All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report:

Ziconotide (Prialt®▼) for the intrathecal treatment of severe, chronic pain

Eisai Ltd.

Advice No: 0708

Recommendation of AWMSG

Ziconotide (Prialt®▼) is not recommended for the treatment of severe, chronic pain in patients who require intrathecal (IT) analgesia.

Key factor influencing the recommendation:
The case for cost effectiveness of ziconotide (Prialt®▼) has not been proven.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Friday, 13th June 2008

The recommendation of AWMSG is:

Ziconotide (Prialt®▼) is not recommended for the treatment of severe, chronic pain in patients who require intrathecal (IT) analgesia.

Key factor influencing the recommendation:

The case for cost effectiveness of ziconotide (Prialt®▼) has not been proven.

2.0 PRODUCT DETAILS:

2.1 Licensed indication:
Ziconotide (Prialt®▼) is indicated for the treatment of severe, chronic pain in patients who require intrathecal (IT) analgesia[1].

2.2 Dosing:
Dosing of ziconotide should be initiated at 2.4 micrograms/day and titrated on an individual patient basis according to the patient's analgesic response and adverse reactions. Patients should be titrated in dose increments of no more than 2.4 micrograms/day, up to a maximum dose of 21.6 micrograms/day. The minimal interval between dose increases should be 24 hours; the recommended interval, for safety reasons, is 48 hours or more[1].

Ziconotide must be administered as a continuous infusion via an intrathecal catheter, using an external or internally implanted mechanical infusion pump capable of delivering an accurate infusion volume. As the risk of meningitis secondary to prolonged catheterisation of the intrathecal space is greater with an external catheter infusion system, internal systems are recommended to administer ziconotide for prolonged periods. An external catheter system should only be used when an internal system cannot be implanted[1].

Caution should be exercised when ziconotide is administered to patients with impaired renal or hepatic function. Ziconotide is not recommended for use in children under the age of 18 years[1].

2.3 Market authorisation (MA) date: 21st February 2005 (Elan Pharmaceuticals as MA holder). MA was transferred to Eisai Ltd. on the13th September 2006[2].
Ziconotide was assigned orphan status by the European Medicines Agency (EMEA) in 2001[2].

2.4 UK Launch date: July 2006[2]

3.0 DECISION CONTEXT
Severe, chronic pain has multiple causes, such as failed back surgery, injury, accident, cancer, auto-immune deficiency syndrome (AIDS), and other nervous system disorders[3]. First line treatment of severe, chronic pain is conservative medical management (CMM) which includes systemic opioids, in accordance with the World Health Organization (WHO) guidance[4]. When conservative treatment is no longer appropriate, intrathecal (IT) medication may be an option.

IT treatment is usually initiated using opioid analgesics, frequently morphine[5]. Although it is not licensed for IT use in the UK, numerous case reports, retrospective studies and a smaller number of prospective studies support the potential for considerable pain relief with IT morphine[5]. However, reported failure rates with IT morphine range from 23% to 80%, and following long-term IT morphine treatment the incidence of side effects is relatively high (e.g. constipation, urinary retention, nausea, impotence, vomiting, nightmares, pruritus)[5].

Ziconotide is a synthetic peptide based on the toxin of the marine snail, *Conus magus*. It achieves its anti-nociceptive effects by selective blocking of the neuronal N-type calcium channels, thus disrupting the spinal signalling of pain[5,6].

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

Studies 95-001 and 96-002 demonstrated the short-term (five to six day) efficacy and safety profile of ziconotide for both chronic malignant and chronic non-malignant pain refractory to opioid treatment. However the rapid dose escalation and high doses used are outside licensed recommendations and therefore the relevance within this submission is not clear.

Study 301 was a three week study in patients with pain of any aetiology, the majority (74%) having severe, chronic neuropathic pain. This showed a limited overall efficacy of ziconotide, which may in part be due to the refractory patient population studied; all patients already had implanted pumps and most had failed previous IT therapy.

Cognitive and neuropsychiatric adverse effects (AEs), particularly confusion, are common in patients treated with ziconotide. The incidence of meningitis with IT ziconotide is similar to that with other IT analgesics, and increases when external, rather than internal, infusion systems are used. Serious adverse events and those leading to treatment discontinuation can be minimised when ziconotide is titrated slowly according to the licensed recommendations. As ziconotide does not appear to induce respiratory depression from studies to date, it may be useful for treatment of patients at risk of acute respiratory depression.

Two long-term, open-label studies (95-002 and 98-022) show that patients have been treated for one year or longer, although both these studies had a high drop-out rate; 80% and 61% respectively before 12 months, mostly due to AEs.

Comparative, randomised, controlled studies are needed to determine its place in therapy for severe, chronic pain in both malignant and non-malignant disease.

4.2 Review of the evidence on cost-effectiveness

The economic model compares ziconotide against best supportive care (BSC) in patients who have severe, chronic pain inadequately controlled by systemic and IT administered analgesics. It relates only to patients who already have an IT pump in place.

The base case analysis indicates an incremental cost per QALY gained of £11,087 based on incremental costs of £17,989 and a gain of 1.63 QALYs over BSC. However, there are several issues and uncertainties with the assumptions employed in the base case model. These include the re-analysis of clinical data from the pivotal trial, which has the effect of improving the response to treatment with ziconotide; the assumed dosing and costs of ziconotide over the longer term and the selective incorporation of adverse events. Supplementary analyses have been conducted using a modified base case model in which the response to treatment with ziconotide is reduced in line with the available data and the costs of IT pumps are accrued more appropriately. These indicate that the model is sensitive to the assumed dose of ziconotide: at a possibly more appropriate dose over the long term of 0.525micrograms/hour, the incremental cost/QALY is estimated as £20,426. These analyses are still subject to some uncertainties, including the incorporation of adverse events.

