ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Prialt 25 micrograms/ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution contains 25 µg ziconotide (as acetate).

Each vial contains 500 µg ziconotide (as acetate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear, colourless solution, free of visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ziconotide is indicated for the treatment of severe, chronic pain in adults who require intrathecal (IT) analgesia.

4.2 Posology and method of administration

Treatment with ziconotide should only be undertaken by physicians experienced in intrathecal (IT) administration of medicinal products.

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 of ≤ 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 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.

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. (See section 6.6).

Use in paediatric patients (< 18 years of age)

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.

Use in patients with impaired hepatic function

Studies have not been conducted in patients with impaired hepatic function. Caution should be exercised when ziconotide is administered to patients with impaired hepatic function.

Use in patients with impaired renal function

Studies have not been conducted in patients with impaired renal function. Caution should be exercised when ziconotide is administered to patients with impaired renal function.

Prialt is for intrathecal use only.

For instructions for use and handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Ziconotide is contraindicated in combination with IT chemotherapy (see section 4.5).

4.4 Special warnings and precautions for use

Long-term use
Although ziconotide has been studied in long-term, open label efficacy and safety clinical trials, controlled studies of longer than 3 weeks duration have not been conducted (see section 5.1). Possible long-term local toxic effects on the spinal cord have not been excluded and preclinical data in this respect are limited (see section 5.3). Therefore, caution is needed during long-term treatment.

Route of administration
The administration of medicinal products by the intrathecal (IT) route carries the risk of potentially serious infections, such as meningitis, which may be life threatening. Meningitis due to the entrance of organisms along the catheter track or inadvertent contamination of the infusion system is a known complication of intrathecal medicinal product administration, especially with external systems.

Patients and physicians must be vigilant for typical symptoms and signs of meningitis.

The optimal intrathecal placement of the catheter tip has not been established. Lower catheter tip placement, e.g. at the lumbar level, may reduce the incidence of ziconotide-related neurological adverse reactions. Therefore, catheter tip placement should be carefully considered to allow adequate access to spinal nociceptive segments whilst minimising medicinal product concentrations at cerebral levels.

Only a small number of patients have received systemic chemotherapy and IT ziconotide. Caution should be exercised when ziconotide is administered to patients who are receiving systemic chemotherapy (see section 4.5).

Elevations in creatine kinase
Elevations in creatine kinase, which are usually asymptomatic, are common amongst patients on intrathecal ziconotide. Progressive elevation of the creatine kinase is uncommon. However monitoring of creatine kinase is recommended. In the event of progressive elevation, or clinically significant elevation in association with clinical features of myopathy or rhabdomyolysis, discontinuation of ziconotide should be considered.

Hypersensitivity reactions
Hypersensitivity reactions including anaphylaxis have not been observed during clinical trials and the immunogenicity of ziconotide administered by the IT route appears to be low. However, the potential for severe allergic reactions cannot be excluded.

Cognitive and neuropsychiatric adverse reactions
Cognitive and neuropsychiatric adverse reactions, particularly confusion, are common in patients treated with ziconotide. Cognitive impairment typically appears after several weeks of treatment. Episodes of acute psychiatric disturbances, such as hallucinations, paranoid reactions, hostility, aggressiveness, delirium, psychosis and manic reactions have been reported in patients treated with ziconotide. The ziconotide dose should be reduced or discontinued if signs or symptoms of cognitive impairment or neuropsychiatric adverse reactions develop, but other contributing causes should also be considered. The cognitive effects of ziconotide are typically reversible within 1 - 4 weeks after discontinuation of the medicinal product, but may persist in some cases.

In patients with severe chronic pain there is a higher incidence of suicide and suicide attempts than in the general population. Ziconotide may cause or worsen depression with the risk of suicide in susceptible patients.

Depression of Central Nervous System
Patients have experienced depressed levels of consciousness while receiving ziconotide. The patient usually remains conscious and breathing is not depressed. The event may be self limited, but ziconotide should be discontinued until the event resolves. The re-introduction of ziconotide is not recommended in these patients. Withdrawal of concomitant Central Nervous System (CNS) depressant medicinal products should also be considered as they may contribute to the reduced level of arousal.

4.5 Interaction with other medicinal products and other forms of interaction

Specific clinical medicinal product interaction studies have not been conducted with ziconotide. However, low plasma ziconotide concentrations, metabolism by ubiquitous peptidases and relatively low plasma protein binding (see section 5.2) make metabolic-based interactions or plasma protein displacement type interactions between ziconotide and other medicinal products unlikely.

No clinical data are available on the interaction between IT chemotherapy and IT ziconotide. Ziconotide is contraindicated in combination with IT chemotherapy (see section 4.3).

Only a small number of patients have received systemic chemotherapy and IT ziconotide. Caution should be exercised when ziconotide is administered to patients who are receiving systemic chemotherapy (see section 4.4).

Medicinal products that affect specific peptidases/proteases would not be expected to impact upon ziconotide plasma exposure. Based on very limited clinical investigations, both angiotensin converting enzyme inhibitors (e.g., benazepril, lisinopril and moexipril) and HIV protease inhibitors (e.g., ritonavir, saquinavir, indinavir), have no readily apparent effect on plasma ziconotide exposure.

Ziconotide does not interact with opiate receptors. If discontinuing opiates when initiating ziconotide therapy, opiate withdrawal should be gradual. For patients being withdrawn from IT opiates, the IT opiate infusion dose should be gradually tapered over a few weeks and replaced with a pharmacologically equivalent dose of oral opiates. Adding IT ziconotide to stable doses of IT

morphine (see section 5.1), is possible but requires special attention, as a high rate of neuropsychiatric adverse reactions (confusion/thinking abnormal, paranoid reactions and hallucinations, and abnormal gait), some of them serious, was observed in Study 202 despite a low dose of ziconotide. Vomiting and anorexia, and peripheral oedema were also observed when IT ziconotide was added to IT morphine. The addition of IT morphine to stable doses of IT ziconotide is better tolerated (pruritis has been reported). (See section 5.1).

An increased incidence of somnolence has been observed when ziconotide is administered concomitantly with systemic baclofen, clonidine, bupivacaine or propofol thus for the time being their simultaneous use is discouraged.

No data are available regarding the concomitant use of partial opioid agonists (e.g. buprenorphine) with ziconotide.

4.6 Pregnancy and lactation

There are no adequate data from the use of ziconotide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Ziconotide should not be used during pregnancy unless clearly necessary.

It is not known whether ziconotide is excreted in breast milk, therefore it should not be administered to breast-feeding women unless clearly necessary.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Ziconotide may cause confusion, somnolence and other neurological adverse reactions, therefore patients must be advised not to drive or operate machines if affected.

4.8 Undesirable effects

The safety of ziconotide administered as a continuous intrathecal infusion has been evaluated in more than 1,400 patients participating in acute and chronic pain clinical trials. The duration of treatment has ranged from one-hour bolus infusion to continuous use for more than 6 years. The median exposure time was 43 days. The infusion dose rate ranged from 0.03 - 912 μg/day, with a median final dose rate of 7.2 μg/day.

In clinical trials, 88% of patients experienced adverse drug reactions (ADRs). The most commonly reported ADRs reported in long-term clinical trials were dizziness (42%), nausea (30%), nystagmus (23%), confusional state (25%), gait abnormal (16%), memory impairment (13%), vision blurred (14%), headache (12%), asthenia (13%), vomiting (11%), and somnolence (10%). Most ADRs were mild to moderate in severity and resolved over time.

All ADRs reported in the intrathecal clinical trials with ziconotide (short- and long-term exposure) are listed below in order of frequency.

Very Common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)

Infections and infestations

Uncommon: sepsis, meningitis

Metabolism and nutrition disorders

Common: appetite decreased, anorexia

Psychiatric disorders

Very common: confusional state

Common: anxiety, auditory hallucination, insomnia, agitation, disorientation, hallucination, visual hallucination, depression, paranoia, irritability, depression aggravated, nervousness, affect lability, mental status changes, anxiety aggravated, confusion aggravated

Uncommon: delirium, psychotic disorder, suicidal ideation, suicide attempt, thought blocking, abnormal dreams, aggressiveness

Nervous system disorders

Very common: dizziness, nystagmus, memory impairment, headache, somnolence

Common: dysarthria, amnesia, dysgeusia, tremor, balance impaired, ataxia, aphasia, burning sensation, sedation, paraesthesia, hypoaesthesia, disturbance in attention, speech disorder, areflexia, coordination abnormal, dizziness postural, cognitive disorder, hyperaesthesia, hyporeflexia, ageusia, depressed level of consciousness, dysaesthesia, parosmia, mental impairment

Uncommon: incoherence, loss of consciousness, coma, stupor, convulsions, cerebrovascular accident, encephalopathy

Eye disorders

Very common: vision blurred

Common: diplopia, visual disturbance, photophobia

Ear and labyrinth disorders

Common: vertigo, tinnitus

Cardiac disorders

Uncommon: atrial fibrillation

Vascular disorders

Common: orthostatic hypotension, hypotension

Respiratory, thoracic and mediastinal disorders

Common: dyspnoea

Uncommon: respiratory distress

Gastrointestinal disorders

Very common: nausea, vomiting

Common: diarrhoea, dry mouth, constipation, nausea aggravated, upper abdominal pain

Uncommon: dyspepsia

Skin and subcutaneous tissue disorders

Common: pruritus, sweating increased

Uncommon: rash

Musculoskeletal and connective tissue disorders

Common: pain in limb, myalgia, muscle spasms, muscle cramp, muscle weakness, arthralgia, peripheral swelling

Uncommon: rhabdomyolysis, myositis, back pain, muscle twitching, neck pain

Renal and urinary disorders

Common: urinary retention, urinary hesitation, dysuria, urinary incontinence

Uncommon: acute renal failure

General disorders and administration site conditions

Very Common: gait abnormal, asthenia

Common: fatigue, pyrexia, lethargy, oedema peripheral, rigors, fall, chest pain, feeling cold, pain, feeling jittery, pain exacerbated

Uncommon: difficulty in walking

Investigations

Common: blood creatine phosphokinase increased, weight decreased

Uncommon: electrocardiogram abnormal, aspartate aminotransferase increased, blood creatine phosphokinase MM increased, body temperature increased

Specific comments and particular caution regarding meningitis, elevations of creatine kinase, and CNS adverse events can be found in Section 4.4.

4.9 Overdose

In intravenous infusion studies, healthy male volunteers received ziconotide at doses of up to 70,000 μg/day or 3,200 times the maximum recommended daily intrathecal infusion dose. Postural hypotension was observed in almost all subjects who received high intravenous doses of ziconotide.

