CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-060 / S-001

Trade Name: Prialt

Generic Name: (ziconotide)

Sponsor: Elan Biopharmaceuticals, Inc.

Approval Date: May 26, 2005

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APPLICATION NUMBER:

21-060 / S-001

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-060 / S-001

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-060/S-001

Elan Biopharmaceuticals, Inc
7475 Lusk Boulevard
San Diego, CA 92121

Attention: Mark Brunswick, Ph.D.
Director, Regulatory Affairs

Dear Dr. Brunswick:

Please refer to your supplemental new drug application dated April 15, 2005, received April 18, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prialt (ziconotide intrathecal infusion).

This "Changes Being Effected" supplemental new drug application provides for revisions to the package insert regarding the pump manufacturer and minor editorial changes.

We have completed our review of this application and it is approved, effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted labeling dated April 15, 2005.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-060/S-001**." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Sara E. Stradley, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, MD
Director
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bob Rappaport
5/26/05 12:03:38 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-060 / S-001

APPROVED LABELING

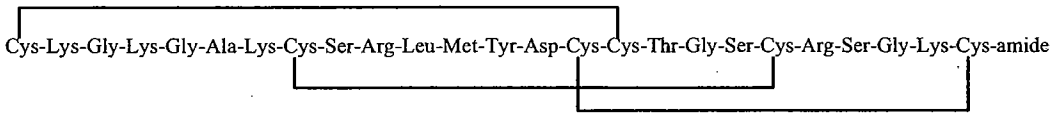
PRIALT (ziconotide **intrathecal infusion**)

For use only in the Medtronic SynchroMed® EL, SynchroMed® II Infusion System, Cadd-Micro® ambulatory infusion pump

WARNING:
Severe psychiatric symptoms and neurological impairment may occur during treatment with PRIALT. Patients with a pre-existing history of psychosis should not be treated with PRIALT. All patients should be monitored frequently for evidence of cognitive impairment, hallucinations, or changes in mood or consciousness. PRIALT therapy can be interrupted or discontinued abruptly without evidence of withdrawal effects in the event of serious neurological or psychiatric signs or symptoms.

DESCRIPTION

PRIALT® contains ziconotide, a synthetic equivalent of a naturally occurring conopeptide found in the piscivorous marine snail, *Conus magus.* Ziconotide is a 25 amino acid, polybasic peptide containing three disulfide bridges with a molecular weight of 2639 daltons and a molecular formula of $C_{102}H_{172}N_{36}O_{32}S_7$. The amino acid sequence and disulfide bridging pattern are given below:



Ziconotide is a hydrophilic molecule that is freely soluble in water and is practically insoluble in methyl t-butyl ether.

PRIALT is formulated as a sterile, preservative-free, isotonic solution for intrathecal (IT) administration using an appropriate microinfusion device (see Dosage and Administration). Each 1, 2, or 5 mL vial of PRIALT (100 mcg/mL) respectively contains 100, 200, or 500 mcg of ziconotide acetate, and the 20 mL vial of PRIALT (25 mcg/mL) contains 500 mcg of ziconotide acetate, with L-methionine and sodium chloride as excipients at pH 4.0–5.0. Each vial is

intended for single use only, either undiluted or after dilution to the appropriate concentration with 0.9% Sodium Chloride Injection, USP (preservative free).

CLINICAL PHARMACOLOGY

Pharmacodynamics

Mechanism of Action

Ziconotide binds to N-type calcium channels located on the primary nociceptive (A-δ and C) afferent nerves in the superficial layers (Rexed laminae I and II) of the dorsal horn in the spinal cord. Although the mechanism of action of ziconotide has not been established in humans, results in animals suggest that its binding blocks N-type calcium channels, which leads to a blockade of excitatory neurotransmitter release from the primary afferent nerve terminals and antinociception.

Interaction with opioids

Ziconotide does not bind to opioid receptors and its pharmacological effects are not blocked by opioid antagonists. In animal models, IT ziconotide potentiated opioid-induced reduction in gastrointestinal (GI) motility, but did not potentiate morphine-induced respiratory depression. In rats receiving IT ziconotide, additive analgesic effects were observed with concurrent administration of morphine, baclofen, or clonidine. Concurrent administration of IT ziconotide and morphine did not prevent the development of morphine tolerance in rats.

PHARMACOKINETICS

The cerebrospinal fluid (CSF) pharmacokinetics (PK) of ziconotide have been studied after one-hour IT infusions of 1–10 mcg of PRIALT to patients with chronic pain. The plasma PK following intravenous (IV) infusion (0.3–10 mcg/kg/day) have also been studied. Both IT and IV data are shown below (Table 1).