5.0 LIMITATIONS OF DECISION CONTEXT:

- The patient group for which ziconotide is licensed is broader than the specific patient groups included within the randomised, controlled studies (RCTs) used for this submission[1,5].
- There is little experience with long-term ziconotide treatment in patients with malignant pain. This concern is reflected in the "Warning/Precautions" (section 4.4) of the SPC[1,5] .
- The recruitment of patients with severe, chronic pain of malignancy eligible for IT long-term treatment has been reported to be very difficult. The majority of patients across all studies had neuropathic pain.
- The cost-effectiveness model is based on patients in study 301 who already had an IT pump in place and were very refractory to pain-relieving treatments[3].
- It is uncertain whether or not the number of patients eligible for treatment with ziconotide meets the AWMSG's criteria for ultra-orphan drug status.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

6.1 Clinical efficacy:

The company submission is based on three pivotal randomised, double-blind, placebo-controlled short-term studies[6,7,8] and two longer term studies[9,10].

The primary efficacy outcome measure in all studies 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 100mm visual analogue scale where 0mm = no pain and 100mm = worst possible pain. Responders were defined as those who experienced a 30% or greater decrease in VASPI score compared to baseline, without any increase in concomitant opioid therapy or change in opioid type [6,7,8,9,10] .The longer term study, 98-022, was intended to evaluate the safety of ziconotide and therefore no minimum VASPI score was required for study participation[10].

A modified intention to treat population (mITT) was defined as randomised patients who had received any amount of study medication, had a baseline VASPI score and had at least one follow up VASPI score during the initial titration phase[5].

6.1.1 Study 95-001 (Chronic-malignant pain)[3,7]

This was a study in 112 patients with chronic, severe, malignant, intractable pain associated with cancer or AIDS. Patient age ranged from 24 to 85 years (mean age was 55.5 years) and the average pain score was equal to, or more than, 50 mm on the VASPI score[7]. Patients were randomly assigned to receive ziconotide (n = 72) or placebo (n = 40) in a ratio of 2:1 and were discontinued of all IT medication three days prior to study enrolment, however oral analgesic treatment could be continued. Treatment consisted of an initial titration phase of five days, with a maintenance phase of five to six days. At the end of the titration phase, non-responders crossed over to the alternative blinded treatment[7].

The mean baseline opioid usage was very high, at 5.4 grammes per 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 300mg daily and for placebo was 600mg daily. An average of 32% (n = 36) of patients across both arms had received prior IT morphine[5].

The dosing regimen titration was fast, escalating from 2.4 micrograms/day to a maximum of 56 micrograms/day[3].

Results

The primary efficacy end point in the 111 patients within the 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 ($p < 0.001$). Mean VASPI scores were 74.1mm (± 13.82) and 77.9mm (± 13.6) at baseline and were reduced to 35.7mm (± 33.27) and 61mm (± 22.91) after five to six days with ziconotide and placebo respectively[5].

Points to note

- The titration regimen was rapid and overall hourly infusion doses of ziconotide ranged from 0.1 to 2.4 micrograms/hour, with a number of amendments to the titration regimen being made during the study. This study used a more rapid dose escalation with higher doses than recommended in the SPC[1].
- Study 95-001 had a high drop-out rate; 20/72 patients on ziconotide withdrew before the end of the titration phase and 8/29 patients on placebo crossed over to ziconotide[5].
- The mean baseline opioid usage was very high, and as patients were allowed to continue with systemic analgesia and adjuvant treatment this may have had an influence on the response to ziconotide.

6.1.2. Study 96–002 (severe, chronic, non-malignant pain)[3,6]

This was a study in 257 patients with chronic, severe non-malignant pain, of whom 76% had neuropathic pain. The mean patient age was 52 years and the mean baseline opioid use was 528 milligrams/day oral morphine equivalents. 58% of patients had previously been treated with IT morphine and 98% of patients had pain of greater than one year's duration[5].

Patients were randomised to receive ziconotide (n=170) or placebo (n=87) in a ratio of 2:1. 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[5].

Non-responders to initial therapy were crossed over to the alternative blinded treatment at the end of the initial titration phase[6].

Results

Of the 169 patients receiving initial ziconotide, 40 patients discontinued during initial titration and eight withdrew during the maintenance phase with ziconotide. 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[5].

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%) (95% CI: 0 to 11.9%) in the mITT population (p ≤0.001). Mean VASPI scores were 80.1mm(± 15.1mm) and 76.9mm (± 14.58mm) at baseline and were reduced to 54.4mm (± 29.3mm) and 71.9mm (30.93mm) after 6 days with ziconotide and placebo respectively[5].

Use of concomitant opiate treatment did not change significantly for either treatment group during the titration phase[6].

Sub-group analysis showed that the non-neuropathic pain patient group, although much smaller in number (n = 22, 16% change in VASPI score), had a much lower response than the neuropathic pain patient group (n = 124, 31.6% change in VASPI score)[6].

Points to note

- The mean baseline VASPI score was significantly higher for the ziconotide group (80.1mm) than for the placebo group (76.9mm) (p = 0.029).
- The titration regimen used within this study was also more rapid with higher doses being utilised than recommended in the SPC[1].
- There were very few patients treated exclusively with placebo, due to the initial crossover, that could be considered as a true comparator group[6].
- The washout period for patients on IT opiates and conversion to systemic opiates was only seven days prior to the study start date, which may have resulted in opiate withdrawal and affected the response rate within the study.

6.1.3 Study 301 (severe, chronic pain)[3,8]

This was a three week study in 220 adult patients with chronic severe intractable pain of any aetiology. The mean duration of pain was 14 to15 years and the majority (97%) of patients were considered refractory to treatment by their physicians and 90% had already been treated with IT morphine. All patients in this study already had implanted pumps and more than one IT drug had already been used by 58% of the patients prior to enrolment[8]. 96% of patients suffered from non-malignant pain and 98.6% had tried oral opioids prior to enrolment[3]. 74% of all patients had neuropathic pain, and 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[5]. In both treatment groups, the mean VASPI score was 80.7mm (± 14.9mm) at baseline[5].

