HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

14 May 2008

PRIALT 100 µg/ml, solution for infusion
Box of one 1 ml glass vial – CIP Code: 569727-6
Box of one 2 ml glass vial – CIP Code: 569728-2
Box of one 5 ml glass vial – CIP Code: 569729-9

Applicant: EISAI S.A.S.

Ziconotide

Date of Marketing Authorization: 21 February 2005 (centralized procedure, marketing authorization under exceptional circumstances)

Medicinal product for hospital use only, orphan drug

Reason for request: inclusion in the list of medicinal products approved for hospital use.

Medical, Economic and Public Health Evaluation Department

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

ziconotide

1.2. Originality

Ziconotide is an N-type voltage-sensitive calcium channel blocker (NCCB). It is an orphan drug.

1.3. Indication

"Treatment of severe, chronic pain in patients who require intrathecal analgesia."

1.4. Dosage

"Treatment with ziconotide should only be undertaken by physicians experienced in intrathecal administration of medicinal products.
PRIALT is for intrathecal use only.

Adults (including the elderly ≥ 65 years of age)
Dosing of ziconotide should be initiated at 2.4 µg/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 ≤ 2.4 µg/day, up to a maximum dose of 21.6 µg/day. The minimal interval between dose increases is 24 hours; the recommended interval, for safety reasons, is 48 hours or more. If necessary the dose can be decreased by any amount (including stopping the infusion) for the management of adverse reactions. Approximately 75% of patients who respond satisfactorily to treatment require a dose less than 9.6 µg/day.

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 catheterization 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.

When low doses of ziconotide are required, for example when initiating titration, ziconotide must be diluted before use with preservative-free sodium chloride 9 mg/ml (0.9%) solution for injection.

Children (<18 years)
PRIALT is not recommended for use in children below 18 years due to a lack of data on safety and efficacy. There is no experience in children.

Impaired hepatic and renal function
Studies have not been conducted in patients with impaired hepatic or renal function. Caution should be exercised when ziconotide is administered to this type of patient."

2 COMPARABLE MEDICINAL PRODUCTS

2.1. ATC Classification (2007)

N : nervous system
N02 : analgesics
N02B : other analgesics and antipyretics
N02BG : other analgesics and antipyretics
N02BG08 : ziconotide

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

PRIALT is the only N-type voltage-sensitive calcium channel blocker indicated for the treatment of severe chronic pain.

2.3. Medicines with a similar therapeutic aim

All strong opioids and non-opioid analgesics administered systemically or intrathecally which are indicated for severe chronic pain.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

Evaluation of the efficacy of ziconotide (PRIALT) in the treatment of chronic malignant and non-malignant pain is based on three phase III placebo-controlled trials (95-001[1], 96-002[2] and 301[3]). Only trial 301 was conducted in accordance with the dosage regimen (initial dose and titration) validated by the marketing authorization. The manufacturer also presented the results of four non-comparative trials (201, 202, 351, 352) and published case studies, which will not be described because of their methodological deficiencies.

- Short-term efficacy (5-6 days' treatment) – trials 95-001 and 96-002

Two placebo-controlled, randomized, double-blind trials with similar methodologies evaluated the analgesic efficacy of intrathecal administration of ziconotide in 366 patients suffering from malignant pain (trial 95-001, n=112) and non-malignant pain (trial 96-002, n=257), with a VAS score > 50 mm (mean score of 75 mm in trial 95-001 and 78 mm in trial 96-002).

In trial 95-001, the patients included (mean age 55.5 years) suffered from cancer pain (88%) or pain associated with AIDS (11%) not controlled by systemic and/or intrathecal opioid treatment. On inclusion, the patients received 5.4 g of oral morphine on average. 32% of them had been previously treated with intrathecal morphine.

[1] Staats P. Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS. JAMA 2003; 291 : 63-70.

[2] Wallace MS, Charapata SG, Fisher R et al. Intrathecal ziconotide in the treatment of chronic nonmalignant pain : a randomised double blind placebo controlled clinical trial. Neuromodulation 2006 9.75.

3 Rauck RL. A randomized, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain. J Pain Symptom Manage 2006; 31:393-406.

In trial 96-002, the patients included (mean age 52 years) suffered from severe non-malignant chronic pain, mainly of neuropathic origin (76%), which did not respond to systemic opioid treatment or at least two other analgesics. On inclusion, the patients received 5.28 g of oral morphine on average. 58% of them had been previously treated with intrathecal morphine.

The patients were randomized to receive either ziconotide or the placebo for 5 or 6 days. The initial doses of ziconotide were higher than those recommended by the marketing authorization, with a shorter titration interval. The mean dose of ziconotide at the end of titration was 0.91 µg/h (median 0.60 µg/h) in trial 95-001 and 1.02 µg/h (median 0.50 µg/h) in trial 96-002. The analgesic treatments, except for those administered intrathecally, were maintained throughout the trials.