Table 1: PRIALT PK Parameters
(Mean ± SD)

Route	Fluid	N	CL (mL/min)	Vd (mL)	$T1/2_{elim}$ (hr)
IT	CSF	23	0.38 ± 0.56	155 ± 263	4.6 ± 0.9
IV	Plasma	21	270 ± 44	30,460 ± 6366	1.3 ± 0.3

Following one-hour IT administration of 1–10 mcg of PRIALT, both total exposure (AUC; range: 83.6–608 ng·h/mL) and peak exposure (Cmax; range: 16.4–132 ng/mL) values in the CSF were variable and dose-dependent, but appeared approximately dose-proportional. During 5 or 6 days of continuous IT infusions of PRIALT at infusion rates ranging from 0.1 to 7.0 mcg/hr in patients with chronic pain, plasma ziconotide levels could not be quantified in 56% of patients using an assay with a lower limit of detection of approximately 0.04 ng/mL. Predictably, patients requiring higher IT infusion dose rates were more likely to have quantifiable ziconotide levels in plasma. Plasma ziconotide levels, when detectable, remain constant after many months of IT PRIALT infusion in patients followed for up to 9 months.

Distribution

Ziconotide is about 50% bound to human plasma proteins. The mean CSF volume of distribution (Vd) of ziconotide following IT administration approximates the estimated total CSF volume (140 mL).

Metabolism

Ziconotide is cleaved by endopeptidases and exopeptidases at multiple sites on the peptide. Following passage from the CSF into the systemic circulation during continuous IT administration, ziconotide is expected to be susceptible to proteolytic cleavage by various ubiquitous peptidases/proteases present in most organs (e.g., kidney, liver, lung, muscle, etc.), and thus readily degraded to peptide fragments and their individual constituent free amino acids. Human and animal CSF and blood exhibit minimal hydrolytic activity toward ziconotide *in*

vitro. The biological activity of the various expected proteolytic degradation products of ziconotide has not been assessed.

Elimination

Minimal amounts of ziconotide (<1%) were recovered in human urine following IV infusion. The terminal half-life of ziconotide in CSF after an IT administration was around 4.6 hours (range 2.9–6.5 hours). Mean CSF clearance (CL) of ziconotide approximates adult human CSF turnover rate (0.3–0.4 mL/min).

Special populations

No formal studies were conducted to assess the effect of demographic factors (age, race, gender, and weight), renal or hepatic dysfunction, or to assess the effect of concomitant drugs on the pharmacokinetics of ziconotide due to the low systemic exposure of ziconotide following IT administration.

CLINICAL TRIALS

The safety and efficacy of IT PRIALT in the management of severe chronic pain were studied in three double-blind, placebo-controlled, multicenter studies in a total of 457 patients (268 PRIALT, 189 placebo) using two different titration schedules. The slow titration schedule tested dose increases 2–3 times per week with a maximum dose of 19.2 mcg/day (0.8 mcg/hr) at 21 days. The fast titration schedule used daily increases up to a maximum dose of 57.6 mcg/day (2.4 mcg/hr) in 5–6 days. The safety in chronic use was studied in four additional open-label, long-term studies in 977 patients.

A randomized, double-blind, placebo-controlled study was conducted at 39 centers to evaluate the efficacy of IT PRIALT administered using a slow titration schedule in 220 patients with severe chronic pain. Patients were randomized 1:1 between PRIALT (112 patients) and placebo (108 patients). At baseline, 97% of these patients reported that their pain was refractory to treatment including IT morphine, IT bupivacaine (an off-label use for this drug), and/or IT clonidine (an

off-label use for this drug) in addition to their systemic analgesics and adjunctive therapy. All IT medications were discontinued over a one to three week period, and patients were maintained on a stable regimen of non-IT analgesics, including opiates, for at least 7 days prior to randomization. This period was successfully completed by 93% of the patients screened. Dosing with PRIALT was started at 2.4 mcg/day (0.1 mcg/hr) and the dose could be increased by 2.4 mcg/day (0.1 mcg/hr) two to three times/week (minimum titration interval 24 hours) to a maximum dose of 19.2 mcg/day (0.8 mcg/hr). The final mean dose at the end of the trial at 21 days was 6.9 mcg/day (0.29 mcg/hr).