As with studies 95-001 and 96-002, there were no exclusions for coexisting medical or psychiatric conditions; all systemic medications, including opioids, anti-depressants, anti-convulsants, muscle relaxants, anxiolytics, NSAIDs and sedative hypnotics were allowed[8].

Patients had a three week weaning period to discontinue IT therapy, followed by a one week stabilisation period without IT drugs. Patients were randomised to placebo (n=108) or ziconotide (n=112), receiving a starting dose of 0.1 microgram/hour IT with titration in dose increments of 0.05 microgram to 0.1 microgram/hour at 24 hour intervals to a maximum dose of 0.9 microgram/hour. Treatment was for three weeks with the mean dose at the study end being 0.29 microgram/hour (6.96 micrograms/day)[3,8]. The range of therapeutic doses in study 301 was 0.05 to 0.6 micrograms/hour[5].

Results

There was a significantly greater mean percentage change in VASPI score from baseline to week three (using the last observation carried forward (LOCF) method to impute missing data) for ziconotide (14.7%) compared to placebo (7.2%) (p=0.036). The mean VASPI score was reduced to 67.9mm (± 22.89mm) and 74.1mm (± 21.28mm) after three weeks with ziconotide and placebo respectively[4].

Response to treatment was a secondary endpoint and was defined as a decrease in VASPI score of greater than or equal to 30%.The proportion of treatment responders did not differ significantly between groups (16.1% for ziconotide, 12.0% for placebo [p = 0.39]) at week three[3,8].

There was a 23.7% mean decrease in weekly opioid use from the pre-treatment stabilisation period to week three in the ziconotide group, compared to a 17.3% decrease in the placebo group (p=0.44, non-significant)[8].

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

Points to note

- The dosage used in study 301 was lower than in studies 95-001 and 96-002, and titrated upwards at a much slower rate.
- The decrease in opioid use in this study showed that there was no impact of concomitant therapy on the improvement in VASPI scores.

6.1.4 Study 95–002 (severe, chronic malignant and non-malignant pain)[9]

This prospective, open-label study enrolled 155 patients (48 with malignant pain, 107 with non-malignant pain) who had achieved an analgesic response to IT ziconotide from either of the short-term trials; 95-001 and 96-002. Each patient was initially maintained on their specific dose established from the earlier trial for 30 days, with the dosage adjusted as necessary after this, with a maximum two-fold increase per 12 hour period. The study intended to evaluate the safety and efficacy of ziconotide in the longer term[9].

The mITT population was composed of 145 patients (44 with malignant pain, 101 with non-malignant pain)[9]. VASPI score, AE occurrence, and vital sign measurement were recorded twice during the first 30 days and monthly thereafter.

During the trial, non IT concomitant analgesia was allowed, with 98.7% of patients taking additional opioids and 38.1% non-steroidal anti-inflammatory drugs. Three patients required short term epidural infusion of opioid, local anaesthetic or corticosteroid for pain exacerbation.

During the 12 month period, the mean dose varied between 0.3 and 0.6 micrograms/hour. This data was taken from the cohort of 31 patients who remained in the study for ≥ 12 months.

Results

Patients remained in the study for a mean of 288 days (median = 86 days; range 3 to 2,047 days). 31 patients participated in the study for at least one year and the mean ziconotide dose remained stable over this period. The results only reflect the VASPI scores collected up to and including month 12, as the large drop-out rate limited the usefulness of data collected later on in the study.

In the mITT population VASPI scores had decreased by a mean of 36.9% from baseline in the short term trial to the last available measurement (n=144; 95% CI: 30.1 to 43.7%; $p < 0.0001$). Analysis of the cohort of 31 patients who remained in the study for at least 12 months indicated sustained analgesic effect through to month 12 ($p < 0.0001$). Similar observations were noted in subgroups remaining in the trial for three months and six months, but this data was not made available[10].

The most common reasons for study discontinuation were AEs (61 out of 155 patients; 39.4%), death (26 out of 155 patients; 16.8%), patient request (25 out of 155 patients; 16.1%) and lack of efficacy (24 out of 155; 15.5%). All four patients with external IT infusion systems experienced device-related AEs; one SAE of meningitis and another SAE of catheter site infection. Neurological AEs were the most commonly reported AEs in this study; confusion, dizziness, nystagmus, abnormal gait and memory impairment being the most frequently occurring. Elevated creatine kinase (CK) levels were also reported, but did not lead to serious events such as myopathy or renal impairment. Ziconotide was implicated in the death of one patient within this trial due to aspiration[10].

Points to note

- This study had a large drop-out rate, which was mostly related to AEs. Only 31 patients (20%) remained in the study for at least one year.
- Patient drop-out would have confounded the interpretation in change of VASPI scores, so only post-hoc analysis of the 31 patients who remained in the study was assessed for the potential sustained efficacy of ziconotide.
- This trial was terminated in 2002 and the ten patients still participating were transferred to another long-term trial.

6.1.5 Study 98–022 (severe, chronic malignant and non-malignant pain)[10]

644 patients with severe, chronic pain (16 with pain of malignancy, 626 with non-malignant pain and 2 with missing data) participated in this open-label long-term study. Patients were deemed eligible for inclusion in the study if IT therapy was recommended as the next clinically indicated treatment or if they had experienced an unsatisfactory response to IT opioids alone or in conjunction with adjunctive drugs, e.g. clonidine and bupivacaine. Patient age ranged from 16 to 88 years (mean 52.1 years) with the mean duration of pain being 11.6 years[10].

As this study was intended to evaluate the safety of ziconotide, no minimum VASPI score was required for study participation. IT medications were discontinued prior to treatment with ziconotide, whilst systemic analgesia was permitted (although regimes were stabilised for at least seven days). All 644 patients used at least one concomitant medication with 90.1% using strong analgesics[10].

Ziconotide treatment consisted of an initial titration period commencing with ≤2.4 micrograms/day and subsequent dose increases were restricted to a maximum of 2.4 micrograms/day at any adjustment and were not permitted more than once every 24 hours. There was no maximum dose limit.