The maximum recommended intrathecal dose is 21.6 μg/day. The maximum intended intrathecal dose of ziconotide in clinical trials was 912 μg/day following upward titration over 7 days.

In one clinical study a male cancer patient received an accidental IT ziconotide overdose of 744 μg over a 24-hour period (31 μg/hour) and resumed treatment at the intended dose after experiencing a reduction in Visual Analog Scale of Pain Intensity (VASPI) from 82 to 2.5 mm. In some patients who received intrathecal doses greater than the maximum recommended dose, exaggerated pharmacological effects, e.g., ataxia, nystagmus, dizziness, stupor, depressed level of consciousness, muscle spasms, confusional state, sedation, hypotension, aphasia, speech disorder, nausea and

vomiting were observed. There was no indication of respiratory depression. Most patients under observation recovered within 24 hours of withdrawal of the medicinal product.

General medical supportive measures should be administered to patients who receive an overdose until the exaggerated pharmacological effects of the medicinal product have resolved.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics; Other analgesics and antipyretics ATC code: N02BG08

This medicinal product has been authorised under "Exceptional Circumstances". This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information, which may become available every year and this SmPC will be updated as necessary.

Ziconotide is a synthetic analogue of a ω-conopeptide, MVIIA, found in the venom of the *Conus magus* marine snail. It is an N-type calcium channel blocker (NCCB). NCCs regulate neurotransmitter release in specific neuronal populations responsible for the spinal processing of pain. In binding to these neuronal NCCs ziconotide inhibits the voltage sensitive calcium current into primary nociceptive afferents terminating in the superficial layers of the dorsal horn of the spinal cord. In turn, this inhibits their release of neurotransmitters (including Substance P) and therefore, the spinal signalling of pain.

Though statistically significant relationships and reasonable correlation between cerebrospinal fluid (CSF) exposure (AUC, C_{max}) and clinical response measures have been observed following 1 hour IT administration, no well-defined dose-concentration-response relationships have yet been identified. Many responsive patients obtain near-maximal analgesia within a few hours of delivery of an appropriate dose. However, maximal effects may be delayed for approximately 24 hours in some patients. Given the occurrence of analgesia and adverse drug reactions at similar doses, the recommended interval between dose increases is 48 hours or more. If necessary the dose can be decreased by any amount (including stopping the infusion) for the management of adverse drug reactions.

Nervous system adverse reactions, particularly dizziness, nausea and abnormal gait appear to be correlated with CSF exposure, though a definitive relationship has not been established.

Low plasma exposure occurs during IT infusion due to the low recommended IT infusion rates and relatively rapid plasma clearance (see section 5.2). Therefore, pharmacological effects related to systemic exposure should be minimal.

The median dose at response is approximately 6.0 μg/day and approximately 75% of responsive patients require ≤ 9.6 μg/day. To limit the occurrence of serious adverse drug reactions, a maximum dose of 21.6 μg/day is recommended. However, in clinical trials it has been observed that patients who tolerate doses of 21.6 μg/day following slow titration over a 3 to 4-week period, generally tolerate higher doses up to 48.0 μg/day.

There is no evidence of the development of pharmacological tolerance to ziconotide in patients. However, in view of limited data, the development of tolerance cannot be excluded. Examination of the patency of the intrathecal catheter should be considered if the required ziconotide dose continually increases and there is no benefit or increase in drug reactions.

There were three placebo-controlled clinical trials of IT ziconotide.

Two short-term studies, 95-001 (malignant pain) and 96-002 (non malignant pain), involving 366 patients, demonstrated the efficacy of IT ziconotide in severe chronic pain using the percent change in Visual Analog Scale of Pain Intensity (VASPI) as the primary efficacy measure. These studies were of short duration, 5 and 6 days respectively, and used a more rapid dose escalation and higher doses than recommended in Section 4.2.

Efficacy results from study 95-001

	Initial Treatment Assignment		
Parameter	**Ziconotide (n = 71)**	**Placebo (n = 40)**	**p-value**
Mean VASPI score at baseline in mm (SD)	74.1 (± 13.82)	77.9 (± 13.60)	_
Mean VASPI score at end of initial titration in mm (SD)	35.7 (± 33.27)	61.0 (± 22.91)	_
% improvement in VASPI score at end of initial titration (SD)	51.4 (± 43.63)	18.1 (± 28.28)	< 0.001
Responder[a] n (%)	34 (47.9%)	7 (17.5%)	0.001
Dose at end of titration (μg/hr)			
Mean	0.91		
Median	0.60		
Range	0.074 - 9.36		

[a]Responders were defined as those patients who 1) experienced a ≥ 30% drop in VASPI score compared to baseline; 2) had stable or decreased concomitant opioid analgesics; and 3) had opiate type unchanged from preinfusion if receiving opiates.
SD – Standard Deviation.

Efficacy results from study 96-002

	Initial Treatment Assignment		
Parameter	**Ziconotide (n = 169)[b]**	**Placebo (n = 86)**	**p-value**
Mean VASPI score at baseline in mm (SD)	80.1 (± 15.10)	76.9 (± 14.58)	_
Mean VASPI score at end of initial titration in mm (SD)	54.4 (± 29.30)	71.9 (± 30.93)	_
% improvement in VASPI score at end of initial titration (SD)	31.2 (± 38.69)	6.0 (± 42.84)	< 0.001
Responder[a] n (%)	57 (33.7%)	11 (12.8%)	< 0.001
Dose at end of titration (μg/hr)			
Mean	1.02		
Median	0.50		
Range	0.019 - 9.60		

[a]Responders were defined as those patients who 1) experienced a ≥ 30% drop in VASPI score compared to baseline; 2) had stable or decreased concomitant opioid analgesics; and 3) had opiate type unchanged from preinfusion if receiving opiates.
[b]164 patients provided VASPI scores for ziconotide at the end of titration.
SD – Standard Deviation.

The aetiologies of pain in studies 95-001 (malignant pain) and 96-002 (non-malignant pain) were varied and included bone pain (n = 38) mostly due to bone metastases (n = 34), myelopathy (n = 38), half of whom had spinal cord injury with paralysis (n = 19), neuropathy (n = 79), radiculopathy (n = 24), spinal pain (n = 91) mostly due to failed back surgery (n = 82), and other aetiologies

(n = 82). Some patients had more than one cause of pain. The efficacy of IT ziconotide was apparent in all groups.

Study 301 (n = 220) was of longer duration (21 days), involved more cautious up-titration and lower doses of IT ziconotide, and enrolled the most refractory population of patients studied in the three studies. All patients in the 301 study had failed IT therapy with combinations of analgesics and their physicians considered that 97% of the patients were refractory to currently available treatments. The majority had spinal pain (n = 134), especially failed back surgery (n = 110); a lower proportion had neuropathy (n = 36). Only five had malignant pain. The primary endpoint was the percent change in VASPI score. The efficacy of IT ziconotide in study 301 was lower than in the previous two, short-term studies. The frequency and severity of adverse events were also lower.

Efficacy results from study 301

	Initial Treatment Assignment		
Parameter	**Ziconotide (n = 112)**	**Placebo (n = 108)**	**p-value**
Mean VASPI score at baseline in mm (SD)	80.7 (± 14.98)	80.7 (± 14.91)	-
Mean VASPI score at end of initial titration in mm (SD)	67.9 (± 22.89)	74.1 (± 21.28)	_
% improvement in VASPI score at end of initial titration (SD)	14.7 (± 27.71)	7.2 (± 24.98)	0.0360
Responder[a] n (%)	18 (16.1%)	13 (12.0%)	0.390
Dose at end of titration (µg/hr)			
Mean	0.29		
Median	0.25		
Range	0.0 - 0.80		

[a]Responders were defined as those who experienced a ≥ 30% drop in VASPI score compared to baseline.
SD – Standard Deviation.

Combination studies with IT Morphine

Clinical studies 201 and 202 indicate that the combination of IT ziconotide and IT morphine may effectively reduce pain and decrease systemic opioid use over a sustained period of time for patients whose pain was inadequately controlled with their maximum tolerated dose of IT ziconotide (median 8.7 µg/day, mean 25.7 µg/day – study 201) or with IT morphine (study 202) alone. When adding IT ziconotide to stable doses of IT morphine, as with the initiation of IT ziconotide monotherapy, the appearance of psychotic adverse events (e.g., hallucinations, paranoid reactions) or discontinuation due to increased adverse events may occur. (see section 4.5).

5.2 Pharmacokinetic properties

The CSF pharmacokinetics of ziconotide have been studied following one-hour IT infusions of 1 - 10 µg of ziconotide in patients with chronic pain. The plasma pharmacokinetics following intravenous doses (0.3 – 10 µg/kg/24 hr) were also studied. IT and intravenous pharmacokinetics data are summarised below.

CSF and Plasma Pharmacokinetics of Ziconotide [mean ± SD (median)]

Route of administration	Fluid matrix	Number of patients	CL (ml/min)	Vd (ml)	$t_{½}$ (hr)
Intrathecal	CSF	23	0.38 ± 0.56 (0.26)	155 ± 263 (99)	4.6 ± 0.9 (4.5)
Intravenous	Plasma	21	270 ± 44 (260)	30,460 ± 6,366 (29,320)	1.3 ± 0.3 (1.3)

CL = clearance; Vd = distribution volume; $t_{½}$ = half life

Absorption: Following one-hour IT administration (1 – 10 µg), both cumulative exposure (AUC; range: 83.6 – 608 ng/h/ml) and peak exposure (C_{max}; range: 16.4 – 132 ng/ml) values were variable and dose-dependent, but appeared only approximately dose-proportional. Plasma concentrations following continuous (≥ 48 h) IT infusion (≤ 21.6 µg/day) appear to be relatively low and typically undetectable (i.e., about 80% of plasma samples collected from pain patients contain no quantifiable medicinal product; < 0.04 ng/ml). No accumulation of ziconotide in plasma following long-term IT administration (up to 9 months) has been observed.

Distribution: Median ziconotide CSF volume of distribution (Vd: 99 ml) is between the spinal cord CSF volume (approximately 75 ml) and total CSF volume (approximately 130 ml). Ziconotide appears to distribute mainly within the CSF until transferred to the systemic circulation. Upon reaching the systemic circulation, ziconotide appears to be more extensively distributed, based on a plasma distribution volume of approximately 30 l and is only about 53% bound (non-specifically) to human plasma proteins.

