotherapy only.

Table 1. Results of the base case analysis

	Ziconotide monotherapy	Morphine monotherapy	Difference
Medicine acquisition cost	¶¶	£26,509	¶¶
Medicine administration cost	£23,070	£23,642	−£572
Adverse event cost	£15,292	£14,828	£464
Monitoring cost	£130,186	£132,200	−£2,014
ITTD insertion cost	£5,283	£4,357	£927
ITTD removal cost	£2,150	£2,396	−£246
Total cost	¶¶	£203,932	¶¶
Total life-years	28.922	28.922	0
Total QALYs	−1.677	−1.954	**0.277**
ICER (£/QALY gained)	¶¶		

	Ziconotide monotherapy	Morphine monotherapy	Difference
Expected net health benefit valuing a QALY at £20,000	¶¶		
Expected net health benefit valuing a QALY at £30,000	¶¶		
¶¶: commercial in confidence figure removed ICER: incremental cost-effectiveness ratio; ITTD: intrathecal drug delivery device; QALY: quality-adjusted life year			

The results of the univariate sensitivity analysis show that the ICER is most sensitive to the relative treatment discontinuation rate, utility values and monitoring costs. Variations in parameter estimates produce ICERs within the usual accepted thresholds, the ICER is robust to univariate sensitivity analyses.

Probabilistic sensitivity analyses indicate that ziconotide monotherapy has a [commercial in confidence figures removed] probability of being cost-effective at a threshold of £20,000 and £30,000 per QALY gained, respectively. A range of scenario analyses is reported in Table 2.

An AWTTC requested scenario which explores the impact of vial sharing for ziconotide, resulted in ICER of [commercial in confidence figure removed] per QALY gained and expected net health benefit of [commercial in confidence figure removed] when valuing a QALY at £20,000 and [commercial in confidence figure removed] when valuing a QALY at £30,000.

Table 2. Results of scenario and sensitivity analyses

Scenario	ICER	Plausibility
Median dose ziconotide 5.0 micrograms daily	¶¶	This scenario offers insight into potential higher doses required.
Time horizon reduced to 20 years (base case 40 years)	¶¶	This scenario demonstrates the robustness of the ICER to changes in the model time horizon.
Ratio of discontinuation rate between ziconotide and morphine 0.84 (base case 0.70)	¶¶	The base case ratio of treatment discontinuation is an assumption. This change to the ratio shows the ICER increasing as the relative rate of discontinuation moves towards equality (1.0).
AWTTC requested scenario		
No vial sharing	¶¶	This scenario demonstrates the impact of increased costs resulting from no vial sharing.
¶¶: commercial in confidence figure removed		

4.3 Critique

The submission is characterised by both strengths and limitations:

Strengths:

- The submission gives a detailed, transparent account of the methods and data sources used in the analysis.
- The approach of including second-line and BSC treatments aims to more closely replicate the experience of people with chronic refractory pain treated in Wales.
- Extensive sensitivity and scenario analyses have been conducted.
- In the absence of robust clinical evidence conservative assumptions are made and supported with narrative evidence.

Limitations:

- The cost-utility analysis presented does not reflect the decision problem being considered. Clinical experts have advised that ziconotide monotherapy would not be used instead of intrathecal morphine monotherapy but only used when intrathecal morphine monotherapy is not an option. Therefore, the most appropriate comparator for ziconotide monotherapy, based on clinical expert advice, would be best supportive care.
- There are numerous model assumptions and there is use of surrogate end point in the absence of robust clinical evidence, these modelling approaches reduce the confidence in the ICER.
- There is an absence of comparative clinical evidence and applying an equivalent treatment response rate for ziconotide and morphine monotherapy based on assumption alone introduces the risk of bias and reduces confidence

in the model outcomes. Clinical effectiveness estimates applied to morphine monotherapy appear conservative; however, the impact of the assumption on the ICER is unknown.