Results

The median VASPI scores at baseline, one month, and the last available observation up to month two were 76mm (± 20.3mm), 68mm (±27.7mm) and 73mm (±25.4mm), respectively. One hundred and twenty nine of the 394 patients (32.7%) with VASPI scores ≥50mm at baseline (who completed one month of treatment) had a ≥30% improvement in VASPI score at month one. Of the 59 patients with a baseline VASPI score <50mm (who completed one month of treatment), 9 (15.3%) had ≥30% improvement in VASPI score at month one. The distribution of scores for pain impact on daily life differed significantly between baseline and month two ($p<0.001$, $n=339$)[10].

Most patients (99.7%) reported at least one AE, with 91% reporting an AE in the first 14 days. The following AEs were experienced by over 25% of patients: nausea, dizziness, headache, confusion, pain, somnolence and memory impairment. CK levels rose from a normal baseline level in a significant proportion of patients; 21.2%, 17.1% and 17.5% for months one, two and final ziconotide discontinuation, respectively. Most AEs were described as mild (43.5%) or moderate (42.3%) and 58.6% were considered unrelated to ziconotide (the latter being based on investigator judgement). 233 patients (36.2%) experienced at least one serious adverse effect (SAE) during the study. Meningitis was reported in 20 patients, 19 of whom had external infusion systems showing that this AE is related to device rather than the drug. Ziconotide therapy was discontinued temporarily or permanently due to an AE in 12.1% and 48.9% of patients respectively. The other primary reasons for permanent discontinuation from the study were lack of efficacy (29.7%) and rollover to a new study (10.6%)[10].

Points to note

- The dose of ziconotide could be decreased by any amount at any time, and a single voluntary discontinuation of ziconotide infusion for up to 30 days was permitted (referred to as a 'drug holiday'). The justification for this was that patients in other trials have discontinued treatment and then later requested re-entry to the study.
- This study was intended to evaluate the safety of ziconotide and therefore no minimum VASPI score was required for study participation.
- VASPI score measurement was limited to two months.

6.2 Safety:

Cognitive and neuropsychiatric adverse reactions, particularly confusion, are common in patients treated with ziconotide. In study 301, confusion occurred in 33.8% of patients in the combined IT group (versus 6.6% in the placebo group) and caused SAEs in 4.1% of patients. The mean duration of confusion was 15.3 days (range 1 to 292 days) and was the reason for discontinuation in 11.7% of patients. The Committee for Medicinal Products for Human Use (CHMP) have stated that confusion is a most "undesirable" effect for patients suffering from severe chronic pain, because of the perception of pain control and the need for hospitalisation[5]. This issue was part of the company decision to recommend a dose interval of 48 hours in order to minimise all potential AEs[5].

Nine patients across ziconotide studies have committed suicide during or within a month of discontinuing ziconotide therapy[5,10]. This needs to be further compared with other cohorts of IT opiate treated chronic pain patients.

The incidence of meningitis with IT ziconotide is similar to that with other IT analgesics, and increases when external, rather than internal, infusion systems are used[5,10].

SAEs associated with ziconotide therapy include dizziness, diarrhoea, confusion, abnormal gait and nausea, some of which were persistent throughout treatment. These were more common in study 95-001 (30% for ziconotide versus 10% for placebo) which was most likely due to the fast titration phase and high dosage. SAEs are less frequent when ziconotide is titrated slowly in accordance with the licensed recommendations[3,5].

In study 301, the rate of adverse events was reportedly lower with placebo (BSC) than for ziconotide recipients (0.57 versus 1.17 over the three week period)[8].

Ziconotide does not show any evidence to date of tolerance or physical dependence, additionally it does not appear to induce respiratory depression[3,6].

Elevation of CK, although usually asymptomatic with only one report of myositis, is common in IT ziconotide treated patients. Monitoring of CK level is therefore recommended[2,5,10].

As evidenced from the relationship between rapid dosage titration and adverse effects in studies 96-001 and 96-002, it is likely that ziconotide has a narrow therapeutic index[6].

Appendix 1, table 1, shows the AEs experienced within the short term studies included within the company submission[3]. The AEs reported from the longer term studies have been specified within discussion of each respective study[9,10].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:

There are no other UK licensed medicines for IT analgesia. Morphine is the main analgesic used via the IT route of administration within Wales, although unlicensed. Additionally, other unlicensed “special” products may be available for IT use within different hospitals and prepared in pharmacy aseptic units[3].

7.2 Comparative effectiveness:

There are no direct comparative studies of IT ziconotide versus other active IT therapies, only against placebo. Ziconotide has shown it is effective in reduction of VASPI scores for patients with severe, chronic intractable pain refractory to systemic and/or IT opioids. Longer-term randomised controlled studies are needed to evaluate its true place in therapy, particularly with regard to pain associated with malignancy.

Pump refills for ziconotide are required every 60 days, due to limited stability data. There are also special reconstitution/stability requirements which mean that if the solution is not transferred to the infusion pump immediately, it is only stable for 24 hours at two to eight degrees centigrade, unless dilution has taken place in controlled and validated aseptic conditions[1].

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE:

8.1 Overview of the key economic issues for the AWMSG to consider

The key economic issue for the AWMSG to consider is whether any additional benefits offered by the use of ziconotide over relevant comparators justify any associated increase in costs.

8.2 Review of published evidence on cost-effectiveness

Standard searches conducted by WMP have not identified any other published economic studies of the use of ziconotide in the treatment of severe, chronic pain in patients who require IT analgesia.

8.3 Review of the company submission on cost-effectiveness

8.3.1 Description and critique of the company submission

The company submission describes a cost-utility analysis of ziconotide delivered by IT infusion versus best supportive care (BSC) in patients who have severe, chronic pain that is inadequately controlled by systemic and IT analgesics[3]. It relates only to patients who already have an implanted IT pump.