The primary efficacy endpoint was the change in the pain intensity score after 5 or 6 days' treatment. The protocol required ITT analysis of the results.

The secondary endpoints included:

- response to treatment (≥ 30% improvement in the VASPI score[4] and concomitant analgesic treatment unchanged or reduced);
- improvement in pain on the CPRS categorical scale[5];
- change in the WBPI pain questionnaire[6]

Primary endpoint results:

In trial 95-001, 11 (15.3%) of the 72 patients treated with ziconotide discontinued the treatment (6 due to adverse events), while 3 (7.5%) of the 40 patients who received the placebo discontinued the treatment, 2 of them due to adverse events.

In trial 96-002, 40 of the 169 patients treated with ziconotide discontinued the treatment (27 of them due to adverse events), while 7 of the 86 patients who received the placebo discontinued the treatment, 1 of them due to adverse effects.

These large percentages of drop-outs in the two trials were observed at higher initial doses of PRIALT and more rapid titration than the dosage regimen recommended in the Marketing Authorization for this product.

The therapeutic responses observed in the mITT population (randomized patients who received at least one dose of treatment and whose VAS data were available) are set out in table 1.

4 VASPI - Visual Analogue Scale of Pain Intensity. This scale is commonly used to assess pain.

[5] Categorical Pain Relief Scale – from 0 = pain worse to 5 = complete relief

[6] Wisconsin Brief Pain Inventory - interference by pain (from 0 = does not interfere to 4 = completely interferes) with 6 spheres of life: mood, relations with other people, walking, sleep, work, enjoyment of life.

Table no. 1: Change in the pain intensity score after 5 or 6 days' treatment in trials 95-001 and 96-002 (mITT population).

	Trial 95-001		**Trial 96-002**	
	Ziconotide (n=71)	Placebo (n=40)	Ziconotide (n=169)*	Placebo (n=86)
Mean VAS at baseline (mm)	74.1± 1.8	77.9± 2.3	80.1± 1.1	76.9± 1.5
Mean VAS after 5 or 6 days' treatment	35.7± 3.5	61± 4.9	54.4± 2.6	71.9± 2.5
Change in VAS score between baseline and D5 or D6 (%)	51.4 (±4.6)	18.1 (± 6.8)*	31.2 (± 3.4)	6 (± 3.1)**

* p=0.0003, ** p≤ 0.001

Secondary endpoints results:

Trial 95-001

- the proportion of responders was 47.9% in the ziconotide group vs. 17.5% in the placebo group, p=0.001;
- the proportion of patients who improved on the CPRS scale ("moderate" to "complete" improvement) was 50.7% in the ziconotide group vs. 17.5% in the placebo group, p=0.001;
- no significant difference emerged between the two groups on the basis of the WBPI questionnaire.

Trial 96-002

- the proportion of responders was 33.7% in the ziconotide group vs. 12.8% in the placebo group, p=0.001;
- the proportion of patients who improved on the CPRS scale ("moderate" to "complete" improvement) was 43.8% in the ziconotide group vs. 17.4% in the placebo group, (p=0.001);
- a significant difference in favour of ziconotide was found on the basis of the WBPI questionnaire.

➢ Efficacy at 3 weeks **-** trial 301

The objective of this randomized, double-blind, placebo-controlled trial was to confirm the results of trials 95-001 and 96-002 over a longer treatment period (3 weeks instead of 5-6 days). The doses of ziconotide used were smaller, and the titration was slower.

Two hundred and twenty (220) patients with severe chronic pain (mean VAS = 80.7 mm), poorly controlled by analgesics administered systemically and/or intrathecally, were included.

The patients mainly suffered from neuropathic pain (75.9% of cases in the ziconotide group and 71.3% in the placebo group); only 5 patients had malignant pain. Most of them had undergone spinal surgery (60.7% of the patients treated with ziconotide and 55.6% of those who received the placebo).

On inclusion, 97% of the patients were deemed unresponsive to analgesic treatment, and 90% of them had already been treated with IT morphine.

The patients were randomized to receive either the placebo or ziconotide for 3 weeks at the initial dose of 0.1 µg/h, with progressive increases by increments of 0.05-0.1 µg/h every 24h until the analgesic effect was obtained, without exceeding 0.9 µg/h.

The patients could receive other analgesic treatments during the trial, including opioids, with the exception of intrathecal medication.

The primary efficacy endpoint was the change in the pain intensity score.

Nine of the 112 patients treated with ziconotide discontinued the treatment (6 of them due to adverse events), while 8 of the 108 patients treated with the placebo discontinued the treatment, 5 of them due to adverse events. The percentage of drop-outs was lower in this trial than in the 2 earlier ones because the starting dose was lower and the titration interval longer.