Biotransformation: Ziconotide is a peptide consisting of 25 naturally-occurring amino acids of the L-configuration, and does not appear to be appreciably metabolised in the CSF. Following passage into the systemic circulation, ziconotide is expected to be primarily susceptible to proteolytic cleavage by various ubiquitous peptidases/proteases present in most organs (e.g., kidney, liver, lung, muscle, etc.), and thus degraded to peptide fragments and its individual constituent free amino acids. The generated free amino acids are expected to be taken up by cellular carrier systems and either subjected to normal intermediary metabolism or used as substrates for constitutive biosynthetic processes. Due to the wide distribution of these peptidases it is not expected that hepatic or renal impairment would affect the systemic clearance of ziconotide. The biological activity of the various expected proteolytic degradation products has not been assessed. It is unlikely that the degradation products of ziconotide will have significant biological activity, as peptides consisting of the individual peptide loop structures have been found to have binding affinities for N-type voltage sensitive calcium channels that are several orders of magnitude lower than that of the parent (ziconotide) compound.

Elimination: Mean ziconotide CL (0.38 ml/min) approximates adult human CSF turnover rate (0.3 - 0.4 ml/min). Hence, ziconotide appears to be mainly eliminated from the CSF (mean $t_{½}$ = 4.6 hr) by bulk flow of CSF out of the CNS through the arachnoid villi with subsequent transfer into the systemic circulation. Very low circulating plasma concentrations of ziconotide may be observed following IT administration due to both the low IT infusion rate and relatively rapid plasma clearance. The mean plasma elimination half-life ($t_{½}$) is 1.3 hr. Ziconotide is a relatively small molecular weight peptide (MW = 2,639) and is filtered by the kidney glomerulus, but only minimal amounts of ziconotide (< 1%) are recovered in human urine following intravenous infusion. This is because almost all of the filtered active substance is rapidly endocytosed and ultimately transported back to the systemic circulation.

Specific populations: Although only limited data are available, there is no obvious effect of race, height, weight, gender or age on CSF ziconotide exposure after IT administration. No formal studies assessing the impact of renal or hepatic dysfunction have been conducted; however, given that peptidases are present in various body organs, it is not anticipated that renal or hepatic dysfunction will significantly impact systemic exposure of ziconotide.

5.3 Preclinical safety data

Preclinical toxic effects related to ziconotide administration were observed only at exposures considered sufficiently in excess of the human exposure to indicate little risk in clinical use.

In subchronic continuous intrathecal infusion studies in rats and dogs, behavioural effects were seen at doses ≥ 8-fold the maximum recommended clinical intrathecal infusion dose of 21.6 μg/day (on a mg/kg basis). These effects were defined by exaggerated pharmacological actions of ziconotide and not by neurotoxic lesions or target organ toxicity. Observations included transient and reversible neurological effects consisting of tremors, uncoordinated movements and hyper- and hypoactivity.

The long-term consequences to neuronal function of continuous N-type calcium-channel block have not been demonstrated in experimental animals. Changes in neurological signalling have not been studied in experimental animals. Ziconotide did not induce bacterial gene mutation and was not genotoxic. Chronic animal studies have not been performed to assess the carcinogenic potential of ziconotide. However, ziconotide did not induce cell transformation in the *in vitro* Syrian hamster embryo (SHE) assay and did not increase cell proliferation (pre-neoplastic lesion formation) or apoptosis after subchronic intrathecal exposure in dogs.

In rat fertility studies, there were no effects in males while reductions in corpora lutea; implantation sites and number of live embryos were observed in females. No adverse effects on female reproduction and post-natal development in rats were seen at systemic exposures up to 2,300 times human exposures at the maximum recommended intrathecal dose.

Ziconotide was not teratogenic in rats and rabbits at exposures < 100 times human plasma levels.

These results do not indicate a significant risk to humans due to the relatively high systemic exposures needed to elicit these effects in rats and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methionine
Sodium chloride
Water for injections
Hydrochloric acid (pH adjuster)
Sodium hydroxide (pH adjuster)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

Chemical and physical in use stability has been demonstrated for 60 days at 37°C.

From a microbiological point of view, if the product is diluted it should be transferred to the infusion pump immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze. Keep the vial in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Single-use Type I glass vials with butyl rubber stoppers coated with fluorinated polymer.

Each vial contains 20 ml solution for infusion.

One vial per carton.

6.6 Special precautions for disposal and other handling

If dilution is required, Prialt must be diluted aseptically with preservative-free sodium chloride 9 mg/ml (0.9%) solution for injection before use. The concentration of the solution used in the infusion pump must be no lower than 5 µg/ml ziconotide in an external pump and 25 µg/ml in an internal pump.

Strict aseptic procedures must be used during the preparation and handling of the solution for infusion and refilling of the pump. The patient and health-care providers must be familiar with the handling of the external or internal infusion system and be aware of the need to guard against infection.

Prialt has been shown to be chemically and physically compatible with the implantable Synchromed pump and the external CADD-Micro pump at the concentration levels indicated above. Chemical and physical in-use stability has been demonstrated for 14 days at 37ºC in the Synchromed pump when the pump has not previously been exposed to the medicinal product. The initial fill must therefore be replaced after 14 days.

Prialt was stable for 60 days at 37°C in the Synchromed pump previously exposed to the medicinal product. Stability has been demonstrated for 21 days at room temperature in the CADD-Micro pump.

Specific instructions for using the pumps must be obtained from the manufacturer. CE marked pumps equivalent to the Synchromed and CADD-Micro pump should be used to deliver Prialt. Pumps previously used to deliver other medicinal products must be washed out three times with sodium chloride 9 mg/ml (0.9%) solution for injection (preservative-free) before being filled with Prialt. The introduction of air into the pump reservoir or cartridge should be minimized, as oxygen can degrade ziconotide.

Prior to initiation of therapy, an internal pump must be rinsed three times with 2 ml of Prialt at 25 µg/ml. The concentration of Prialt in a naïve pump may be reduced due to adsorption onto the surfaces of the device, and/or dilution by the residual space of the device. Because of this, after the first use of Prialt, the reservoir should be emptied and refilled after 14 days. Subsequently the pump should be emptied and refilled every 60 days.

Prialt is a clear and colourless solution. It should be inspected visually for particulate matter and discolouration prior to administration. The solution should not be used if discoloured or cloudy or if particulate matter is observed.

For single use only. Any unused solution should be discarded according to local regulations.

7. MARKETING AUTHORISATION HOLDER

Eisai Ltd.,
European Knowledge Centre
Mosquito Way
Hatfield
Herts
AL10 9SN
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/302/004 – 20 ml solution for infusion

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20/03/2006
Date of latest renewal: 12/01/2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Prialt 100 micrograms/ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution contains 100 µg ziconotide (as acetate).

1 ml vial: Each vial contains 100 µg ziconotide (as acetate).

2 ml vial: Each vial contains 200 µg ziconotide (as acetate).

5 ml vial: Each vial contains 500 µg ziconotide (as acetate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear, colourless solution, free of visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ziconotide is indicated for the treatment of severe, chronic pain in adults who require intrathecal (IT) analgesia.

4.2 Posology and method of administration

Treatment with ziconotide should only be undertaken by physicians experienced in intrathecal (IT) administration of medicinal products.

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 of ≤ 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 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.

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. (see section 6.6).

Use in paediatric patients (< 18 years of age)

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.

Use in patients with impaired hepatic function

Studies have not been conducted in patients with impaired hepatic function. Caution should be exercised when ziconotide is administered to patients with impaired hepatic function.

Use in patients with impaired renal function

Studies have not been conducted in patients with impaired renal function. Caution should be exercised when ziconotide is administered to patients with impaired renal function.

Prialt is for intrathecal use only.

For instructions for use and handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Ziconotide is contraindicated in combination with IT chemotherapy (see section 4.5).

4.4 Special warnings and precautions for use

Long-term use
Although ziconotide has been studied in long-term, open label efficacy and safety clinical trials, controlled studies of longer than 3 weeks duration have not been conducted (see section 5.1). Possible long-term local toxic effects on the spinal cord have not been excluded and preclinical data in this respect are limited (see section 5.3). Therefore, caution is needed during long-term treatment.

Route of administration
The administration of medicinal products by the intrathecal (IT) route carries the risk of potentially serious infections, such as meningitis, which may be life threatening. Meningitis due to the entrance of organisms along the catheter track or inadvertent contamination of the infusion system is a known complication of intrathecal medicinal product administration, especially with external systems.

Patients and physicians must be vigilant for typical symptoms and signs of meningitis.

The optimal intrathecal placement of the catheter tip has not been established. Lower catheter tip placement, e.g. at the lumbar level, may reduce the incidence of ziconotide-related neurological adverse reactions. Therefore, catheter tip placement should be carefully considered to allow adequate access to spinal nociceptive segments whilst minimising medicinal product concentrations at cerebral levels.

Only a small number of patients have received systemic chemotherapy and IT ziconotide. Caution should be exercised when ziconotide is administered to patients who are receiving systemic chemotherapy (see section 4.5).

Elevations in creatine kinase
Elevations in creatine kinase, which are usually asymptomatic, are common amongst patients on intrathecal ziconotide. Progressive elevation of the creatine kinase is uncommon. However monitoring of creatine kinase is recommended. In the event of progressive elevation, or clinically significant elevation in association with clinical features of myopathy or rhabdomyolysis, discontinuation of ziconotide should be considered.

Hypersensitivity reactions
Hypersensitivity reactions including anaphylaxis have not been observed during clinical trials and the immunogenicity of ziconotide administered by the IT route appears to be low. However, the potential for severe allergic reactions cannot be excluded.

Cognitive and neuropsychiatric adverse reactions
Cognitive and neuropsychiatric adverse reactions, particularly confusion, are common in patients treated with ziconotide. Cognitive impairment typically appears after several weeks of treatment. Episodes of acute psychiatric disturbances, such as hallucinations, paranoid reactions, hostility, aggressiveness, delirium, psychosis and manic reactions have been reported in patients treated with ziconotide. The ziconotide dose should be reduced or discontinued if signs or symptoms of cognitive impairment or neuropsychiatric adverse reactions develop, but other contributing causes should also be considered. The cognitive effects of ziconotide are typically reversible within 1 - 4 weeks after discontinuation of the medicinal product, but may persist in some cases.

In patients with severe chronic pain there is a higher incidence of suicide and suicide attempts than in the general population. Ziconotide may cause or worsen depression with the risk of suicide in susceptible patients.