A discrete-event simulation model is described, using patient level data from a pivotal double blind RCT (study 301), and utility weights derived from a separate research study. The model is constructed as two time periods: a three week titration phase and a long term phase. The base case model simulates a population of 10,000 with the same characteristics as patients in study 301, using Monte Carlo sampling of the distributions of these characteristics. The simulated patients are then sent to the ziconotide and the BSC arms of the model. Patients who respond to ziconotide in the three week titration phase continue to receive ziconotide in the long term phase until discontinuation due to adverse events or death. Patients who fail to adequately respond to ziconotide in the three week titration phase receive BSC, as do those who discontinue ziconotide due to adverse events[3].

There are several issues with the assumptions around efficacy, adverse effects, utility weights and drug costs that introduce uncertainty and are likely to bias the model significantly in favour of ziconotide.

8.3.2 Population

The population in study 301[3], on which the model is based, meets the licensed indication for ziconotide[1]. It is reported that the majority of patients in this trial (90%) had not responded adequately to IT opioid treatment, and approximately 60% had failed on combination IT treatment[3]. This patient population is therefore very refractory to treatment. The age range of patients in study 301 was 27–86 years (mean 53.7 years). Pain was of non-malignant, neuropathic origin in 74% of patients. The treatment regimen used in this trial is the same as recommended in the SPC[1].

8.3.3 Perspective and time horizon

The model considers direct costs from the NHS perspective in Wales[3]. A lifetime time horizon has been used in the base case analysis on the basis that patients are never cured of their pain. Although the company submission reports that some patients have received continuous ziconotide infusion for over six years, the median exposure across 1,400 patients is 43 days[3]. Three-week data from study 301 has been extrapolated to the long term (see section 8.3.5).

8.3.4 Comparator

The comparator used in the model is BSC, which has been assumed in the model to include IT analgesia. However, the comparator of ziconotide in study 301 was placebo IT analgesia (with both treatment groups also allowed other systemic treatments including opioids, antidepressants, anticonvulsants, NSAIDs, etc)[8]. As almost all of those in the placebo group (93%) were able to be weaned off of IT opioids and on to oral opioids before the start of study 301, the company submission asserts that IT opioids were no more effective than oral opioids in this patient group. Therefore, the model assumes that data from the placebo arm of study 301 adequately represents BSC as defined for the model[3].

There are some issues with this assumption. The company submission suggests that patients receiving BSC (including treatment with IT opioids) would require more frequent dose titration and treatment changes, with associated increases in adverse effects[3]. However, the company submission also states that patients receiving opioids via IT infusion require lower total doses of opioids (perhaps only one-tenth of the dose) than would be required if administered systemically, which would help minimise adverse effects and complications[3]. In the placebo arm of study 301, opioids were only systemically administered (only placebo was administered by the IT route)[8], which based on the assertions in the company submission would be associated with a greater incidence of adverse effects than if they were administered by the IT route. Therefore, the extent to which data from the placebo arm of study 301 adequately represents BSC, as defined in this analysis, with respect to adverse effects is uncertain. It is assumed in the model that 50% of patients receiving BSC use the IT pump. This is a potentially important point as there are some other issues with the incorporation of the impact of adverse effects in the model, as discussed in sections 8.3.5.2 and 8.3.5.3.

8.3.5 Clinical inputs

8.3.5.1 Efficacy data

The proportion of patients achieving specified categories of change from baseline in their VASPI scores at the end of the three week study 301 were derived for ziconotide and placebo, the latter being assumed for BSC in the model. Response to treatment was a secondary endpoint in study 301 and was defined as a decrease in VASPI score of $\geq$ 30%. There was no statistically significant difference between the treatment groups for the percentage of recipients achieving this response in the published study (16.1% of ziconotide recipients versus 12% for placebo, p = 0.39)[8]. The data presented for the different categories of response used in the model differ from these (response rates of 20.5% and 14.8%, respectively, are suggested by the data presented in the economic section)[3]. It is unclear why this anomaly exists and the figures derived for use in the model cannot be verified from the available data. The use of the latter figures in the model has the effect of increasing the absolute difference between the two treatment arms by 1.6% (i.e. a 40% relative increase) compared with the former figures. A one-way sensitivity analysis has been conducted using data only from patients with a VASPI reading at baseline and a three week reading defined as week 16 to 22. This alternative analysis is reported to have resulted in responder rates of 14.29% for ziconotide and 12.04% for BSC, and is reported to have little influence on the model outputs.

The model assumes that once a ziconotide recipient responds to treatment in the first three week phase, that response is maintained throughout the remainder of the long-term phase (unless intolerable adverse effects necessitate discontinuation) without the need for dose increase or increased use of concomitant systemic analgesics[3]. However, there are several uncertainties in this assumption. In study 301 the mean

change from baseline in VASPI score for ziconotide recipients at the 3-week cut off was reported as 14.7% (versus 7.2% for placebo)[8]. "Commercial in confidence" data was supplied from the company with regard to VASPI score change over a longer time period[11]. Given all these factors, the assumptions regarding the long term efficacy of ziconotide at stable dosing may be subject to some uncertainty.

The model runs until each simulated patient dies. Life expectancy for patients with non-malignant pain is taken from the UK Government Actuaries Department. For patients with malignancy, the model assumes a life expectancy of one year[3].

8.3.5.2 Adverse events

Data on AEs used in the first three week titration phase of the model for ziconotide and BSC are taken from study 301. The long term adverse event data for ziconotide has been obtained from a database of safety data from all ziconotide trials, and discontinuations due to adverse events have been obtained from study 352[11]. The long term adverse event data for BSC is extrapolated from the three week data from study 301. The company submission states that ziconotide recipients are more likely to experience adverse events during the three week titration phase and that, once they respond satisfactorily, they will not require any upwards adjustment of dose and hence are less likely to experience adverse events in the long term. It also states that BSC recipients are more likely to require changes to their treatments and doses in the long term, so that in the long term the rates of adverse events will be greater for BSC responders[3].