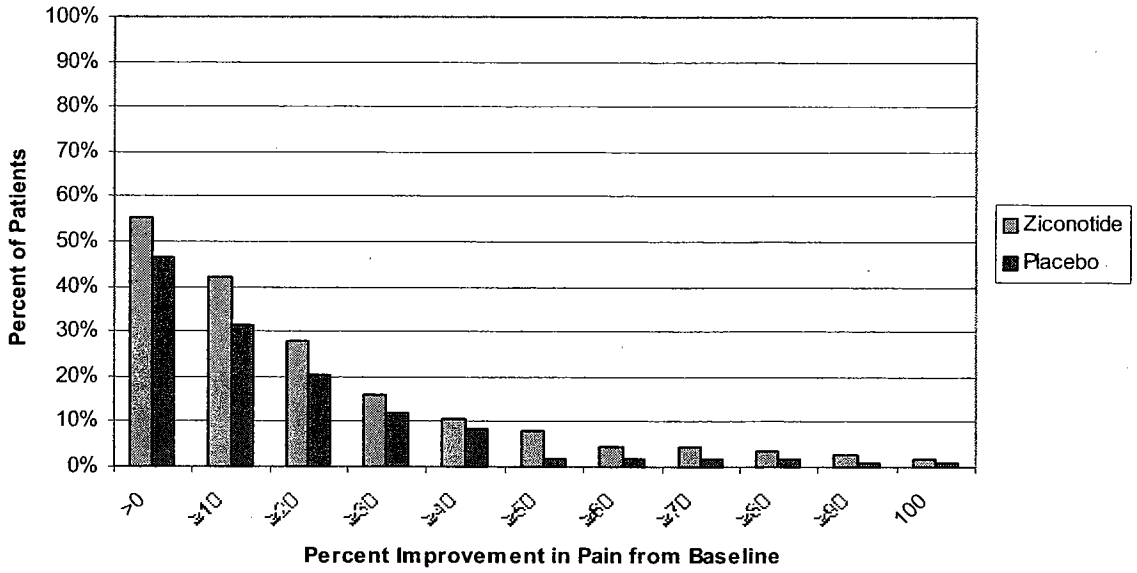
Using a 100 mm Visual Analog Scale of Pain Intensity (VASPI) where 100 mm=worst possible pain, mean baseline pain scores were 81 in both the PRIALT and placebo groups. The primary efficacy variable was the mean percent change in the VASPI score from baseline to day 21. In the intent-to-treat (ITT) efficacy analysis, there was a statistically significant difference between groups in the mean percent change in VASPI score from baseline with the PRIALT group having a 12% mean improvement at Week 3 compared to a 5% mean improvement in the placebo group (p=0.04). The 95% confidence interval for the treatment difference (PRIALT–placebo) was 0.4%, 13%.

The effect of IT PRIALT on pain was variable over the time period of treatment for some patients. Some patients had a reduction in VASPI in the first or second week but did not maintain pain relief by the end of the third week. Other patients, who did not exhibit a reduction in VASPI early in treatment, did have a reduction in VASPI by the third week.

Patients exhibited various degrees of improvement in pain after three weeks of treatment compared with baseline pain assessment. Figure 1 depicts the fraction of patients by their degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 30%, are also included at every level of improvement below 30%. Patients who did not have a VASPI score recorded at Week 3 (Study days 17-23, inclusive) were assigned 0%

improvement. The improvement in the proportion of "responders," defined as having a ≥30% improvement from baseline in VASPI, was 16% in the PRIALT group compared to 12% in the placebo group, for a net difference of 4%. The use of non-IT opioids decreased by 24% in the PRIALT group and by 17% in the placebo group.

Figure 1: Patients Achieving Various Levels of Pain Relief from Baseline to Week 3



INDICATIONS AND USAGE

PRIALT (ziconotide intrathecal infusion) is indicated for the management of severe chronic pain in patients for whom intrathecal (IT) therapy is warranted, and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies, or IT morphine.

CONTRAINDICATIONS

PRIALT is contraindicated in patients with a known hypersensitivity to ziconotide or any of its formulation components and in patients with any other concomitant treatment or medical condition that would render IT administration hazardous.

Patients with a pre-existing history of psychosis should not be treated with ziconotide.

Contraindications to the use of IT analgesia include conditions such as the presence of infection at the microinfusion injection site, uncontrolled bleeding diathesis, and spinal canal obstruction that impairs circulation of CSF.

WARNINGS

Severe psychiatric symptoms and neurological impairment may occur during treatment with PRIALT. Patients with a pre-existing history of psychosis should not be treated with PRIALT. All patients should be monitored frequently for evidence of cognitive impairment, hallucinations, or changes in mood or consciousness. PRIALT therapy can be interrupted or discontinued abruptly without evidence of withdrawal effects in the event of serious neurological or psychiatric signs or symptoms.