Depression of Central Nervous System
Patients have experienced depressed levels of consciousness while receiving ziconotide. The patient usually remains conscious and breathing is not depressed. The event may be self limited, but ziconotide should be discontinued until the event resolves. The re-introduction of ziconotide is not recommended in these patients. Withdrawal of concomitant Central Nervous System (CNS) depressant medicinal products should also be considered as they may contribute to the reduced level of arousal.

4.5 Interaction with other medicinal products and other forms of interaction

Specific clinical medicinal product interaction studies have not been conducted with ziconotide. However, low plasma ziconotide concentrations, metabolism by ubiquitous peptidases and relatively low plasma protein binding (see section 5.2) make metabolic-based interactions or plasma protein displacement type interactions between ziconotide and other medicinal products unlikely.

No clinical data are available on the interaction between IT chemotherapy and IT ziconotide. Ziconotide is contraindicated in combination with IT chemotherapy (see section 4.3).

Only a small number of patients have received systemic chemotherapy and IT ziconotide. Caution should be exercised when ziconotide is administered to patients who are receiving systemic chemotherapy (see section 4.4).

Medicinal products that affect specific peptidases/proteases would not be expected to impact upon ziconotide plasma exposure. Based on very limited clinical investigations, both angiotensin converting enzyme inhibitors (e.g., benazepril, lisinopril and moexipril) and HIV protease inhibitors (e.g., ritonavir, saquinavir, indinavir), have no readily apparent effect on plasma ziconotide exposure.

Ziconotide does not interact with opiate receptors. If discontinuing opiates when initiating ziconotide therapy, opiate withdrawal should be gradual. For patients being withdrawn from IT opiates, the IT opiate infusion dose should be gradually tapered over a few weeks and replaced with a pharmacologically equivalent dose of oral opiates. Adding IT ziconotide to stable doses of IT

morphine (see section 5.1), is possible but requires special attention, as a high rate of neuropsychiatric adverse reactions (confusion/thinking abnormal, paranoid reactions and hallucinations, and abnormal gait), some of them serious, was observed in Study 202 despite a low dose of ziconotide. Vomiting and anorexia, and peripheral oedema were also observed when IT ziconotide was added to IT morphine. The addition of IT morphine to stable doses of IT ziconotide is better tolerated (pruritis has been reported). (See section 5.1).

An increased incidence of somnolence has been observed when ziconotide is administered concomitantly with systemic baclofen, clonidine, bupivacaine or propofol thus for the time being their simultaneous use is discouraged.

No data are available regarding the concomitant use of partial opioid agonists (e.g. buprenorphine) with ziconotide.

4.6 Pregnancy and lactation

There are no adequate data from the use of ziconotide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Ziconotide should not be used during pregnancy unless clearly necessary.

It is not known whether ziconotide is excreted in breast milk, therefore it should not be administered to breast-feeding women unless clearly necessary.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Ziconotide may cause confusion, somnolence and other neurological adverse reactions, therefore patients must be advised not to drive or operate machines if affected.

4.8 Undesirable effects

The safety of ziconotide administered as a continuous intrathecal infusion has been evaluated in more than 1,400 patients participating in acute and chronic pain clinical trials. The duration of treatment has ranged from one-hour bolus infusion to continuous use for more than 6 years. The median exposure time was 43 days. The infusion dose rate ranged from 0.03 - 912 μg/day, with a median final dose rate of 7.2 μg/day.

In clinical trials, 88% of patients experienced adverse drug reactions (ADRs). The most commonly reported ADRs reported in long-term clinical trials were dizziness (42%), nausea (30%), nystagmus (23%), confusional state (25%), gait abnormal (16%), memory impairment (13%), vision blurred (14%), headache (12%), asthenia (13%), vomiting (11%), and somnolence (10%). Most ADRs were mild to moderate in severity and resolved over time.

All ADRs reported in the intrathecal clinical trials with ziconotide (short- and long-term exposure) are listed below in order of frequency.

Very Common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)

Infections and infestations

Uncommon: sepsis, meningitis

Metabolism and nutrition disorders

Common: appetite decreased, anorexia

Psychiatric disorders

Very common: confusional state

Common: anxiety, auditory hallucination, insomnia, agitation, disorientation, hallucination, visual hallucination, depression, paranoia, irritability, depression aggravated, nervousness, affect lability, mental status changes, anxiety aggravated, confusion aggravated

Uncommon: delirium, psychotic disorder, suicidal ideation, suicide attempt, thought blocking, abnormal dreams, aggressiveness

Nervous system disorders

Very common: dizziness, nystagmus, memory impairment, headache, somnolence

Common: dysarthria, amnesia, dysgeusia, tremor, balance impaired, ataxia, aphasia, burning sensation, sedation, paraesthesia, hypoaesthesia, disturbance in attention, speech disorder, areflexia, coordination abnormal, dizziness postural, cognitive disorder, hyperaesthesia, hyporeflexia, ageusia, depressed level of consciousness, dysaesthesia, parosmia, mental impairment

Uncommon: incoherence, loss of consciousness, coma, stupor, convulsions, cerebrovascular accident, encephalopathy

Eye disorders

Very common: vision blurred

Common: diplopia, visual disturbance, photophobia

Ear and labyrinth disorders

Common: vertigo, tinnitus

Cardiac disorders

Uncommon: atrial fibrillation

Vascular disorders

Common: orthostatic hypotension, hypotension

Respiratory, thoracic and mediastinal disorders

Common: dyspnoea

Uncommon: respiratory distress

Gastrointestinal disorders

Very common: nausea, vomiting

Common: diarrhoea, dry mouth, constipation, nausea aggravated, upper abdominal pain

Uncommon: dyspepsia

Skin and subcutaneous tissue disorders

Common: pruritus, sweating increased

Uncommon: rash

Musculoskeletal and connective tissue disorders

Common: pain in limb, myalgia, muscle spasms, muscle cramp, muscle weakness, arthralgia, peripheral swelling

Uncommon: rhabdomyolysis, myositis, back pain, muscle twitching, neck pain

Renal and urinary disorders

Common: urinary retention, urinary hesitation, dysuria, urinary incontinence

Uncommon: acute renal failure

General disorders and administration site conditions

Very Common: gait abnormal, asthenia

Common: fatigue, pyrexia, lethargy, oedema peripheral, rigors, fall, chest pain, feeling cold, pain, feeling jittery, pain exacerbated

Uncommon: difficulty in walking

Investigations

Common: blood creatine phosphokinase increased, weight decreased

Uncommon: electrocardiogram abnormal, aspartate aminotransferase increased, blood creatine phosphokinase MM increased, body temperature increased

Specific comments and particular caution regarding meningitis, elevations of creatine kinase, and CNS adverse events can be found in Section 4.4.

4.9 Overdose

In intravenous infusion studies, healthy male volunteers received ziconotide at doses of up to 70,000 μg/day or 3,200 times the maximum recommended daily intrathecal infusion dose. Postural hypotension was observed in almost all subjects who received high intravenous doses of ziconotide.

The maximum recommended intrathecal dose is 21.6 μg/day. The maximum intended intrathecal dose of ziconotide in clinical trials was 912 μg/day following upward titration over 7 days.

In one clinical study a male cancer patient received an accidental IT ziconotide overdose of 744 μg over a 24-hour period (31 μg/hour) and resumed treatment at the intended dose after experiencing a reduction in Visual Analog Scale of Pain Intensity (VASPI) from 82 to 2.5 mm. In some patients who received intrathecal doses greater than the maximum recommended dose, exaggerated pharmacological effects, e.g., ataxia, nystagmus, dizziness, stupor, depressed level of consciousness, muscle spasms, confusional state, sedation, hypotension, aphasia, speech disorder, nausea and vomiting were observed. There was no indication of respiratory depression. Most patients under observation recovered within 24 hours of withdrawal of the medicinal product.

General medical supportive measures should be administered to patients who receive an overdose until the exaggerated pharmacological effects of the medicinal product have resolved.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics; Other analgesics and antipyretics ATC code: N02BG08

This medicinal product has been authorised under "Exceptional Circumstances". This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information, which may become available every year and this SmPC will be updated as necessary.

Ziconotide is a synthetic analogue of a ω-conopeptide, MVIIA, found in the venom of the *Conus magus* marine snail. It is an N-type calcium channel blocker (NCCB). NCCs regulate neurotransmitter release in specific neuronal populations responsible for the spinal processing of pain. In binding to these neuronal NCCs ziconotide inhibits the voltage sensitive calcium current into primary nociceptive afferents terminating in the superficial layers of the dorsal horn of the spinal cord. In turn, this inhibits their release of neurotransmitters (including Substance P) and therefore, the spinal signalling of pain.

Though statistically significant relationships and reasonable correlation between cerebrospinal fluid (CSF) exposure (AUC, C_{max}) and clinical response measures have been observed following 1 hour IT administration, no well-defined dose-concentration-response relationships have yet been identified. Many responsive patients obtain near-maximal analgesia within a few hours of delivery of an appropriate dose. However, maximal effects may be delayed for approximately 24 hours in some patients. Given the occurrence of analgesia and adverse drug reactions at similar doses, the recommended interval between dose increases is 48 hours or more. If necessary the dose can be decreased by any amount (including stopping the infusion) for the management of adverse drug reactions.

Nervous system adverse reactions, particularly dizziness, nausea and abnormal gait appear to be correlated with CSF exposure, though a definitive relationship has not been established.

Low plasma exposure occurs during IT infusion due to the low recommended IT infusion rates and relatively rapid plasma clearance (see section 5.2). Therefore, pharmacological effects related to systemic exposure should be minimal.

The median dose at response is approximately 6.0 μg/day and approximately 75% of responsive patients require ≤ 9.6 μg/day. To limit the occurrence of serious adverse drug reactions, a maximum dose of 21.6 μg/day is recommended. However, in clinical trials it has been observed that patients who tolerate doses of 21.6 μg/day following slow titration over a 3 to 4-week period, generally tolerate higher doses up to 48.0 μg/day.

There is no evidence of the development of pharmacological tolerance to ziconotide in patients. However, in view of limited data, the development of tolerance cannot be excluded. Examination of the patency of the intrathecal catheter should be considered if the required ziconotide dose continually increases and there is no benefit or increase in drug reactions.

There were three placebo-controlled clinical trials of IT ziconotide.

Two short-term studies, 95-001 (malignant pain) and 96-002 (non malignant pain), involving 366 patients, demonstrated the efficacy of IT ziconotide in severe chronic pain using the percent change in Visual Analog Scale of Pain Intensity (VASPI) as the primary efficacy measure. These

studies were of short duration, 5 and 6 days respectively, and used a more rapid dose escalation and higher doses than recommended in Section 4.2.