During study 301, the rate of adverse events was reportedly lower with placebo (BSC) than for ziconotide recipients (0.57 versus 1.17 over the three week period), and this was in patients receiving opioids via systemic routes that may be associated with higher rates of adverse events than those delivered by the IT route (see section 8.3.4)[3]. In addition, of those patients who receive ziconotide beyond three weeks (i.e in the long term), 64% discontinued due to reasons unrelated to efficacy. It should also be noted that the assumption of no upward dose adjustment with ziconotide in the long term is subject to some uncertainty (see 8.3.5.1). The impact of setting the adverse event rate for BSC equal to those used for ziconotide in the base case, and vice versa, has been explored in one-way sensitivity analyses[3], which suggest the model is relatively insensitive to these. However, there are some issues with the application of utility weights to the adverse events (see section 8.3.5.3).

8.3.5.3 Utility weights

Patient reported outcome instruments were administered in study 301, but no further details are provided in the company submission in terms of what these were or the results obtained[3]. The published study 301 paper indicates that there was no significant difference in quality of life scores between the ziconotide and placebo groups at three weeks when assessed with the Treatment Outcomes in Pain instrument[3]. There was also no significant difference in five of the six subscales of the Brief Pain Inventory tool; however, a company-defined sleep questionnaire indicated improvements in sleep duration and quality, and the Global McGill Pain Relief total score was improved for ziconotide compared with placebo[3].

A separate research study was reported to have been undertaken in 102 members of the UK general public to capture societal preferences for eight VASPI health states (VASPI score ranges 0 to 40, 41 to 60, 61 to 80, 81 to 100 for malignant and non-malignant pain). Eight health states representing common adverse events associated with IT analgesic therapy were also constructed and time trade off approaches were used to estimate utility weights for each VASPI and adverse event health state[3].

Utility values for each VASPI score in the range 0–100mm were derived by linear extrapolation of the utility values associated with the mid points of the VASPI intervals. The VASPI-related utility value was then adjusted for the presence of side effects by multiplying the utility of the side effect by the utility of the VASPI score at a given time point. It is assumed that the impact of the adverse event on utility lasts for two weeks. The adverse events considered in the model are dizziness, nausea/vomiting, pruritis, confusional state, abnormal gait, urinary retention, weight gain, and erectile dysfunction. The content and description of these adverse events was reported to have been tested with five UK clinical experts. However, it is noteworthy that some of the adverse events considered among these eight appear not to have occurred frequently (e.g. in greater than 5% of patients, such as weight gain, erectile dysfunction) in the ziconotide trial programme, whilst other adverse events that have occurred commonly, and might reasonably be expected to have a significant impact on quality of life, are not considered in the model (e.g. memory impairment, headache, somnolence)[3]. The extent to which adverse events have been appropriately and comprehensively incorporated in the model is therefore not clear.

In addition to these issues with incorporation of adverse events, the approach taken to adjust the VASPI-related utility values for the presence of adverse events appears to have a significant influence on the model outputs. In the base case analysis, any negative VASPI-related utility values, which indicate a state of being regarded as worse than death, are multiplied by (1+ disutility of adverse event), where disutility is calculated as (1- utility of the adverse event). This ensures that any negative VASPI-related utility values decrease when adjusted by adverse event utility values, rather than increasing. However, an alternative approach has been presented in the company submission, in which negative VASPI-related utility values are simply not adjusted for adverse events[3]. This approach leads to an estimated incremental cost per QALY almost double that estimated via the first approach.

It should be noted that negative VASPI-related utility values apply to high VASPI scores (the company submission states that VASPI scores greater than 61mm attract negative utility values based on the study undertaken in 102 members of the public). At baseline, mean VASPI scores in study 301 were 80.7mm (which, according to this study is a state of being worse than death). To achieve a VASPI score less than 61mm (i.e. to achieve a positive VASPI-related utility value) a 25% change from baseline in VASPI score would be needed. The vast majority of patients in the ziconotide (68%) and placebo (77%) arms of study 301 failed to achieve a change in VASPI score of $\geq$20% at three weeks[3]. Only those who achieve $\geq$30% decrease in VASPI score at three weeks continue with ziconotide treatment in the model; the remainder who fail to achieve this level of response (79.5% of those initiated on ziconotide in study 301) would be switched to BSC[3].

8.3.6 Healthcare resource utilisation and cost

Estimates of healthcare resource have been obtained from five physicians experienced in managing patients with chronic pain in the UK. A structured interview guide was prepared to elicit information on practice patterns and resource use. The information collected has reportedly been endorsed by a neurosurgeon as being sufficiently representative of resource use patterns in Wales. Responses were collated to produce mean use of resources per patient and unit costs were attached using published sources (e.g. Personal Social Services Research Unit (PSSRU), NHS Reference costs, British National Formulary (BNF)) inflated to 2006 prices. Standard deviations around the mean costs were calculated using bootstrapping.

It is noteworthy that some areas of resource use appeared to differ substantially between the five physicians[3].

8.3.6.1 Treatment related costs

The annual cost of ziconotide assumed in the model was £6,191 based on the mean dose being used at the termination of study 301 (0.26 micrograms/hour). Further data with regard to mean dosage in the longer term treatment was supplied as "commercial in confidence"[11]. The assumed ziconotide dose used for the long term phase of the model would therefore seem to be under-estimation and has the potential to significantly influence the model outputs. For BSC, a yearly cost of £500 was assumed, based on an average of estimates provided by five clinical experts. Different costs for BSC are explored in sensitivity analyses. Concurrent therapies with ziconotide were estimated from the physician interviews (only two of the five physicians provided information in relation to ziconotide).

The model assumes that all patients have an internal pump in place upon entry. Based on expert opinion, it is assumed that 50% of BSC patients do not use the pump and that 10% have the pump removed after the three week short term model phase. The remaining 50% of BSC patients are assumed to use the pump and keep it in the short term. However, in the long term, all BSC patients are assumed to have the pump removed by 6.5 years and that those not using the pump will not have a new one implanted.