Patients should be cautioned against engaging in hazardous activity requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle during treatment with PRIALT. Patients should also be cautioned about possible combined effects with other CNS-depressant drugs. Dosage adjustments may be necessary when PRIALT is administered with such agents because of the potentially additive effects.

WITHDRAWAL FROM OPIATES

PRIALT is not an opiate and cannot prevent or relieve the symptoms associated with the withdrawal of opiates. To avoid withdrawal syndrome when opiate withdrawal is necessary, patients must NOT be abruptly withdrawn from opiates. For patients being withdrawn from IT opiates, the IT opiate infusion should be gradually tapered over a few weeks and replaced with a pharmacologically equivalent dose of oral opiates. PRIALT does not interact with opiate receptors and does not potentiate opiate-induced respiratory depression.

PRECAUTIONS

General

MENINGITIS AND OTHER INFECTIONS

Meningitis can occur due to inadvertent contamination of the microinfusion device and other means such as CSF seeding due to hematogenous or direct spread from an infected pump pocket or catheter tract. While meningitis is rare with an internal microinfusion device and surgically-implanted catheter, the incidence increases substantially with external devices. In the 1254 patients in PRIALT clinical trials with an exposure of 662 patient-years, meningitis occurred at 3% (40 cases) in the PRIALT group using either internal or external microinfusion devices and 1% (1 case) in the placebo group with an exposure of only 5 patient-years. The risk of meningitis with external microinfusion devices and catheters was higher with 93% cases (38/41) occurring with external infusion systems (37 PRIALT, 1 placebo).

Patients, caregivers, and healthcare providers must be particularly vigilant for the signs and symptoms of meningitis, including but not limited to fever, headache, stiff neck, altered mental status (e.g., lethargy, confusion, disorientation), nausea or vomiting, and occasionally seizures. Serious infection or meningitis can occur within 24 hours of a breach in sterility such as a disconnected catheter, the most common cause of meningitis with external microinfusion devices. The patient and health care provider should be familiar with the handling of the external microinfusion device and care of the catheter skin exit site at risk of infection. Strict aseptic procedures must be used during the preparation of the PRIALT solution or refilling of the microinfusion device to prevent accidental introduction of any contaminants or other environmental pathogens into the reservoir. In suspected cases (especially in immuno-compromised patients) or in confirmed cases of meningitis, CSF cultures must be obtained and appropriate antibiotic therapy must be promptly instituted. Treatment of meningitis usually requires removal of the microinfusion system, catheter, and any other foreign body materials within the IT space and therefore discontinuation of PRIALT therapy.

COGNITIVE AND NEUROPSYCHIATRIC ADVERSE EVENTS

Use of PRIALT has been associated with CNS-related adverse events, including psychiatric symptoms, cognitive impairment, and decreased alertness/unresponsiveness. For the 1254 patients treated, the following cognitive adverse event rates were reported: confusion (33%), memory impairment (22%), speech disorder (14%), aphasia (12%), thinking abnormal (8%), and amnesia (1%). Cognitive impairment may appear gradually after several weeks of treatment. The PRIALT dose should be reduced or discontinued if signs or symptoms of cognitive impairment develop, but other contributing causes should also be considered. The various cognitive effects of PRIALT are generally reversible within 2 weeks after drug discontinuation. The medians for time to reversal of the individual cognitive effects ranged from 3 to 15 days. The elderly (≥65 years of age) are at higher risk for confusion. (see GERIATRIC USE.)

In placebo-controlled trials, there was a higher incidence of suicide, suicide attempts, and suicide ideations in PRIALT-treated patients (N=3) than in the placebo group (N=1). The incidence was 0.10/patient year for placebo patients and 0.27/patient year for PRIALT patients.

Events of acute psychiatric disturbances such as hallucinations (12%), paranoid reactions (3%), hostility (2%), delirium (2%), psychosis (1%), and manic reactions (0.4%) have been reported in patients treated with PRIALT. Patients with pretreatment psychiatric disorders may be at an increased risk. PRIALT may cause or worsen depression with the risk of suicide in susceptible patients. If appropriate, management of psychiatric complications should include discontinuation of PRIALT, treatment with psychotherapeutic agents if appropriate, and/or short-term hospitalization. Before drug is reinitiated, careful evaluation must be performed on an individual basis.

