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 20 mL vial contains 500 μg ziconotide (as acetate).

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for infusion (infusion).

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prialt 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.

Patients should undergo a neuropsychiatric evaluation before, after starting and during intrathecal ziconotide and immediately when any depressive signs or symptoms appear. (See Section 4.3, 4.4, 4.8 and 5.1).

Posology

Dose initiation

Dosing of ziconotide should be initiated at *no more than* 2.4 μg/day and titrated on an individual patient basis according to analgesic response and adverse reactions.

Dose titration

For each dose titration, assess the dosing requirements and adjust the pump infusion flow rate as required to achieve the new dosing.

Patients may 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.

The maximum daily dose is 21.6 μg/day (0.9 μg/h).

The median dose at response is approximately 6.0 μg/day and approximately 75% of responsive patients required ≤ 9.6 μg/day in placebo-controlled clinical trials. However, to limit the occurrence of serious adverse reactions, reports from clinical practice indicate that responsive patients may require a smaller daily dose of approximately 3.0 - 4.5 μg/day or lower.

Adjust the dose of intrathecal ziconotide according to the severity of pain, the patient's response to therapy, and the occurrence of adverse reactions.

General management of side effects

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.

Stopping rule

Treatment should be discontinued in case of lack or insufficient efficacy, defined as pain reduction by less than 20% at the maximal tolerated dose. The benefit/risk should always be evaluated by the physician on an individual basis.

Renal impairment

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.

Hepatic impairment

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.

Older patients ≥ 65 years of age

Dose adjustment is not required in older adults. However, it should be taken into account that renal and/or hepatic insufficiency is more common in patients ≥ 65 years of age.

Paediatric population

The safety and efficacy of ziconotide in children aged 0 to 18 years have not been established.

No data are available.

Method of administration

Intrathecal use.

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 (see section 4.4). 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.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Combination with IT chemotherapy (see section 4.5).

Pre-existing history of psychosis with ziconotide.

History of suicidal attempt or suicidal ideation with ziconotide (see Section 4.2, 4.4 and 4.8).

Infection at the microinfusion injection site, uncontrolled bleeding diathesis, and spinal canal obstruction that impairs circulation of cerebrospinal fluid (CSF).

4.4 Special warnings and precautions for use

Patients should undergo a neuropsychiatric evaluation before, after starting and during intrathecal ziconotide, and immediately when any depressive signs or symptoms appear (see Sections 4.3, 4.4 and 4.8).
Caregivers should contact a physician immediately if the patient experiences symptoms of potentially life-threatening adverse event.

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.

Risk of infection

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 and spontaneous reports of anaphylactic reactions have been received.

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. It is recommended that patients undergo a neuropsychiatric evaluation before and after starting intrathecal ziconotide.
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. Patients with a history of suicide-related events prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicidal behaviour, and should receive careful monitoring during treatment. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge. Patients with a pre-existing history of suicidal attempt with ziconotide should not be given ziconotide

again. Ziconotide is contraindicated in patients with a history of suicidal attempt or ideation with ziconotide (section 4.3).

Depression of Central Nervous System (CNS)
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 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 (pruritus 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 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of ziconotide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Ziconotide is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding
It is unknown whether ziconotide/metabolites are excreted in human milk.
A risk to newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Prialt therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
No specific studies with ziconotide in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects in males while reductions in corpora lutea; implantation sites and number of live embryos were observed in females (see section 5.3).

4.7 Effects on ability to drive and use machines

Prialt has moderate influence on the ability to drive and use machines.

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

Summary of the safety profile

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 reactions. The most common adverse reactions 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 adverse reactions were mild to moderate in severity and resolved over time.

Tabulated list of adverse reactions

Unless otherwise noted the table shows the incidence rates of adverse reactions reported in the intrathecal clinical trials with ziconotide (short- and long-term exposure). Within each frequency grouping undesirable effects are presented in order of decreasing frequency.

Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

System organ class	**Very common**	**Common**	**Uncommon**	**Not known**
Infections and infestations			sepsis, meningitis	
Immune system disorders				anaphylactic reaction[a]
Metabolism and nutrition disorders		appetite decreased, anorexia		
Psychiatric disorders	confusional state	anxiety, auditory hallucination, insomnia, agitation, disorientation, hallucination, visual hallucination, depression, paranoia, irritability, depression aggravated, nervousness, affect lability, mental status changes, anxiety aggravated, confusion aggravated	delirium, psychotic disorder, suicidal ideation, suicide attempt, thought blocking, abnormal dreams, aggressiveness	
Nervous system disorders	dizziness, nystagmus, memory impairment, headache, somnolence	dysarthria, amnesia, dysgeusia, tremor, balance impaired, ataxia, aphasia, burning sensation, sedation, paraesthesia, hypoaesthesia, disturbance in attention, speech disorder, areflexia, coordination	incoherence, loss of consciousness, coma, stupor, convulsions, cerebrovascular accident, encephalopathy	

System organ class	Very common	Common	Uncommon	Not known
		abnormal, dizziness postural, cognitive disorder, hyperaesthesia, hyporeflexia, ageusia, depressed level of consciousness, dysaesthesia, parosmia, mental impairment		
Eye disorders	vision blurred	diplopia, visual disturbance, photophobia		
Ear and labyrinth disorders		vertigo, tinnitus		
Cardiac disorders			atrial fibrillation	
Vascular disorders		Orthostatic hypotension, hypotension		
Respiratory, thoracic and mediastinal disorders		dyspnoea	respiratory distress	
Gastrointestinal disorders	nausea, vomiting	diarrhoea, dry mouth, constipation, nausea aggravated, upper abdominal pain	dyspepsia	
Skin and subcutaneous tissue disorders		pruritus, sweating increased	rash	
Musculoskeletal and connective tissue disorders		pain in limb, myalgia, muscle spasms, muscle cramp, muscle weakness, arthralgia, peripheral swelling	rhabdomyolysis, myositis, back pain, muscle twitching, neck pain	

System organ class	Very common	Common	Uncommon	Not known
Renal and urinary disorders		urinary retention, urinary hesitation, dysuria, urinary incontinence	acute renal failure	
General disorders and administration site conditions	gait abnormal, asthenia	fatigue, pyrexia, lethargy, oedema peripheral, rigors, fall, chest pain, feeling cold, pain, feeling jittery, pain exacerbated	difficulty in walking	
Investigations		blood creatine phosphokinase increased, weight decreased	electrocardiogram abnormal, aspartate aminotransferase increased, blood creatine phosphokinase MM increased, body temperature increased	

a. From spontaneous reporting

Description of selected adverse reactions

Meningitis

Administration of medicinal products by the intrathecal route carries the risk of potential serious infections, such as meningitis, which may be life threatening. Patients and physicians must be vigilant for typical symptoms and signs of meningitis (see section 4.4).

Elevations of creatine phosphokinase

Elevations in creatine phosphokinase were usually asymptomatic. Monitoring of creatine phosphokinase is recommended. Discontinuation of ziconotide should be considered in the event of progressive or significant elevation of creatine phosphokinase in association with clinical features of myopathy or rhabdomyolysis (see section 4.4).

CNS adverse reactions

Cognitive and neuropsychiatric adverse reactions 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.

The available data do not exclude the possibility of an increased risk of suicide when using ziconotide. Prialt is contra-indicated in patients with a history of suicidal attempt or suicidal ideation with ziconotide (Section 4.3). It is recommended that patients undergo a neuropsychiatric evaluation before and after starting intrathecal ziconotide (see section 4.2 and 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

Symptoms

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.

Management

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

Mechanism of action

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.

Pharmacodynamic effects

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 in some patients. Given the occurrence of analgesia and adverse reactions at similar doses, the recommended minimum 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.