- A significant influence in the economic model is the relative time on treatment. The assumption-based discontinuation rate for morphine monotherapy increases the uncertainty of all findings.
- The parameter modelling of treatment discontinuation is based on the assumption of a constant rate of discontinuation in the absence of either a Kaplan–Meier or a parametric survival model. It is unknown what impact this approach would have on the ICER.
- The model utilises data from a three-week efficacy trial and discontinuation rates based on a median treatment duration of 2.55 years. Confidence in the robustness of the ICER results is consequently reduced as a result of extrapolating the findings of a limited dataset over a 40-year time horizon.
- The mortality for patients is assumed to be equal to the general population, this assumption may underestimate the mortality rate of the patient group. Higher mortality rates may reduce the cost effectiveness of interventions characterised by a higher initial cost offset by savings in healthcare resources over time.
- Resource use levels are based on assumptions and are key cost drivers for the cost-effectiveness. The impact these assumptions have on the ICER is unknown.
- The model assumes equivalent adverse events and rates for ziconotide and morphine despite the treatments having different adverse event profiles. Whilst this likely favours the morphine treatment arm, it introduces further uncertainty into the findings.
- Utility values are based on VASPI scores time trade off analysis and not a generic health-related quality of life measure, such as the EQ5D. This approach may add bias to the analysis.
- Adverse events are included in the model as an additive QALY decrement. This approach may induce bias to the analysis if there are interaction effects between health states and adverse events.
- There is an assumption of no pack sharing for BSC. This bias impacts the costings in favour of ziconotide.

4.4 Review of published evidence on cost-effectiveness

A literature review conducted by All Wales Therapeutics and Toxicology Centre (AWTTC) did not identify any studies relevant to the cost-effectiveness of comparing ziconotide monotherapy with ziconotide in combination with morphine or morphine monotherapy in adult patients with chronic pain that is refractory, or minimally responsive to opioid analgesics.

5.0 Budget impact

5.1 Context and methods

The company has estimated that there will be nine people with refractory chronic pain in Year 1, increasing to 25 patients in Year 5. This estimate is based on Office for National Statistics population statistics for Wales and condition specific incidence and prevalence data published by Yu et al., 2020[24]. To calculate the number of people who need treatment in Wales, the company has combined incidence and prevalence estimates, with an 0.0087% eligible patient population rate from Duarte et al., 2020[25] together with a general population mortality rate[26]. A 50% sub-population of patients who are considered as having chronic refractory pain was assumed. An assumed market share of 40% in Year 1, remaining constant at 40% through to Year 5 is further applied to estimate the number of people likely to be prescribed ziconotide in Wales for chronic refractory pain covered in the submission. The company provides a breakdown of how comparator medicines are likely to be displaced as a result. Sensitivity analyses explore a range of scenarios and parameter variability including the impact of market share percentage increasing/decreasing by 20% and ziconotide price increasing/decreasing by 30%.

5.2 Results

The budget impact is presented in Table 3. Value added tax (VAT) has not been added. The company estimates that introducing ziconotide would lead to a net medicine acquisition cost of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. This estimate incorporates cost differences resulting from the displacement of morphine monotherapy. The company carried out a sensitivity analysis including an increase to the dose of ziconotide to 5 micrograms per day; this increased the overall cost to [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5.

Table 3. Company-reported costs associated with use of ziconotide for the treatment of refractory chronic pain

	Year 1	Year 2	Year 3	Year 4	Year 5
Sub-population of eligible patients (indication under consideration)	9	13	17	21	25
Uptake of new medicine (%)	40%	40%	40%	40%	40%
Number of patients receiving new medicine allowing for discontinuations	3	4	5	6	7
Medicine acquisition costs in a market without new medicine	£2,446	£3,262	£4,485	£5,708	£6,523
Medicine acquisition costs in a market with new medicine	¶¶	¶¶	¶¶	¶¶	¶¶

	Year 1	Year 2	Year 3	Year 4	Year 5
Net medicine acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶
Net supportive medicines costs	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs* (savings/costs) including supportive medicines where applicable	¶¶	¶¶	¶¶	¶¶	¶¶
*Costs are net of VAT – this intervention is delivered in secondary care which will incur additional VAT costs. ¶¶: commercial in confidence figure removed					

The company estimates that net resource implications arising from the introduction of ziconotide monotherapy will lead to a cost of [commercial in confidence figure removed] in Year 1 decreasing to [commercial in confidence figure removed] in Year 5. This is a consequence of increased administration, diagnostic, monitoring and higher adverse event costs primarily driven by the reduced treatment discontinuation rate for ziconotide compared to morphine. These resource type costs are included for potential planning purposes but may not be realised in practice.