REDUCED LEVEL OF CONSCIOUSNESS

Patients have become unresponsive or stuporous while receiving PRIALT. The incidence of unresponsiveness or stupor in clinical trials was 2%. During these episodes, the patient sometimes appears to be conscious and breathing is not depressed. If reduced levels of consciousness occur, PRIALT should be discontinued until the event resolves, and other etiologies (e.g., meningitis) should be considered. There is no known pharmacologic antagonist for this effect. Patients taking concomitant antiepileptics, neuroleptics, sedatives, or diuretics may be at higher risk of depressed levels of consciousness. If altered consciousness occurs, other CNS-depressant drugs should also be discontinued as clinically appropriate.

ELEVATION OF SERUM CREATINE KINASE (CK-MM)

In clinical studies (mostly open label), 40% of patients had serum creatine kinase (CK) levels above the upper limit of normal, and 11% had CK levels that were ≥ 3 X ULN. In cases where CK was fractionated, only the muscle isoenzyme (MM) was elevated. The time to occurrence was sporadic, but the greatest incidence of CK elevation was during the first two months of treatment. Elevated CKs were more often seen in males, in patients who were being treated with anti-depressants or anti-epileptics, and in patients treated with IT morphine. Most patients who experienced elevations in CK, even for prolonged periods of time, did not have limiting side effects. However, one case of symptomatic myopathy with EMG findings, and two cases of acute renal failure associated with rhabdomyolysis and extreme CK elevations (17,000–27,000 IU/L) have been reported.

Therefore, it is recommended that physicians monitor serum CK in patients undergoing treatment with PRIALT periodically (e.g., every other week for the first month and monthly as appropriate thereafter). Patients should be clinically evaluated and CK measurements obtained in the setting of new neuromuscular symptoms (e.g., myalgias, myasthenia, muscle cramps, asthenia) or a reduction in physical activity. Should these symptoms continue and CK levels remain

elevated or continue to rise, it is recommended that the physician consider PRIALT dose reduction or discontinuation.

INFORMATION FOR PATIENTS

Patients should be cautioned against engaging in hazardous activity requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle during treatment with PRIALT Patients should also be cautioned about possible combined effects with other CNS-depressant drugs. Dosage adjustments may be necessary when PRIALT is administered with such agents because of the potentially additive effects. The physician should be contacted if the patient experiences new or worsening muscle pain, soreness, weakness with or without darkened urine.

PATIENTS AND THEIR CAREGIVERS SHOULD BE INSTRUCTED TO CONTACT A PHYSICIAN IMMEDIATELY IF THE PATIENT HAS

- A change in mental status (e.g., lethargy, confusion, disorientation, decreased alertness)
- A change in mood, perception (hallucinations, including unusual tactile sensations in the oral cavity)
- Symptoms of depression or suicidal ideation
- Nausea, vomiting, seizures, fever, headache, and/or stiff neck, as these may be symptoms of developing meningitis

LABORATORY TESTS

In clinical studies (mostly open label), up to 40% of patients had serum creatine kinase (CK) levels above the upper limit of normal, and 11% had CK levels that were ≥ 3 times the upper limit of normal (see Elevation of Serum Creatine Kinase). Most cases of CK elevation were not associated with muscle

weakness, however one case of myopathy with EMG findings, and two cases of acute renal failure associated with rhabdomyolysis and extreme CK elevations (17,000–27,000 IU/L) were reported..

DRUG INTERACTIONS

Formal PK drug-drug interaction studies have not been performed with PRIALT. As ziconotide is a peptide, it is expected to be completely degraded by endopeptidases and exopeptidases (Phase I hydrolytic enzymes) widely located throughout the body, and not by other Phase I biotransformation processes (including the cytochrome P450 system) or by Phase II conjugation reactions. Thus, IT administration, low plasma ziconotide concentrations, and metabolism by ubiquitous peptidases make metabolic interactions of other drugs with ziconotide unlikely. Further, as ziconotide is not highly bound in plasma (approximately 50%) and has low plasma exposure following IT administration, clinically relevant plasma protein displacement reactions involving ziconotide and co-administered medications are unlikely.

Over 90% of patients treated with IT PRIALT used systemic opiates and in the slow titration study, 98% of patients received opioids.

Combination of PRIALT with intrathecal opiates has not been studied in placebo-controlled clinical trials and is not recommended.

Interaction with CNS Depressants

Almost all patients in the PRIALT clinical trials received concomitant non-IT medication. Of the 1254 patients treated, most received several concomitant drugs, including antidepressants (66%), anxiolytics (52%), antiepileptics (47%), neuroleptics (46%), and sedatives (34%). The use of drugs with CNS-depressant activities may be associated with an increased incidence of CNS adverse events such as dizziness and confusion (see PRECAUTIONS).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been conducted in animals.