Efficacy results from study 95-001

	Initial Treatment Assignment		
Parameter	**Ziconotide (n = 71)**	**Placebo (n = 40)**	**p-value**
Mean VASPI score at baseline in mm (SD)	74.1 (± 13.82)	77.9 (± 13.60)	_
Mean VASPI score at end of initial titration in mm (SD)	35.7 (± 33.27)	61.0 (± 22.91)	_
% improvement in VASPI score at end of initial titration (SD)	51.4 (± 43.63)	18.1 (± 28.28)	< 0.001
Responder[a] n (%)	34 (47.9%)	7 (17.5%)	0.001
Dose at end of titration (μg/hr) Mean Median Range	 0.91 0.60 0.074 - 9.36		

[a]Responders were defined as those patients who 1) experienced a ≥ 30% drop in VASPI score compared to baseline; 2) had stable or decreased concomitant opioid analgesics; and 3) had opiate type unchanged from preinfusion if receiving opiates.
SD – Standard Deviation.

Efficacy results from study 96-002

	Initial Treatment Assignment		
Parameter	**Ziconotide (n = 169)[b]**	**Placebo (n = 86)**	**p-value**
Mean VASPI score at baseline in mm (SD)	80.1 (± 15.10)	76.9 (± 14.58)	_
Mean VASPI score at end of initial titration in mm (SD)	54.4 (± 29.30)	71.9 (± 30.93)	_
% improvement in VASPI score at end of initial titration (SD)	31.2 (± 38.69)	6.0 (± 42.84)	< 0.001
Responder[a] n (%)	57 (33.7%)	11 (12.8%)	< 0.001
Dose at end of titration (μg/hr) Mean Median Range	 1.02 0.50 0.019 - 9.60		

[a]Responders were defined as those patients who 1) experienced a ≥ 30% drop in VASPI score compared to baseline; 2) had stable or decreased concomitant opioid analgesics; and 3) had opiate type unchanged from preinfusion if receiving opiates.
[b]164 patients provided VASPI scores for ziconotide at the end of titration.
SD – Standard Deviation.

The aetiologies of pain in studies 95-001 (malignant pain) and 96-002 (non-malignant pain) were varied and included bone pain (n = 38) mostly due to bone metastases (n = 34), myelopathy (n = 38), half of whom had spinal cord injury with paralysis (n = 19), neuropathy (n = 79), radiculopathy (n = 24), spinal pain (n = 91) mostly due to failed back surgery (n = 82), and other aetiologies (n = 82). Some patients had more than one cause of pain. The efficacy of IT ziconotide was apparent in all groups.

Study 301 (n = 220) was of longer duration (21 days), involved more cautious up-titration and lower doses of IT ziconotide, and enrolled the most refractory population of patients studied in the three studies. All patients in the 301 study had failed IT therapy with combinations of analgesics and their physicians considered that 97% of the patients were refractory to currently available treatments. The majority had spinal pain (n = 134), especially failed back surgery (n = 110); a lower proportion had neuropathy (n = 36). Only five had malignant pain. The primary endpoint was the percent change in VASPI score. The efficacy of IT ziconotide in study 301 was lower than in the previous two, short-term studies. The frequency and severity of adverse events were also lower.

Efficacy results from study 301

	Initial Treatment Assignment		
Parameter	**Ziconotide (n = 112)**	**Placebo (n = 108)**	**p-value**
Mean VASPI score at baseline in mm (SD)	80.7 (± 14.98)	80.7 (± 14.91)	-
Mean VASPI score at end of initial titration in mm (SD)	67.9 (± 22.89)	74.1 (± 21.28)	_
% improvement in VASPI score at end of initial titration (SD)	14.7 (± 27.71)	7.2 (± 24.98)	0.0360
Responder[a] n (%)	18 (16.1%)	13 (12.0%)	0.390
Dose at end of titration (µg/hr) Mean Median Range	 0.29 0.25 0.0 - 0.80		

[a]Responders were defined as those who experienced a ≥ 30% drop in VASPI score compared to baseline.
SD – Standard Deviation.

Combination studies with IT Morphine

Clinical studies 201 and 202 indicate that the combination of IT ziconotide and IT morphine may effectively reduce pain and decrease systemic opioid use over a sustained period of time for patients whose pain was inadequately controlled with their maximum tolerated dose of IT ziconotide (median 8.7 µg/day, mean 25.7 µg/day – study 201) or with IT morphine (study 202) alone. When adding IT ziconotide to stable doses of IT morphine, as with the initiation of IT ziconotide monotherapy, the appearance of psychotic adverse events (e.g., hallucinations, paranoid reactions) or discontinuation due to increased adverse events may occur. (see section 4.5).

5.2 Pharmacokinetic properties

The CSF pharmacokinetics of ziconotide have been studied following one-hour IT infusions of 1 - 10 µg of ziconotide in patients with chronic pain. The plasma pharmacokinetics following intravenous doses (0.3 – 10 µg/kg/24 hr) were also studied. IT and intravenous pharmacokinetics data are summarised below.

CSF and Plasma Pharmacokinetics of Ziconotide [mean ± SD (median)]

Route of administration	**Fluid matrix**	**Number of patients**	**CL (ml/min)**	**Vd (ml)**	**$t_{½}$ (hr)**
Intrathecal	CSF	23	0.38 ± 0.56 (0.26)	155 ± 263 (99)	4.6 ± 0.9 (4.5)
Intravenous	Plasma	21	270 ± 44 (260)	30,460 ± 6,366 (29,320)	1.3 ± 0.3 (1.3)

CL = clearance; Vd = distribution volume; t½ = half life

Absorption: Following one-hour IT administration (1 – 10 µg), both cumulative exposure (AUC; range: 83.6 – 608 ng/h/ml) and peak exposure (C_{max}; range: 16.4 – 132 ng/ml) values were variable and dose-dependent, but appeared only approximately dose-proportional. Plasma concentrations following continuous (≥ 48 h) IT infusion (≤ 21.6 µg/day) appear to be relatively low and typically undetectable (i.e., about 80% of plasma samples collected from pain patients contain no quantifiable medicinal product; < 0.04 ng/ml). No accumulation of ziconotide in plasma following long-term IT administration (up to 9 months) has been observed.

Distribution: Median ziconotide CSF volume of distribution (Vd: 99 ml) is between the spinal cord CSF volume (approximately 75 ml) and total CSF volume (approximately 130 ml). Ziconotide appears to distribute mainly within the CSF until transferred to the systemic circulation. Upon reaching the systemic circulation, ziconotide appears to be more extensively distributed, based on a plasma distribution volume of approximately 30 l and is only about 53% bound (non-specifically) to human plasma proteins.

Biotransformation: Ziconotide is a peptide consisting of 25 naturally-occurring amino acids of the L-configuration, and does not appear to be appreciably metabolised in the CSF. Following passage into the systemic circulation, ziconotide is expected to be primarily susceptible to proteolytic cleavage by various ubiquitous peptidases/proteases present in most organs (e.g., kidney, liver, lung, muscle, etc.), and thus degraded to peptide fragments and its individual constituent free amino acids. The generated free amino acids are expected to be taken up by cellular carrier systems and either subjected to normal intermediary metabolism or used as substrates for constitutive biosynthetic processes. Due to the wide distribution of these peptidases it is not expected that hepatic or renal impairment would affect the systemic clearance of ziconotide. The biological activity of the various expected proteolytic degradation products has not been assessed. It is unlikely that the degradation products of ziconotide will have significant biological activity, as peptides consisting of the individual peptide loop structures have been found to have binding affinities for N-type voltage sensitive calcium channels that are several orders of magnitude lower than that of the parent (ziconotide) compound.

Elimination: Mean ziconotide CL (0.38 ml/min) approximates adult human CSF turnover rate (0.3 - 0.4 ml/min). Hence, ziconotide appears to be mainly eliminated from the CSF (mean $t_{½}$ = 4.6 hr) by bulk flow of CSF out of the CNS through the arachnoid villi with subsequent transfer into the systemic circulation. Very low circulating plasma concentrations of ziconotide may be observed following IT administration due to both the low IT infusion rate and relatively rapid plasma clearance. The mean plasma elimination half-life ($t_{½}$) is 1.3 hr. Ziconotide is a relatively small molecular weight peptide (MW = 2,639) and is filtered by the kidney glomerulus, but only minimal amounts of ziconotide (< 1%) are recovered in human urine following intravenous infusion. This is because almost all of the filtered active substance is rapidly endocytosed and ultimately transported back to the systemic circulation.

Specific populations: Although only limited data are available, there is no obvious effect of race, height, weight, gender or age on CSF ziconotide exposure after IT administration. No formal studies assessing the impact of renal or hepatic dysfunction have been conducted; however, given that peptidases are present in various body organs, it is not anticipated that renal or hepatic dysfunction will significantly impact systemic exposure of ziconotide.

5.3 Preclinical safety data

Preclinical toxic effects related to ziconotide administration were observed only at exposures considered sufficiently in excess of the human exposure to indicate little risk in clinical use.

In subchronic continuous intrathecal infusion studies in rats and dogs, behavioural effects were seen at doses ≥ 8-fold the maximum recommended clinical intrathecal infusion dose of 21.6 µg/day (on a mg/kg basis). These effects were defined by exaggerated pharmacological actions of ziconotide and not by neurotoxic lesions or target organ toxicity. Observations included transient and reversible neurological effects consisting of tremors, uncoordinated movements and hyper- and hypoactivity.

The long-term consequences to neuronal function of continuous N-type calcium-channel block have not been demonstrated in experimental animals. Changes in neurological signalling have not been studied in experimental animals. Ziconotide did not induce bacterial gene mutation and was not genotoxic. Chronic animal studies have not been performed to assess the carcinogenic potential of ziconotide. However, ziconotide did not induce cell transformation in the *in vitro* Syrian hamster embryo (SHE) assay and did not increase cell proliferation (pre-neoplastic lesion formation) or apoptosis after subchronic intrathecal exposure in dogs.

In rat fertility studies, there were no effects in males while reductions in corpora lutea; implantation sites and number of live embryos were observed in females. No adverse effects on female reproduction and post-natal development in rats were seen at systemic exposures up to 2,300 times human exposures at the maximum recommended intrathecal dose.

Ziconotide was not teratogenic in rats and rabbits at exposures < 100 times human plasma levels.

These results do not indicate a significant risk to humans due to the relatively high systemic exposures needed to elicit these effects in rats and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methionine
Sodium chloride
Water for injections
Hydrochloric acid (pH adjuster)
Sodium hydroxide (pH adjuster)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

Chemical and physical in use stability has been demonstrated for 60 days at 37°C.