The secondary endpoints included:
- response to the treatment (≥ 30% improvement in VASPI pain score),
- a Clinical Global Impression (CGI) scale filled in by the patient (global satisfaction and pain control)
- changes in pain on the CPRS categorical scale;

Primary endpoint results:

Table no. 2 – Efficacy results of trial 301

Parameter	**Ziconotide (n = 112)**	**Placebo (n =108)**	**Value of p**
Mean VAS score at baseline, in mm (standard deviation)	80,7 (± 15)	80,7 (± 14,9)	-
Mean VAS score at end of titration of initial doses, in mm (standard deviation)	67,9 (± 22,9)	74,1 (± 21,3)	-
Change in VAS score between baseline and D5 or D6 (%)	**14,7 (± 27,7)**	**7,2 (± 24,9)**	**0,036**

The mean dose of ziconotide at the end of titration was 0.29 µg/h (median 0.25 µg/h), which complies with the recommendations of the marketing authorization.

A statistically significant difference emerged for the primary endpoint: change in VAS score. However, the difference observed was minimal (a difference of 7 points out of 100 compared with the placebo).

Secondary endpoint results:
No difference emerged between the two groups as regards the proportion of responders (16.1% in the ziconotide group vs. 12% in the placebo group) or on the CPRS scale. However, a statistically significant difference was found in favour of ziconotide on the CGI scale.

3.2. Safety

The safety of ziconotide (PRIALT), administered by continuous intrathecal infusion, was evaluated in over 1400 patients.
In clinical trials, 88% of the patients had adverse events. The adverse events most frequently reported were as follows: dizziness (42%), nausea (30%), nystagmus (23%), confusional state (25%), walking disorders (16%), memory disorders (13%), blurred vision (14%), headache (12%), asthenia (13%), vomiting (11%) and drowsiness (10%). Four cases considered not severe and one severe case of elevated creatine phosphokinase (CPK) were reported. Two cases of rhabdomyolysis classed as severe were also notified.
Seventy-six (76) deaths occurred during the trials, and ziconotide was held responsible in 3 cases: two cases of inhalation pneumopathy, in which oropharyngeal dyskinesia and consciousness disorders during treatment may have played a part, and one case of suicide. Four patients attempted suicide during the trials.
Forty-two cases (42) of meningitis were reported (40 in patients treated with ziconotide and 2 with the placebo). Ziconotide was administered by external pump in the majority of cases (38), and by an implanted system in only two cases.
No cases of respiratory depression were reported.

3.3. Conclusion

The intrathecal analgesic efficacy of PRIALT (ziconotide) was evaluated in three placebo-controlled trials on a total of 589 patients with severe chronic pain (mean VAS > 75 mm) who had failed to respond to other analgesic treatments.
In two trials, the efficacy of ziconotide was evaluated in the short term (5-6 days) for malignant pain (trial 95-001) and non-malignant pain (trial 96-002).
On inclusion, 32% of the patients in trial 95-001 and 58% of the patients in trial 96-002 had already been treated intrathecally with morphine.
The third trial lasted 3 weeks, and mainly comprised patients with neuropathic pain (70%) and patients who had undergone spinal surgery. On inclusion, 97% of the patients were deemed unresponsive to analgesic treatment, and 90% of them had already been treated with IT morphine.

In the three trials, the primary endpoint was the change in the pain intensity score evaluated with the aid of the visual analogue scale (VAS).

In the two short-term trials, where the initial dose of ziconotide was higher and the titration more rapid than recommended in the marketing authorization, a statistically significant difference emerged in favour of ziconotide compared with the placebo:

- in trial 95-001, the change in the mean VAS score was 51.4% in the patients treated with ziconotide vs. 18.1% with the placebo, p=0.0003, ie. a difference of 33.3 points.
- in trial 95-002, the change in the mean VAS score was 31.2% in the patients treated with ziconotide vs. 6% with the placebo, p≤0.001, ie. a difference of 25.2 points.

In trial 301, where the initial dose of ziconotide was lower and the titration interval longer (as recommended by the marketing authorization), a statistically significant difference (p = 0.036) emerged for the primary endpoint, but this difference is very low: 7 points out of 100 compared with the placebo.

88% of the patients in the clinical trials experienced adverse events.
A severe case of elevated creatine phosphokinase (CPK) and two cases of rhabdomyolysis considered severe were reported. Ziconotide was considered to be responsible for 3 deaths: two cases of inhalation pneumopathy and one case of suicide. Forty-two cases (42) of meningitis were reported (40 in patients treated with ziconotide and 2 with the placebo). Ziconotide was administered by external pump in the majority of cases (38), and by an implanted system in only two cases. The use of the implantable system seems to reduce the incidence of meningitis.