Ziconotide was negative in the *in vitro* bacterial reverse mutation assay, *in vitro* mouse lymphoma assay, *in vivo* mouse micronucleus assay, and in the *in vitro* Syrian hamster embryo (SHE) cell transformation assay.

Ziconotide did not affect male fertility in rats when administered as a continuous intravenous (IV) infusion at a dose of up to 10 mg/kg/day when administered for approximately 8 weeks, including a 28-day pre-mating period, or female fertility at a dose of 3 mg/kg/day when administered for approximately 6 weeks, including a 14-day pre-mating period. Estimated exposures for the male and female rats were approximately 6500-fold and 1700-fold higher, respectively, than the expected exposure resulting from the maximum recommended human daily intrathecal (IT) dose of 0.8 mcg/hr (19.2 mcg/day) based on plasma exposure.

Female fertility in rats was significantly affected following continuous IV infusion at a dose of 10 mg/kg/day. Significant reductions in corpora lutea, implantation sites, and number of live fetuses were observed.

Pregnancy

Pregnancy Category C:

Ziconotide was embryolethal in rats when given as a continuous IV infusion during the major period of organogenesis as evidenced by significant increases in post-implantation loss because of an absence or a reduced number of live fetuses. Estimated exposure for embryolethality in the rat was approximately 700-fold above the expected exposure resulting from the maximum recommended human daily intrathecal (IT) dose of 0.8 mcg/hr (19.2 mcg/day). Ziconotide was not teratogenic in female rats when given as a continuous IV infusion at doses up to 30 mg/kg/day or in female rabbits up to 5 mg/kg/day during the major period of organ development. Estimated exposures in the female rat and rabbit were approximately 26,000-fold and 940-fold higher than

the expected exposure resulting from the maximum recommended human daily intrathecal (IT) dose of 0.8 mcg/hr (19.2 mcg/day) based on plasma exposure. Maternal toxicity in the rat and rabbit, as evidenced by decreased body weight gain and food consumption, was present at all dose levels. Maternal toxicity in the rat led to reduced fetal weights and transient, delayed ossification of the pubic bones at doses ≥15 mg/kg/day, which is approximately 8900-fold higher than the expected exposure resulting from the maximum recommended human daily IT dose of 0.8 mcg/hr (19.2 mcg/day) based on plasma exposure. The no observable adverse effect level (NOAEL) for embryo-fetal development in rats was 0.5 mg/kg/day and in rabbits was 5 mg/kg/day. Estimated NOAEL exposures in the rat and rabbit were approximately 400-fold and 940-fold higher than the expected exposure resulting from the maximum recommended human daily IT dose of 0.8 mcg/hr (19.2 mcg/day) based on plasma exposure.

In a pre- and post-natal study in rats, ziconotide given as a continuous IV infusion did not affect pup development or reproductive performance up to a dose of 10 mg/kg/day, which is approximately 3800-fold higher than the expected exposure resulting from the maximum recommended human daily intrathecal (IT) dose of 0.8 mcg/hr (19.2 mcg/day) based on plasma exposure. Maternal toxicity, as evidenced by clinical observations, and decreases in body weight gain and food consumption were observed at all doses.

No adequate and well-controlled studies have been conducted in pregnant women. Because animal studies are not always predictive of human response, PRIALT should be used during pregnancy only if the potential benefit justifies risk to the fetus.

Labor and Delivery

The effect of PRIALT on labor and delivery in humans is not known.

Nursing Mothers

It is not known whether PRIALT is excreted in human breast milk. Because many drugs are excreted in human milk, and because of the potential for serious

adverse reactions in nursing infants from PRIALT, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total number of subjects in clinical studies of PRIALT, 22% were 65 and over, while 7% were 75 and over. In all trials, there was a higher incidence of confusion in older patients (42% for ≥65 year old versus 29% for <65 year old subgroups). Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, the dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Hepatic and Renal Impairment

Formal PK studies were not conducted in patients with hepatic or renal impairment.

ADVERSE REACTIONS

The safety of IT PRIALT administered as a continuous infusion has been evaluated in 1254 patients participating in acute and severe chronic pain trials. The duration of treatment has ranged from a one-hour IT infusion to treatment lasting for more than 7.5 years. The mean duration of treatment was 193 days with 173 patients (14%) treated for at least 1 year. The average final dose was 17.6 mcg/day (0.73 mcg/hr).