5.3 Critique

- The company estimates the eligible patient population in a transparent manner. However, the reliance on using population data from an epidemiology study of chronic low back pain and osteoarthritis patients combined with prevalence and incidence data that is inconsistent with what would be expected in practice may not accurately reflect the indicative patient population.
- Plausible assumptions are made for medicine uptake and cost inputs.
- The estimated per patient net costs are based on costs included in the company's economic model. The limitations and uncertainties of the economic model feed through to the uncertainty of the budget impact estimates.

6.0 Additional factors to consider

6.1 AWMSG's policy for medicines for severe conditions

The applicant company believes that the use of ziconotide in the given patient population (adults with refractory chronic pain) meets the QALY shortfall criteria set by the AWMSG policy on appraising medicines for severe conditions.

The AWMSG QALY shortfall criteria for appraising medicines for severe conditions, and a discussion of the extent to which the medicine may meet these criteria, are provided in Table 4.

Table 4. Severity modifier considerations for New Medicines Group (NMG)/AWMSG

AWMSG criteria for applying a severity modifier weight	Ziconotide considerations
AWMSG can: · apply a QALY weight of 1 if the medicine is indicated for patients with a condition associated with an absolute QALY shortfall < 12 and/or a proportional QALY shortfall < 0.85. · apply a QALY weight of 1.2 if the medicine is indicated for patients with a condition associated with an absolute QALY shortfall ranging between 12 and 18 and/or a proportional QALY shortfall ranging between 0.85 and 0.95. · apply a QALY weight of 1.7 if the medicine is indicated for patients with a condition associated with an absolute QALY shortfall >18 and/or a proportional QALY shortfall ≥ 0.95. If the absolute and proportional QALY shortfalls imply different levels of severity, QALY weighting selection is guided by the shortfall that shows greatest severity.	The general population expected life-year and expected total QALY estimates are taken from the pooled 2017–2019 life table[26] and Alava et al., (2022)[27] in combination with McNamara et al., (2023)[28]. Expected life-year and expected total QALY estimates for patients being treated with morphine monotherapy are taken from the company submission Markov model, utility scores are sourced from Eldabe, et al. 2010[23]. Mortality within the company submission Markov model is assumed to be equal to the population average. An annual discount rate of 3.5% has been used to calculate QALY shortfall estimates. AWTTC considers the QALY shortfall estimates to be informed by recent and robust data sources. AWTTC considers the most plausible absolute QALY loss to be around 16.1, given this estimate the relative and absolute shortfall meet the AWMSG criteria for the 1.7 QALY modifier weight. This estimate is deemed plausible due to the very low utility scores experienced by patients with these symptoms. Utility scores used in this analysis were elicited from the general public for severe chronic pain[23]. There is no mortality difference included in the analysis, equal life years are assumed, the disparity in QALYs is therefore driven by utility scores, with the limitations in these noted in Section 4.3.
QALY: quality-adjusted life-year	

If NMG/AWMSG conclude that ziconotide should be considered under the AWMSG policy for appraising medicines for severe conditions, NMG/AWMSG will need to consider:

- the effect of the severity QALY weight applied, and whether the weighted QALY benefits in this patient group result in a most plausible ICER that falls within the current cost-effectiveness threshold range.

In addition, NMG/AWMSG will need to be satisfied that:

- The estimates of the expected life years and total QALYs for the general population and for patients being treated with the comparator medicines(s) are sourced from recent and robust data sources.
- The assumptions used in the economic modelling are plausible, objective and robust.

Using the company's base case of ziconotide monotherapy compared to morphine monotherapy the application of a QALY weighting of 1.7 produces an ICER of [commercial in confidence figure removed] per QALY gained. Using the scenario AWTTC considers to be the most plausible alternative to the company's base case and application of a QALY weighting of 1.7 results in an ICER of [commercial in confidence figure removed] per QALY gained.

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