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 required ≤ 9.6 μg/day in placebo-controlled clinical trials. However, to limit the occurrence of serious adverse reactions, reports from clinical practice indicate that responsive patients may require a smaller daily dose of approximately 3.0 - 4.5 μg/ay or lower.

To limit the occurrence of serious adverse reactions, a low starting dose and slow titration interval is recommended, always considering the narrow therapeutic window. 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 adverse reactions.

Alternative dosing regimens including initiation of dosing with lower doses of ziconotide and bolus administration have been explored in a limited number of studies available in the literature.

Bolus administration studies suggest that bolus dosing may be useful in identifying patients who may benefit from long term use of ziconotide, however, bolus administration may result in more adverse reactions than administration by continuous infusion.

These studies suggest that alternative methods of administration of ziconotide may be possible however, due to the limited numbers of patients, the results are inconclusive and there is currently insufficient evidence to make definitive recommendations for such alternative dosing regimens.

Clinical efficacy and safety

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 (malignant pain and non-malignant pain, Staats et al. 2004)

	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
Starting dose of ziconotide	9.6 μg/d (0.4 μg/h)		
Titration frequency	every 12 h		
Amended[b] starting dose	2.4 μg/d (0.1 μg/h) or less		
Amended[b] titration	every 24 h to max		

frequency	dose or analgesia		
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.

[b]Protocol amendments for better tolerance were necessary after high number of neurological adverse effects occurred coming with a high rate of discontinuation. Adverse effects were reversible and their incidence decreased with decreased initial dose and decreased frequency of titration.

Study Duration: Five days

SD – Standard Deviation.

Efficacy results from study 96-002 (non-malignant pain; Wallace et al. 2006)

	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
Starting dose of ziconotide	9.6 μg/d (0.4 μg/h)		

Titration frequency	every 24 h until analgesia, max dose or AE		
Titration time (h) and dose (µg/h)	0-24 0.4 24-48 0.9 48-72 1.8 72-96 3.4 96-120 5.3 120-144 7.0		
Revised[c] starting dose	2.4 µg/d (0.1 µg/h)		
Revised[c] titration frequency	every 24 h to max dose or analgesia		
Revised[c] titration time (h) and dose (µg/h)	0-24 0.1 24-48 0.2 48-72 0.3 72-96 0.6 96-120 1.2 120-144 2.4		
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.
[c]Protocol amendments for better tolerance were necessary due to onset of adverse events at high doses.
Study duration: Six days, with further 5-day maintenance as outpatient in ziconotide responders
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 reactions were also lower, mainly as a result of lower starting dose at 2.4 µg/d (0.1 µg/h). Titration was allowed after a minimum of 24 hours and dose increments were limited to 1.2-2.4 µg/d.

Efficacy results from study 301 (refractory pain; Rauck et al. 2006)

	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
Starting dose of ziconotide	2.4 µg/d (0.1 µg/h)		
Titration frequency	minimum of 24 h		
Titration dose	limited to 1.2-2.4 µg/d (0.05-0.10 µg/h)		
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.Study duration: 21 days
SD – Standard Deviation.

Post-marketing experience

Since market authorization approval, real-world data were published for long-time pain management with ziconotide monotherapy in <100 patients. In patients responding to initial trialing (about 50% of patients), safe and effective utilization of ziconotide with low starting dose, low titration dose and less frequent titration intervals resulted in pain relief with improved safety profile compared to high initial dose and rapid titration.

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 reactions. (e.g., hallucinations, paranoid reactions) or discontinuation due to increased adverse reactions 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)	$t_{½}$ (h)
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.

Renal and hepatic impairment

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.

Other special 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.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to 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

4 years

In-use shelf-life (diluted product)

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 after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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

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.

Specific instructions for using the pumps must be obtained from the manufacturer.

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.

The technical data are given only for information and should not limit health-care providers' choice. 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 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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