The most frequently reported adverse events (≥25%) in the 1254 patients (662 patient years) in clinical trials were dizziness, nausea, confusion, headache, somnolence, nystagmus, asthenia, and pain. Serious adverse events and discontinuation of PRIALT for adverse events are less frequent when the drug is

slowly titrated over 21 days than with a faster titration schedule. (See CLINICAL TRIALS and DOSAGE and ADMINISTRATION.)

Table 2 summarizes the treatment-emergent adverse events with a frequency of 5% or greater in the PRIALT-treated group from the one placebo-controlled trial using the slow titration schedule in patients with severe chronic pain. All events reported during the initial placebo-controlled period of the studies (21 days in the slow titration schedule) are tabulated, regardless of relationship to PRIALT.

Table 2. Incidence of Treatment-Emergent Adverse Events in Slow Titration Placebo-Controlled Trial by Percent (Events That Occurred in ≥ 5% of Patients and More Commonly with PRIALT than with Placebo)

	PRIALT N=112	Placebo N=108
	Percentages of Patients	
Any AE	93	82
Body as a Whole	57	42
Asthenia	22	12
Headache	15	12
Pain	11	7
Fever	7	3
Digestive	60	51
Nausea	41	31
Diarrhea	19	17
Vomiting	15	13
Anorexia	10	5
Nervous System	81	51
Dizziness	47	13
Somnolence	22	15
Confusion	18	5
Ataxia	16	2
Abnormal Gait	15	2
Memory Impairment	12	1
Hypertonia	11	5
Anxiety	9	5
Speech Disorder	9	2
Aphasia	8	1
Nystagmus	8	0
Dysesthesia	7	2
Hallucinations	7	0
Nervousness	7	4
Paresthesia	7	3
Vertigo	7	0
Special Senses	20	11
Abnormal Vision	10	4
Urogenital	22	12
Urinary Retention	9	0

The following adverse events assessed as related to PRIALT have been reported in 2% or greater of patients participating in the clinical studies. (COSTART terms, by body system):

BODY AS A WHOLE: abdominal pain, accidental injury, asthenia, back pain, catheter complication, catheter site pain, cellulitis, chest pain, chills, fever, flu syndrome, headache, infection, malaise, neck pain, neck rigidity, pain, pump site complication, pump site mass, pump site pain, viral infection. CARDIOVASCULAR SYSTEM: hypertension, hypotension, postural hypotension, syncope, tachycardia, vasodilation. DIGESTIVE SYSTEM: anorexia, constipation, diarrhea, dyspepsia, gastrointestinal disorder, nausea, nausea and vomiting, vomiting. HEMIC AND LYMPHATIC SYSTEM: anemia, ecchymosis. METABOLIC AND NUTRITIONAL DISORDER: creatine phosphokinase increased, dehydration, edema, hypokalemia, peripheral edema, weight loss. MUSCULOSKELETAL SYSTEM: arthralgia, arthritis, leg cramps, myalgia, myasthenia. NERVOUS SYSTEM: abnormal dreams, abnormal gait, agitation, anxiety, aphasia, ataxia, cerebrospinal fluid abnormal, confusion, depression, difficulty concentrating, dizziness, dry mouth, dysesthesia, emotional lability, hostility, hyperesthesia, hypertonia, incoordination, insomnia, memory impairment, mental slowing, meningitis, nervousness, neuralgia, nystagmus, paranoid reaction, paresthesia, reflexes decreased, somnolence, speech disorder, stupor, thinking abnormal, tremor, twitching, vertigo. RESPIRATORY SYSTEM: bronchitis, cough increased, dyspnea, lung disorder, pharyngitis, pneumonia, rhinitis, sinusitis. SKIN AND APPENDAGES: cutaneous surgical complication, dry skin, pruritus, rash, skin disorder, sweating. SPECIAL SENSES: abnormal vision, diplopia, photophobia, taste perversion, tinnitus. UROGENITAL SYSTEM: dysuria, urinary incontinence, urinary retention, urinary tract infection, urination impaired.

At less than 2%, the following events were assessed by the clinical investigators as related to PRIALT: acute kidney failure, atrial fibrillation, cerebrovascular accident, electrocardiogram abnormal, grand mal convulsion, meningitis, myoclonus, psychosis, respiratory distress, rhabdomyolysis, sepsis, and suicidal ideations. Rare instances of fatal aspiration pneumonia and suicide were reported (<1%).