From a microbiological point of view, if the product is diluted it should be transferred to the infusion pump immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze. Keep the vial in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Single-use Type I glass vials with butyl rubber stoppers coated with fluorinated polymer.

Each vial contains 1, 2 or 5 ml solution for infusion.

One vial per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

If dilution is required, Prialt must be diluted aseptically with preservative-free sodium chloride 9 mg/ml (0.9%) solution for injection before use. The concentration of the solution used in the infusion pump must be no lower than 5 μg/ml ziconotide in an external pump and 25 μg/ml in an internal pump.

Strict aseptic procedures must be used during the preparation and handling of the solution for infusion and refilling of the pump. The patient and health-care providers must be familiar with the handling of the external or internal infusion system and be aware of the need to guard against infection.

Prialt has been shown to be chemically and physically compatible with the implantable Synchromed pump and the external CADD-Micro pump at the concentration levels indicated above. Chemical and physical in-use stability has been demonstrated for 14 days at 37ºC in the Synchromed pump when the pump has not previously been exposed to the medicinal product. The initial fill must therefore be replaced after 14 days.

Prialt was stable for 60 days at 37°C in the Synchromed pump previously exposed to the medicinal product. Stability has been demonstrated for 21 days at room temperature in the CADD-Micro pump.

Specific instructions for using the pumps must be obtained from the manufacturer. CE marked pumps equivalent to the Synchromed and CADD-Micro pump should be used to deliver Prialt. Pumps previously used to deliver other medicinal products must be washed out three times with sodium chloride 9 mg/ml (0.9%) solution for injection (preservative-free) before being filled with Prialt. The introduction of air into the pump reservoir or cartridge should be minimized, as oxygen can degrade ziconotide.

Prior to initiation of therapy, an internal pump must be rinsed three times with 2 ml of Prialt at 25 μg/ml. The concentration of Prialt in a naïve pump may be reduced due to adsorption onto the surfaces of the device, and/or dilution by the residual space of the device. Because of this, after the first use of Prialt, the reservoir should be emptied and refilled after 14 days. Subsequently the pump should be emptied and refilled every 60 days.

Prialt is a clear and colourless solution. It should be inspected visually for particulate matter and discolouration prior to administration. The solution should not be used if discoloured or cloudy or if particulate matter is observed.

For single use only. Any unused solution should be discarded according to local regulations.

7. MARKETING AUTHORISATION HOLDER

Eisai Ltd.,
European Knowledge Centre
Mosquito Way
Hatfield
Herts
AL10 9SN
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/302/001 – 1 ml solution for infusion.
EU/1/04/302/002 – 2 ml solution for infusion.
EU/1/04/302/003 – 5 ml solution for infusion.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21/02/2005
Date of latest renewal: 12/01/2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Eisai Manufacturing Limited
European Knowledge Centre
Mosquito Way
Hatfield
Herts
AL10 9SN
United Kingdom

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2.)

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

The MAH will continue to submit yearly PSURs, unless otherwise specified by the CHMP.

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the annual reassessment of the benefit/risk profile.

Clinical aspects
A post-marketing registry study (PRIME) – will be performed. This will be an open-label registry, which will 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, the possible development of tolerance. The use of ziconotide in combination with morphine or baclofen, rescue medication, the evaluation of health related quality of life, and the analysis of adverse events will also be taken into account. Enrollment into the registry will continue until at least 150 patients have received Prialt. The MAH should provide annual updates of the enrollment of patients in the PRIME registry at the time of the annual re-assessment and interim analysis as well. This study commenced in March 2008. The MAH should submit the final study report to the CHMP and consider the need for a submission of a variation to the SPC for any significant results arising from this study.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Prialt 25 micrograms/ml solution for infusion
ziconotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 25 micrograms ziconotide (as acetate), (500 micrograms per vial)

3. LIST OF EXCIPIENTS

methionine, sodium chloride, water for injections, hydrochloric acid and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion.

1 vial of 20 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intrathecal use only

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai Ltd.
Mosquito Way
Hatfield
Herts
AL10 9SN
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/302/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Prialt 25 µg/ml

Intrathecal infusion

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

20 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Prialt 100 micrograms/ml solution for infusion
ziconotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml:
Each ml contains 100 micrograms ziconotide (as acetate), (100 micrograms per vial)

2 ml:
Each ml contains 100 micrograms ziconotide (as acetate), (200 micrograms per vial)

5 ml:
Each ml contains 100 micrograms ziconotide (as acetate), (500 micrograms per vial)

3. LIST OF EXCIPIENTS

methionine, sodium chloride, water for injections, hydrochloric acid and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion.

1 ml:
1 vial of 1 ml

2 ml:
1 vial of 2 ml

5 ml:
1 vial of 5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intrathecal use only

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai Ltd.
Mosquito Way
Hatfield
Herts
AL10 9SN
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

1 ml:
EU/1/04/302/001

2 ml:
EU/1/04/302/002

5 ml:
EU/1/04/302/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Prialt 100 µg/ml

Intrathecal infusion

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml:
1 ml

2 ml:
2 ml

5 ml:
5 ml

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Prialt 25 micrograms/ml solution for infusion
Ziconotide

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. WHAT PRIALT IS AND WHAT IT IS USED FOR

Prialt belongs to a group of medicines, called analgesics or 'painkillers'. Prialt is used for the treatment of long-term pain when your existing treatment is not effective or causes severe side effects.

2. BEFORE YOU USE PRIALT

Do not use Prialt
- If you are allergic (hypersensitive) to ziconotide or any of the other ingredients of Prialt.
- If you are receiving an anticancer medicine into the space around your spinal cord.

Take special care with Prialt
- The effects of long-term treatment of Prialt are uncertain at this time and the possibility of toxic effects on the spinal cord have not yet been ruled out. In case of a need for long term treatment, monitoring may be necessary (as decided by your doctor).
- If you are receiving Prialt via a pump worn outside your body, it is important you check once daily for any signs of infection at the point where the tube enters your body.
- If you observe any signs of infection around the tube, such as skin redness, swelling, pain or discharge, you must tell your doctor immediately and seek treatment for the infection.
- If you develop any tenderness in the area around the tube without signs of infection, you should seek advice from your doctor as soon as possible as tenderness may be an early sign of infection.
- If you are receiving Prialt via a pump worn outside your body and any part of the infusion tubing becomes disconnected, you must contact your doctor immediately.
- If you have any of the following symptoms: high temperature, headache, stiff neck, tiredness, confusion, feeling sick, vomiting or occasional fits, these may be signs of meningitis. You must tell your doctor immediately if you experience any of the above symptoms.
- If you notice any adverse change in your thinking, mood or memory, please tell your doctor.
- If you are receiving chemotherapy please tell your doctor.
- You may have an increased level of an enzyme called creatine kinase in your blood and although this does not usually cause any symptoms or problems, your doctor is likely to monitor its level. In addition, you may also occasionally experience muscular problems. If such is the

case, you should immediately notify your doctor, as he/she may decide to halt your Prialt treatment.
- Severe allergic reactions have not been seen in clinical studies so far, however it is not yet possible to say for certain that a severe allergic reaction will not happen when you are given Prialt. You should tell your doctor immediately if you experience any of the following symptoms after receiving your treatment; sudden wheeziness, difficulty in breathing, pain in the chest, swelling of eyelids, face or lips, rash or itching (especially affecting the whole body).
- In patients that suffer from severe long term pain, there is a higher likelihood of suicide and attempted suicide than in the general population. Prialt may also cause or worsen depression in people that are already susceptible.
- You may experience drowsiness or may not be fully aware of your surroundings whilst receiving treatment. If this happens, you should immediately notify your doctor, as he/she may decide to halt your Prialt treatment.
- Not recommended for use in children and adolescents.

Taking other medicines
Please tell your doctor if you are taking or have recently taken any other medicines (for example, baclofen, clonidine, bupivacaine or propofol), including medicines obtained without a prescription. You may feel drowsy if you are given Prialt with certain other medicines used to treat pain.

Pregnancy and breast-feeding
If you are pregnant, think you may be pregnant, or are breast-feeding ask your doctor for advice before taking any medicine.

Prialt should not be used during pregnancy or breast-feeding unless clearly necessary.

Driving and using machines
The use of Prialt has been reported to cause confusion and drowsiness. Ask your doctor for advice before you drive or operate machinery.

3. HOW TO USE PRIALT

Your treatment with Prialt will be managed by a doctor who has experience of giving medicines into the space around the spinal cord, and in the use of internal and external infusion pumps.

Prialt is given as a very slow continuous injection into the space surrounding the spinal cord. The medicine will be administered continuously from a pump either implanted into your abdominal wall or placed externally in a belt pouch. Your doctor will discuss with you the kind of pump that will be most suitable for you and when you need to have your pump refilled.

The recommended starting dose is no more than 2.4 micrograms per day. Your doctor will adjust the dose of Prialt according to the severity of your pain in dose increments of $\leq$ 2.4 micrograms/day. The maximum dose is 21.6 micrograms/day. At the start of your treatment your doctor may increase your dose every 1 to 2 days or more. If needed, the dose may be decreased or injection stopped if the side effects are too great.

If you feel that you are still in too much pain while taking Prialt, or that the side effects are too great, talk to your doctor.

Before giving you Prialt, your doctor might decide to slowly stop giving you opiates (other types of medicinal product which are used to treat pain) into your spinal cord and instead replace with alternative pain medicinal products.

If you use more Prialt than you should
If you receive more Prialt than your doctor intended, you may feel unwell with signs such as confusion, problems with speech, word finding difficulties, excessive shaking, light-headedness, excessive sleepiness, feeling or being sick. If this happens, consult your doctor or hospital immediately.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Prialt can cause side effects, although not everybody gets them.

The frequency of possible side effects listed below is defined using the following convention:
Very common (affects more than 1 user in 10)
Common (affects 1 to 10 users in 100)
Uncommon (affects 1 to 10 users in 1,000)

Very common:
Confusion, dizziness, blurred vision, headache, rapid back-and-forth movement of the eyes, loss or impairment of memory (forgetfulness), difficulty walking, vomiting, nausea, general weakness and drowsiness.