In the base case, annual pump costs were calculated by dividing the total cost of the pump by the maximum life of a pump (6.5 years). The cost of the surgical procedure to replace the pump and for removal of the pump is included (based on NHS reference costs for elective procedures), along with assumed costs for annual pump maintenance in those not using their pump. Other scenario analyses explored the impact of accruing the cost of the pump at the time it is implanted.

8.3.6.2 Adverse events

The eight adverse events outlined in section 8.3.5.3 were costed on the basis of information obtained from the five physicians, and the application of unit costs. As discussed in section 8.3.5.3, the extent to which these specific adverse events adequately reflect the adverse events for ziconotide and BSC recipients is unclear. Other adverse events that are not incorporated in the model may still require healthcare resources and attract costs. In addition to the above adverse events, the costs of meningitis and injection site reaction/infection was incorporated. However, the actual frequency of these assumed in the model is not stated.

8.3.7 Discounting

All costs and outcomes were discounted at 3.5% in the base case analysis, which is the preferred discount rate. Sensitivity analysis explores discount rates of 0% and 6%.

8.3.8 Results

The incremental cost/QALY in the base case analysis is estimated as £11,087 (95% CI: £10,983 to £11,221). This is based on incremental costs of £17,989 and a gain of 1.63 QALYs. However, this is based on an assumed ziconotide dose of 0.26micrograms/hour, which is not likely to be appropriate for this analysis (see 8.3.9.2)

8.3.9 Sensitivity analysis

8.3.9.1 One way sensitivity analyses in the base case model

A series of one-way sensitivity analyses were conducted (using response rates of 20.5% and 14.8% for ziconotide and BSC (placebo), and annualised pump costs), which indicate that the model is insensitive to the parameter values explored (with the exception of discount rates, the influence of which is as would be expected). These sensitivity analyses did not address the issues around the assumed dose of ziconotide in the long term or the selective use of specific adverse events.

8.3.9.2 Supplementary one-way sensitivity analyses in a modified base case model

A modified base case was created using response rates of 14.29% for ziconotide and 12.04% for BSC (see 8.3.5.1), and assuming that IT pump costs are applied at the point of implantation rather than as annualised costs (see 8.3.6.1). In the modified base case analysis the incremental cost per QALY gained is estimated as £10,856. A range of supplementary one-way sensitivity analyses was then conducted, which indicate that the model is sensitive to the assumed dose of ziconotide: at a dose of 0.4micrograms/hour, the incremental cost per QALY gained is estimated as £15,968, and at a dose of 0.525micrograms/hour it is £20,426. The company have noted that, based on the information contained within the SPC[1], 75% of patients who respond to ziconotide do so at a dose of 0.4micrograms/hour or less, therefore the remaining 25% respond at a dose greater than this. The company therefore suggests that a weighted mean dose of 0.525micrograms/hour (75% at 0.4micrograms/hous and 25% at the maximum dose of 0.9micrograms/hour) may be a more appropriate dose to apply in the analyses.

The supplementary analyses conducted on the modified base case model did not address the issue around the selective incorporation of specific adverse events. It should be noted that these analyses are still under the assumption of a more favourable approach to the adjustment of the VASPI-related utility values for the presence of adverse events, discussed in 8.3.5.3.

8.3.9.3 Adjustment of negative VASPI-related utility values by adverse event utility values (base case model)

The methodology for adjusting the VASPI-related utility values has a significant influence on the model outputs (see section 8.3.5.3). When negative VASPI-related utility values are not adjusted for adverse events, the incremental cost/QALY gained increases to £20,677. This increases further to £24,977 when adverse event rates for BSC are made equal to those used in the base case for ziconotide. The assumptions around adverse events and the approach to accounting for them in the model is therefore a major source of uncertainty. The impact of the approach has not been explored in the modified base case.

8.3.9.4 Probabilistic sensitivity analysis (PSA) in the base case model

Nonparametric bootstrap methods were used to estimate the sampling distribution for mean costs and benefits. Samples of 2,000 patients were drawn with replacement and mean costs and QALYs generated. The process was repeated 2,000 times, generating a cost-effectiveness acceptability curve. This indicates that the probability of ziconotide being cost effective versus BSC in this model is 100% at a willingness to pay of around £12–13,000. However, it should be noted that this curve is a function of the model inputs and does not address the areas of uncertainty outlined in section 8.3.9.1, in particular the dose of ziconotide used in the long term phase. PSA in the modified base case model has not been performed.

8.4 Review of evidence on budget impact:

8.4.1 Description and critique of the company submission
The company submission considers the impact of the use of ziconotide in patients with chronic severe pain who already have an IT pump fitted and have failed to respond to previous IT therapy. There are some areas of uncertainty, including the number of patients who will be eligible for treatment.

8.4.2 Perspective and time horizon
The perspective adopted by the budget impact analysis is that of NHS Wales, with a five-year time horizon[3].

8.4.3 Data sources
8.4.3.1 Incident cases
The company states that no chronic pain incidence data is available but assumes that two to three new patients will become eligible for an IT pump each year over the next five years. The company submission states that this represents a 4.2% increase in eligible numbers and is based on the opinion of a Welsh neurosurgeon.

8.4.3.2 Prevalent cases
The number of patients managed with IT therapy in Wales is based on market research that is referenced to data on file. This is reported to show that 1,258 patients in the UK were managed with IT therapy in 2005 (equivalent to 0.002125% of the UK population). Assuming the percentage prevalence has remained unchanged, and is applicable to Wales, this equates to 63 prevalent cases in 2006, exceeding AWMSG's criterion for ultra-orphan drug status. The company submission reports the number of prevalent cases as 59[3] (based on a rounded prevalence of 0.002%) but the company also notes that, according to the opinion of a Welsh neurosurgeon, this could be a rather conservative estimate.