The Transparency Committee regrets the absence of a controlled trial lasting more than 3 weeks to assess the efficacy and safety of ziconotide, as this substance is indicated for the treatment of chronic pain. Moreover, in the absence of trials comparing ziconotide with an active comparator, it is difficult to position it in relation to other analgesics, especially intrathecal morphine.

The Transparency Committee wishes to receive the results of the PRIME patient registry, the objective of which is to “provide long-term efficacy and safety data for IT ziconotide given to patients experiencing severe, chronic malignant and non-malignant pain. Analyses of patient outcomes by pain aetiology (malignant, non-malignant), pain mechanism (neuropathic, non-neuropathic), and pain severity (VASPI score above or below 50 mm at baseline) will be conducted. The registry will help to define the use of ziconotide in the clinical setting e.g. optimal dosing regimen and the possible development of tolerance. The use of ziconotide in combination with morphine or baclofen, other medicinal products, quality of life, and the analysis of adverse events, will also be taken into account.”

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Intense chronic pain characterized by a clinical course towards disability and/or marked deterioration in the quality of life.
PRIALT (ziconotide) is only used intrathecally.
This proprietary product is a symptomatic treatment.

Public health benefit:

In view of its frequency and psychosocial repercussions (fatigue, anxiety, depression), severe chronic pain represents a moderate public health burden. Forms requiring intrathecal anaesthesia represent a low burden in view of their rarity

Improving the treatment of severe chronic pain constitutes a public health need which is an established priority (GTNDO[7] pain management priority, Rare Disease Plan).

Having regard to the available data, despite the absence of a comparison with intrathecal morphine, this proprietary product is expected to have an impact on morbidity and quality of life, mainly in patients whose pain is resistant to intrathecal morphine. However, in the absence of proof, it is difficult to quantify the expected impact.

The proprietary drug PRIALT is therefore not expected to provide a supplementary response to the identified public health requirement.

Consequently, PRIALT is not expected to have an impact on public health.

The efficacy/adverse effects ratio is high.
Alternative treatments are available.
The actual clinical benefit is substantial in the treatment of chronic pain resistant to other analgesic treatments, including intrathecal morphine.

4.2. Improvement in actual benefit

In view of the limited number of alternative treatments available and the efficacy data resulting from the three placebo-controlled trials, the Transparency Committee considers that PRIALT offers patients resistant to other analgesic treatments, including intrathecal morphine, a minor improvement in actual benefit (IAB IV) in the treatment of severe chronic malignant and non-malignant pain.

[7] *Groupe Technique National de Définition des Objectifs (National Target Definition Group) (DGS-2003)*

4.3. Therapeutic use[89]

The treatment of severe chronic pain is based on strong opioids (step 3 analgesics in the case of malignant pain) and non-opioid analgesics in the case of neuropathic pain.
Oral morphine is administered as the first-line treatment.
If the oral route cannot be used, or the pain is resistant to oral morphine, a change of opioid is recommended (opioid rotation) or a change of administration route (injection or transdermal administration).
As a last resort, more specific analgesic treatments could be offered, including intrathecal administration.
The intrathecal route is rarely indicated because it is invasive, involving the introduction of an implantable device, and involves risk, especially the risk of infection (meningitis) and constraints. Patients suitable for treatment by this route are those in whom none of the alternatives has proved effective.

Place of PRIALT (ziconotide) in the management of chronic pain
Treatment with PRIALT is aimed at a limited number of patients suffering from severe chronic pain of different origins (malignant, AIDS-related or neuropathic) which is resistant to other analgesic treatments, including intrathecal morphine. Treatment with ziconotide should only be undertaken by physicians experienced in intrathecal administration of medicinal products.
In view of the low effect observed in trial 301, PRIALT is not recommended for the treatment of pain after spinal surgery, except in the event of failure or contraindication of all the alternatives.

4.4. Target population

The population liable to benefit from PRIALT is represented by all patients suffering from severe chronic pain of different origins (malignant, neuropathic) not controlled by administration of opioid and non-opioid analgesics, including intrathecal morphine. These patients only represent a very small percentage of patients with chronic pain.
In the absence of specific French epidemiological data on pain, it is difficult to determine the target population of PRIALT precisely.
As a rough guide, according to the experts, this population can be estimated in France at 100 patients at most.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the “treatment of severe, chronic pain in patients who require intrathecal analgesia not controlled by administration of opioid and non-opioid analgesics, including intrathecal morphine”, at the dosage specified in the marketing authorization.

[8] Fédération Nationale des Centres de Lutte contre le Cancer. Standards, options, recommandations 2002 sur les traitements antalgiques médicamenteux des douleurs cancéreuses par excès de nociception chez l’adulte.

[9] Agence Nationale d’Accréditation et d’Evaluation en Santé, ANAES. Modalités de prise en charge de l’adulte nécessitant des soins palliatifs. Décembre 2002.