Common: Decreased appetite, anxiety or worsened anxiety, hallucinations, inability to fall or stay asleep, agitation, disorientation, depression or worsened depression, nervousness, mood swings, mental status changes (thinking abnormal, confusion), paranoia, irritability, worsened confusion, difficulty with learning, memory or thinking, reflexes absent or impaired, problems expressing or understanding words, slurred speech, difficulty with speech or loss of ability to speak, sluggishness, balance or coordination impaired, burning sensation, increased pain sensitivity, reduced level of consciousness (unresponsive or almost unconscious), sedation, difficulty in concentrating, problems with the sense of smell, odd or no sense of taste, shaking, pins and needles, double vision, visual disturbance, intolerance to light, tinnitus (ringing in the ears), dizziness or spinning sensation, lightheadedness or dizziness when standing, low blood pressure, shortness of breath, dry mouth, abdominal pain, worsened nausea, diarrhoea, constipation, sweating, itching, muscle weakness, muscle spasms, muscle cramp, muscle or joint pain, difficult or painful urination, difficulty starting or controlling urination, feeling jittery, falling, pain or pain exacerbated, fatigue, feeling cold, swelling of the face, legs or feet, chest pain, fever, blood chemistry changes, mental impairment and weight decreased.

Uncommon
Infection of the blood stream, meningitis, delirium (feeling of mental confusion), psychotic disorder (abnormal thinking and perceptions), suicidal thought or attempt, thought disorders, abnormal dreams, incoherence (inability to make sense), loss of consciousness, coma, stupor (unresponsive/difficult to arouse), convulsions (fits), stroke, encephalopathy (brain disorder), aggressiveness, abnormal heart rhythm, difficulty breathing, indigestion, rash, muscle breakdown (rhabdomyolysis), muscle inflammation, back pain, muscle twitching, neck pain, acute kidney failure, abnormal heart trace measurements (ECG), raised body temperature.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE PRIALT

Keep out of the reach and sight of children.

Do not use Prialt after the expiry date stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store unopened vial in refrigerator (2°C – 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

Chemical and physical in use stability has been demonstrated for 60 days at 37°C.

From a microbiological point of view, if the product is diluted it should be transferred to the infusion pump immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6. FURTHER INFORMATION

What Prialt contains
- The active substance is ziconotide. One ml solution contains 25 micrograms ziconotide (as acetate). One vial of 20 ml contains 500 micrograms.
- The other ingredients are methionine, sodium chloride, water for injections, hydrochloric acid and sodium hydroxide.

What Prialt looks like and contents of the pack
Prialt is a solution for infusion. The solution is clear and colourless. Prialt is supplied in packs containing a single vial of 20 ml.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Eisai Ltd.
Mosquito Way
Hatfield
Herts
AL10 9SN
United Kingdom

Manufacturer:
Eisai Manufacturing Limited
Mosquito Way
Hatfield
Herts
AL10 9SN
United Kingdom

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Eisai Europe Ltd.
Tél/Tel: + 32 (0) 2 735 45 34

Luxembourg/Luxemburg
Eisai Europe Ltd.
Tél/Tel: + 32 (0) 2 735 45 34
(Belgique/Belgien)

България
Eisai Ltd.
Тел.: + 44 208 600 1400
(Великобритания (Обединеното кралство))

Magyarország
Eisai GesmbH
Tel.: + 36 1 230 43 20

Česká republika
Eisai GesmbH organizační složka
Tel: + 420 242 485 839

Danmark
NordicInfu Care
Tlf: + 46 (0)8 601 24 40
(Sverige)

Deutschland
Eisai GmbH
Tel: + 49 (0) 69 66 58 50

Eesti
Eisai Ltd.
Tel: + 44 208 600 1400
(Ühendkuningriik)

Ελλάδα
Arriani Pharmaceuticals S.A.
Τηλ: +30 210 668 3000

España
Eisai Farmacéutica, S.A.
Tel: +(34) 91 455 94 55

France
Eisai SAS
Tél: + (33) 1 47 67 00 05

Ireland
Eisai Ltd.
Tel: + 44 208 600 1400
(United Kingdom)

Ísland
NordicInfu Care
Sími: + 46 (0)8 601 24 40
(Svíþjóð)

Italia
Eisai S.r.l.
Tel: + 39 02 5181401

Κύπρος
Arriani Pharmaceuticals S.A.
Τηλ: +30 210 668 3000

Malta
Associated Drug Company Ltd
Tel: +356 (0) 227 780 00

Nederland
Eisai B.V.
Tel: + 31 (0) 900 575 3340
(Nederland)

Norge
NordicInfu Care
Tlf: + 46 (0)8 601 24 40
(Sverige)

Österreich
Eisai GesmbH
Tel: + 43 (0) 1 535 1980-0

Polska
Eisai Ltd.
Tel.: + 44 208 600 1400
(Wielka Brytania)

Portugal
Eisai Farmacêutica,
Unipessoal Lda
Tel: + 351 214 875 540

România
Eisai Ltd.
Tel: + 44 208 600 1400
(Marea Britanie)

Slovenija
Eisai Ltd.
Tel: + 44 208 600 1400
(Velika Britanija)

Slovenská republika
Eisai GesmbH organizační složka
Tel: + 420 242 485 839
(Česká republika)

Suomi/Finland
NordicInfu Care
Puh/Tel: + 46 (0)8 601 24 40
(Ruotsi/Sverige)

Sverige
NordicInfu Care
Tel: + 46 (0)8 601 24 40

Latvija
Eisai Ltd.
Tel: + 44 208 600 1400
(Lielbritānija)

Lietuva
Eisai Ltd.
Tel. + 44 208 600 1400
(Jungtinė Karalystė)

United Kingdom
Eisai Ltd.
Tel: 0208 600 1400

This leaflet was last approved in {MM/YYY}.

This medicine has been authorised under "Exceptional Circumstances". This means that because of the rarity of the disease it has been impossible to get complete information on this medicine. The European Medicines Agency will review any new information on the medicine every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for medical or healthcare professionals only:

Instructions for use and handling

Prialt is supplied as a clear, colourless solution in single use vials. It should be inspected visually for particulate matter and discolouration prior to administration. The solution should not be used if discoloured or cloudy or if particulate matter is observed.

For single use only. Any unused solution should be discarded according to local regulations.

If dilution is required, Prialt must be diluted aseptically with preservative-free sodium chloride 9 mg/ml (0.9%) solution for injection before use. The concentration of the solution used in the infusion pump must be no lower than 5 µg/ml ziconotide in an external pump and 25 µg/ml in an internal pump.

Strict aseptic procedures must be used during the preparation and handling of the solution for infusion and refilling of the pump. The patient and health-care providers must be familiar with the handling of the external or internal infusion system and be aware of the need to guard against infection.

Prialt has been shown to be chemically and physically compatible with the implantable Synchromed pump and the external CADD-Micro pump at the concentration levels indicated above. Chemical and physical in-use stability has been demonstrated for 14 days at 37ºC in the Synchromed pump when the pump has not previously been exposed to the medicinal product. The initial fill must therefore be replaced after 14 days.

Prialt was stable for 60 days at 37°C in the Synchromed pump previously exposed to the medicinal product. Stability has been demonstrated for 21 days at room temperature in the CADD-Micro pump.

Specific instructions for using the pumps must be obtained from the manufacturer. CE marked pumps equivalent to the Synchromed and CADD-Micro pump should be used to deliver ziconotide. Pumps previously used to deliver other medicinal products must be washed out three times with sodium chloride 9 mg/ml (0.9%) solution for injection (preservative-free) before being filled with ziconotide. The introduction of air into the pump reservoir or cartridge should be minimized, as oxygen can degrade ziconotide.

Prior to initiation of therapy, an internal pump must be rinsed three times with 2 ml of the solution at 25 μg/ml. The concentration of Prialt in a naïve pump may be reduced due to adsorption onto the surfaces of the device, and/or dilution by the residual space of the device. Because of this, after the first use of Prialt, the reservoir should be emptied and refilled after 14 days. Subsequently the pump should be emptied and refilled every 60 days.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Prialt 100 micrograms/ml solution for infusion
Ziconotide

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet

1. WHAT PRIALT IS AND WHAT IT IS USED FOR

Prialt belongs to a group of medicines, called analgesics or 'painkillers'. Prialt is used for the treatment of long-term pain when your existing treatment is not effective or causes severe side effects.

2. BEFORE YOU USE PRIALT

Do not use Prialt
- If you are allergic (hypersensitive) to ziconotide or any of the other ingredients of Prialt.
- If you are receiving an anticancer medicine into the space around your spinal cord.

Take special care with Prialt
- The effects of long-term treatment of Prialt are uncertain at this time and the possibility of toxic effects on the spinal cord have not yet been ruled out. In case of a need for long term treatment, monitoring may be necessary (as decided by your doctor).
- If you are receiving Prialt via a pump worn outside your body, it is important you check once daily for any signs of infection at the point where the tube enters your body.
- If you observe any signs of infection around the tube, such as skin redness, swelling, pain or discharge, you must tell your doctor immediately and seek treatment for the infection.
- If you develop any tenderness in the area around the tube without signs of infection, you should seek advice from your doctor as soon as possible as tenderness may be an early sign of infection.
- If you are receiving Prialt via a pump worn outside your body and any part of the infusion tubing becomes disconnected, you must contact your doctor immediately.
- If you have any of the following symptoms: high temperature, headache, stiff neck, tiredness, confusion, feeling sick, vomiting or occasional fits, these may be signs of meningitis. You must tell your doctor immediately if you experience any of the above symptoms.
- If you notice any adverse change in your thinking, mood or memory, please tell your doctor.
- If you are receiving chemotherapy please tell your doctor.
- You may have an increased level of an enzyme called creatine kinase in your blood and although this does not usually cause any symptoms or problems, your doctor is likely to monitor its level. In addition, you may also occasionally experience muscular problems. If such is the

case, you should immediately notify your doctor, as he/she may decide to halt your Prialt treatment.
- Severe allergic reactions have not been seen in clinical studies so far, however it is not yet possible to say for certain that a severe allergic reaction will not happen when you are given Prialt. You should tell your doctor immediately if you experience any of the following symptoms after receiving your treatment; sudden wheeziness, difficulty in breathing, pain in the chest, swelling of eyelids, face or lips, rash or itching (especially affecting the whole body).
- In patients that suffer from severe long term pain, there is a higher likelihood of suicide and attempted suicide than in the general population. Prialt may also cause or worsen depression in people that are already susceptible.
- You may experience drowsiness or may not be fully aware of your surroundings whilst receiving treatment. If this happens, you should immediately notify your doctor, as he/she may decide to halt your Prialt treatment.
- Not recommended for use in children and adolescents.