8.4.3.3 Rates of adoption
The analysis assumes that 15% of patients fail all IT therapy annually, which is reportedly supported by Welsh data[3]. In the first year, the model estimates that the number of patients receiving IT treatment will increase by three (reported in the company model as an increase from 59 to 62). The model specifies that only 15% of these patients will fail treatment and will be eligible for ziconotide. This amounts to around 9 patients in the first year. The model assumes that 15% of these nine patients will respond to treatment (based on the percentage of patients achieving a $\geq$30% improvement when data from study 301 was broken down by level of response; see section 8.3.5.1, response rate of 14.29% for ziconotide), which amounts to one patient continuing with ziconotide treatment beyond the three week titration phase.

The licensed indication of ziconotide does not refer to eligibility requiring failure with previous therapy. However, based on clinician opinion, the company suggests that ziconotide will be considered only for those patients who do not respond to IT therapy or in whom existing IT analgesics are inappropriate. Ziconotide can only be used by IT experienced clinicians[1].

8.4.3.4 Costs and resource use
The budget impact analysis includes drug costs, pump costs and the costs of pump maintenance and removal, etc.

The total cost of the pump is presented as a yearly cost by dividing the total cost (plus £1,000 for fitting) by the maximum life of the pump (6.5 years). The fitting of the pump should attract the whole total cost of the pump, irrespective of when the pump is removed. However, it is unclear how the total cost of the pump is accounted for in those patients in who the pump is removed early. In the base case presented, it is assumed that 10% have their pump removed each year, with 15% tested in sensitivity analyses.

The drug cost of ziconotide assumed in the model is based on doses of 0.4micrograms/hour and 0.525micrograms/hour that are considered in the cost utility sensitivity analyses (section 8.3.9.2). It is assumed that the drug costs involved with BSC amount to £500, which is based on an average of five UK clinicians' estimates. The costs of adverse events are also included in the analysis, but it should be noted that the adverse events considered in the economic model were selective.

8.4.4 Results

The base case budget impact results are based on the assumption that 10% of patients have pumps removed each year. At a ziconotide dose of 0.525micrograms/hour, the company estimates that, compared with a base year (2006) cost of £261,295 for BSC, the total cost of therapy in year one will be £279,846, rising to £331,343 in year five. However, these additional costs will include the influence of the increase in the number of patients receiving IT therapy who are receiving BSC, as well as the increase in costs due to ziconotide.

At a dose of 0.4micrograms/hour, the company estimates the total cost of therapy in year one to be £276,011, rising to £315,773 in year five. However, there are some minor discrepancies in the figures presented by the company and the figures calculated in the budget impact model that has been provided.

8.4.5 Sensitivity analysis

When the model assumes that 15% of patients have a pump removed each year, the company estimates that, compared with a base year (2006) cost of £261,295 for BSC, at a ziconotide dose of 0.525micrograms/hour, the total cost of therapy in year 1 will be £295,962, rising to £332,187 in year five. At a dose of 0.4micrograms/hour, the company estimates the total cost of therapy in year 1 to be £278,324 rising to £316446 in year five. Again, there are discrepancies in these reported estimates and those estimated by the model, including the base year cost.

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- There is a Welsh Assembly Government document on treatment of Chronic Non-Malignant Pain, currently in the consultative phase (since July 2007), which recognises that Specialist centres are needed to be in place for delivery of treatment for special patient groups[12]. Any recommendations for use of ziconotide should therefore be mindful of this guidance.
- Guidelines on IT therapy are to be issued shortly by the British Pain Society[3].
- Ziconotide would not be suitable for a shared-care agreement, particularly within the dosage titration phase of therapy. Treatment initiation, monitoring and supervision should be retained under Specialist care[1].

9.2 Previous NICE advice

NICE have produced the final scope for development of guidance on "Low back pain: the acute management of patients with chronic (longer than 6 weeks) non-specific low back pain", which is due for publication in 2009[13].

9.3 Ongoing studies

The company is planning to conduct a multicentre, international phase IV observational study (PRIME), to evaluate the long term efficacy and safety of ziconotide according to the request of the CHMP in the terms of granting marketing authorisation. However, due to the nature of this long term study, results are not anticipated for at least 12 months[3].

9.4 Patient Interest Group Information

A patient interest group submission was not received.

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Appendix 1. Additional Clinical Information

Table 1 - Summary of key safety findings from three randomised controlled studies[2]

Study 95-001	Study 96-002	Study 301
Most common adverse events occurring in a significantly greater incidence in the ziconotide group than in the placebo group: hypotension, nausea and vomiting, abnormal gait, confusion, dizziness, somnolence, nystagmus, fever and urinary retention	**Most common adverse events** occurring in a significantly greater incidence in the ziconotide group than in the placebo group: nausea, vomiting, abnormal gait, dizziness, nystagmus, pain, amblyopia and urinary retention	**Most common adverse events** occurring in a significantly greater incidence in the ziconotide group than in the placebo group: abnormal gait, confusion, dizziness, memory impairment, ataxia
Mean dosages at the time of onset: 14.88µg/day (0.62µg/hr) to 34.56µg/day (14.4µg/hr**). (Please note that these ziconotide doses reached are still higher than currently recommended in the SPC)**	Mean dosages at the time of onset: 9.12µg/day (0.38µg/hr) to 24µg/day (1.0µg/hr). **(Please note that these ziconotide doses reached are still higher than currently recommended in the SPC)**	Mean dosages at the time of onset: 2.64µg/day (0.11 µg/hr) to 7.2µg/day (0.30µg/hr)
Serious adverse events reporting incidence in titration phase: ziconotide group – 30.6% vs. placebo group – 10..0%	**Serious adverse event** reporting incidence in titration phase: ziconotide group – 16.5% vs. placebo group – 2.3%	**Serious adverse events** reporting incidence: ziconotide group – 11.6% vs. placebo group – 9.3% (p=ns)
Discontinuation due to adverse events: ziconotide group – 16.7% vs. placebo group – 10.0%	**Discontinuation due to adverse events:** ziconotide group – 14.1 % vs. placebo group – 0%	**Discontinuation due to adverse events:** ziconotide group – 5.4% vs. placebo group – 4.6% (p=ns)

µg = micrograms