Taking other medicines
Please tell your doctor if you are taking or have recently taken any other medicines (for example, baclofen, clonidine, bupivacaine or propofol), including medicines obtained without a prescription. You may feel drowsy if you are given Prialt with certain other medicines used to treat pain.

Pregnancy and breast-feeding
If you are pregnant, think you may be pregnant, or are breast-feeding ask your doctor for advice before taking any medicine.

Prialt should not be used during pregnancy or breast-feeding unless clearly necessary.

Driving and using machines
The use of Prialt has been reported to cause confusion and drowsiness. Ask your doctor for advice before you drive or operate machinery.

3. HOW TO USE PRIALT

Your treatment with Prialt will be managed by a doctor who has experience of giving medicines into the space around the spinal cord, and in the use of internal and external infusion pumps.

Prialt is given as a very slow continuous injection into the space surrounding the spinal cord. The medicine will be administered continuously from a pump either implanted into your abdominal wall or placed externally in a belt pouch. Your doctor will discuss with you the kind of pump that will be most suitable for you and when you need to have your pump refilled.

The recommended starting dose is no more than 2.4 micrograms per day. Your doctor will adjust the dose of Prialt according to the severity of your pain in dose increments of ≤ 2.4 micrograms/day. The maximum dose is 21.6 micrograms/day. At the start of your treatment your doctor may increase your dose every 1 to 2 days or more. If needed, the dose may be decreased or injection stopped if the side effects are too great.

If you feel that you are still in too much pain while taking Prialt, or that the side effects are too great, talk to your doctor.

Before giving you Prialt, your doctor might decide to slowly stop giving you opiates (other types of medicinal product which are used to treat pain) into your spinal cord and instead replace with alternative pain medicinal products.

If you use more Prialt than you should
If you receive more Prialt than your doctor intended, you may feel unwell with signs such as confusion, problems with speech, word finding difficulties, excessive shaking, light-headedness,

excessive sleepiness, feeling or being sick. If this happens, consult your doctor or hospital immediately.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Prialt can cause side effects, although not everybody gets them.

The frequency of possible side effects listed below is defined using the following convention:
Very common (affects more than 1 user in 10)
Common (affects 1 to 10 users in 100)
Uncommon (affects 1 to 10 users in 1,000)

Very common:
Confusion, dizziness, blurred vision, headache, rapid back-and-forth movement of the eyes, loss or impairment of memory (forgetfulness), difficulty walking, vomiting, nausea, general weakness and drowsiness.

Common:
Decreased appetite, anxiety or worsened anxiety, hallucinations, inability to fall or stay asleep, agitation, disorientation, depression or worsened depression, nervousness, mood swings, mental status changes (thinking abnormal, confusion), paranoia, irritability, worsened confusion, difficulty with learning, memory or thinking, reflexes absent or impaired, problems expressing or understanding words, slurred speech, difficulty with speech or loss of ability to speak, sluggishness, balance or coordination impaired, burning sensation, increased pain sensitivity, reduced level of consciousness (unresponsive or almost unconscious), sedation, difficulty in concentrating, problems with the sense of smell, odd or no sense of taste, shaking, pins and needles, double vision, visual disturbance, intolerance to light, tinnitus (ringing in the ears), dizziness or spinning sensation, lightheadedness or dizziness when standing, low blood pressure, shortness of breath, dry mouth, abdominal pain, worsened nausea, diarrhoea, constipation, sweating, itching, muscle weakness, muscle spasms, muscle cramp, muscle or joint pain, difficult or painful urination, difficulty starting or controlling urination, feeling jittery, falling, pain or pain exacerbated, fatigue, feeling cold, swelling of the face, legs or feet, chest pain, fever, blood chemistry changes, mental impairment and weight decreased.

Uncommon
Infection of the blood stream, meningitis, delirium (feeling of mental confusion), psychotic disorder (abnormal thinking and perceptions), suicidal thought or attempt, thought disorders, abnormal dreams, incoherence (inability to make sense), loss of consciousness, coma, stupor (unresponsive/difficult to arouse), convulsions (fits), stroke, encephalopathy (brain disorder), aggressiveness, abnormal heart rhythm, difficulty breathing, indigestion, rash, muscle breakdown (rhabdomyolysis), muscle inflammation, back pain, muscle twitching, neck pain, acute kidney failure, abnormal heart trace measurements (ECG), raised body temperature.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE PRIALT

Keep out of the reach and sight of children.

Do not use Prialt after the expiry date stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store unopened vial in refrigerator (2°C – 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

Chemical and physical in use stability has been demonstrated for 60 days at 37°C.

From a microbiological point of view, if the product is diluted it should be transferred to the infusion pump immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6. FURTHER INFORMATION

What Prialt contains
- The active substance is ziconotide.
- One ml solution contains 100 micrograms ziconotide (as acetate).
- One vial of 1 ml contains 100 micrograms; one vial of 2 ml contains 200 micrograms; one vial of 5 ml contains 500 micrograms.
- The other ingredients are methionine, sodium chloride, water for injections, hydrochloric acid and sodium hydroxide.

What Prialt looks like and contents of the pack
Prialt is a solution for infusion. The solution is clear and colourless. Prialt is supplied in packs containing a single vial of either 1 ml, 2 ml or 5 ml. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Eisai Ltd.
Mosquito Way
Hatfield
Herts
AL10 9SN
United Kingdom

Manufacturer:
Eisai Manufacturing Limited
Mosquito Way
Hatfield
Herts
AL10 9SN
United Kingdom

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Eisai Europe Ltd.
Tél/Tel: + 32 (0) 2 735 45 34

Luxembourg/Luxemburg
Eisai Europe Ltd.
Tél/Tel: + 32 (0) 2 735 45 34
(Belgique/Belgien)

България
Eisai Ltd.
Тел.: + 44 208 600 1400
(Великобритания (Обединеното кралство))

Magyarország
Eisai GesmbH
Tel.: + 36 1 230 43 20

Česká republika
Eisai GesmbH organizační složka
Tel: + 420 242 485 839

Danmark
NordicInfu Care
Tlf: + 46 (0)8 601 24 40
(Sverige)

Deutschland
Eisai GmbH
Tel: + 49 (0) 69 66 58 50

Eesti
Eisai Ltd.
Tel: + 44 208 600 1400
(Ühendkuningriik)

Ελλάδα
Arriani Pharmaceuticals S.A.
Τηλ: +30 210 668 3000

España
Eisai Farmacéutica, S.A.
Tel: +(34) 91 455 94 55

France
Eisai SAS
Tél: + (33) 1 47 67 00 05

Ireland
Eisai Ltd.
Tel: + 44 208 600 1400
(United Kingdom)

Ísland
NordicInfu Care
Sími: + 46 (0)8 601 24 40
(Svíþjóð)

Italia
Eisai S.r.l.
Tel: + 39 02 5181401

Κύπρος
Arriani Pharmaceuticals S.A.
Τηλ: +30 210 668 3000

Malta
Associated Drug Company Ltd
Tel: +356 (0) 227 780 00

Nederland
Eisai B.V.
Tel: + 31 (0) 900 575 3340
(Nederland)

Norge
NordicInfu Care
Tlf: + 46 (0)8 601 24 40
(Sverige)

Österreich
Eisai GesmbH
Tel: + 43 (0) 1 535 1980-0

Polska
Eisai Ltd.
Tel.: + 44 208 600 1400
(Wielka Brytania)

Portugal
Eisai Farmacêutica,
Unipessoal Lda
Tel: + 351 214 875 540

România
Eisai Ltd.
Tel: + 44 208 600 1400
(Marea Britanie)

Slovenija
Eisai Ltd.
Tel: + 44 208 600 1400
(Velika Britanija)

Slovenská republika
Eisai GesmbH organizační složka
Tel: + 420 242 485 839
(Česká republika)

Suomi/Finland
NordicInfu Care
Puh/Tel: + 46 (0)8 601 24 40
(Ruotsi/Sverige)

Sverige
NordicInfu Care
Tel: + 46 (0)8 601 24 40

Latvija
Eisai Ltd.
Tel: + 44 208 600 1400
(Lielbritānija)

Lietuva
Eisai Ltd.
Tel. + 44 208 600 1400
(Jungtinė Karalystė)

United Kingdom
Eisai Ltd.
Tel: 0208 600 1400

This leaflet was last approved in {MM/YYY}.

This medicine has been authorised under "Exceptional Circumstances". This means that because of the rarity of the disease it has been impossible to get complete information on this medicine. The European Medicines Agency will review any new information on the medicine every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for medical or healthcare professionals only:

Instructions for use and handling

Prialt is supplied as a clear, colourless solution in single use vials. It should be inspected visually for particulate matter and discolouration prior to administration. The solution should not be used if discoloured or cloudy or if particulate matter is observed.

For single use only. Any unused solution should be discarded according to local regulations.

If dilution is required, Prialt must be diluted aseptically with preservative-free sodium chloride 9 mg/ml (0.9%) solution for injection before use. The concentration of the solution used in the infusion pump must be no lower than 5 µg/ml ziconotide in an external pump and 25 µg/ml in an internal pump.

Strict aseptic procedures must be used during the preparation and handling of the solution for infusion and refilling of the pump. The patient and health-care providers must be familiar with the handling of the external or internal infusion system and be aware of the need to guard against infection.

Prialt has been shown to be chemically and physically compatible with the implantable Synchromed pump and the external CADD-Micro pump at the concentration levels indicated above. Chemical and physical in-use stability has been demonstrated for 14 days at 37ºC in the Synchromed pump when the pump has not previously been exposed to the medicinal product. The initial fill must therefore be replaced after 14 days.

Prialt was stable for 60 days at 37°C in the Synchromed pump previously exposed to the medicinal product. Stability has been demonstrated for 21 days at room temperature in the CADD-Micro pump.

Specific instructions for using the pumps must be obtained from the manufacturer. CE marked pumps equivalent to the Synchromed and CADD-Micro pump should be used to deliver ziconotide. Pumps previously used to deliver other medicinal products must be washed out three times with sodium chloride 9 mg/ml (0.9%) solution for injection (preservative-free) before being filled with ziconotide. The introduction of air into the pump reservoir or cartridge should be minimized, as oxygen can degrade ziconotide.

Prior to initiation of therapy, an internal pump must be rinsed three times with 2 ml of the solution at 25 μg/ml. The concentration of Prialt in a naïve pump may be reduced due to adsorption onto the surfaces of the device, and/or dilution by the residual space of the device. Because of this, after the first use of Prialt, the reservoir should be emptied and refilled after 14 days. Subsequently the pump should be emptied and refilled every 60 days.