OVERDOSAGE

The maximum recommended IT PRIALT dose is 19.2 mcg/day. The maximum IT dose of PRIALT in clinical trials was 912 mcg/day. In some patients who received IT doses greater than the maximum recommended dose, exaggerated pharmacological effects (e.g., ataxia, nystagmus, dizziness, stupor, unresponsiveness, spinal myoclonus, confusion, sedation, hypotension, word-finding difficulties, garbled speech, nausea, and vomiting) were observed. There was no indication of respiratory depression. Overdoses may occur due to pump programming errors or incorrect drug concentration preparations. In these cases, patients were observed and ziconotide was either temporarily discontinued or permanently withdrawn. Most patients recovered within 24 hours after withdrawal of drug. In the event of an IT overdose, elimination of ziconotide from CSF would be expected to remain constant (CSF $t_{½}$=4.6 hours). Therefore, within 24 hours of stopping therapy, the ziconotide CSF concentration should be less than 5% of peak levels.

There is no known antidote to ziconotide. General medical supportive measures should be administered to patients who receive an overdose until the exaggerated pharmacological effects of the drug have resolved. Treatment for an overdose is hospitalization, when needed, and symptom-related supportive care. Ziconotide does not bind to opiate receptors and its pharmacological effects are not blocked by opioid antagonists.

In the event of an inadvertent intravenous or epidural administration, adverse events could include hypotension, which can be treated with a recumbent posture and blood pressure support as required. The half-life of PRIALT in serum is 1.3 hours.

DOSAGE AND ADMINISTRATION

IT PRIALT should be initiated at no more than 2.4 mcg/day (0.1 mcg/hr) and titrated to patient response. Doses may be titrated upward by up to 2.4 mcg/day (0.1 mcg/hr) at intervals of no more than 2–3 times per week, up to a recommended maximum of 19.2 mcg/day (0.8 mcg/hr) by Day 21. Dose

increases in increments of less than 2.4 mcg/day (0.1 mcg/hr) and increases in dose less frequently than 2–3 times per week may be used. For each dose titration, assess the dosing requirements and adjust the pump infusion flow rate as required to achieve the new dosing. Controlled studies of pain relief have not been conducted for longer than 3 weeks duration, although 977 patients have been treated with IT PRIALT in long-term open-label trials.

The dose of IT PRIALT should be adjusted according to the patient's severity of pain, their response to therapy, and the occurrence of adverse events. The effective dose of PRIALT for analgesia is variable. The average dose level at the end of the 21-day titration used in the slow titration clinical trial (see CLINICAL TRIALS) was 6.9 mcg/day (0.29 mcg/hr) and the maximum dose was 19.2 mcg/day (0.8 mcg/hr) on Day 21. Due to the frequency of adverse events, 19.2 mcg/day (0.8 mcg/hr) is the maximum recommended dose.

Because of the lower incidence of serious adverse events and discontinuations for adverse events associated with the slower titration (see ADVERSE REACTIONS), a faster titration schedule should only be used if there is an urgent need for analgesia that outweighs the risk to patient safety.

In clinical trials, no rebound or other adverse events related to discontinuation of PRIALT were noted, although treatment was almost always discontinued abruptly.

Vials of PRIALT should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Administration

PRIALT should be administered intrathecally (IT) by or under the direction of a physician experienced in the technique of IT administration and who is familiar with the drug and device labeling. PRIALT is not intended for intravenous administration.

PRIALT is intended for IT delivery using a programmable implanted variable-rate microinfusion device or an external microinfusion device and catheter (see PRECAUTIONS-Meningitis and Other Infections). Refer to the manufacturer's manual for specific instructions and precautions for programming the microinfusion device and/or refilling the reservoir.

PRIALT is used for therapy undiluted (25 mcg/mL in 20mL vial) or diluted (100 mcg/mL in 1, 2, or 5 mL vials). Diluted PRIALT is prepared with 0.9% Sodium Chloride Injection, USP (preservative free) using aseptic procedures to the desired concentration prior to placement in the microinfusion pump. The 100 mcg/mL formulation may be administered undiluted once an appropriate dose has been established. SALINE SOLUTIONS CONTAINING PRESERVATIVES ARE NOT APPROPRIATE FOR IT DRUG ADMINISTRATION AND SHOULD NOT BE USED. Refrigerate but do not freeze all PRIALT solutions after preparation and begin infusion within 24 hours. Discard any PRIALT solution with observed particulate matter or discoloration and any unused portion left in the vial.

Medtronic SynchroMed EL or SynchroMed II Infusion System (see PRECAUTIONS-Meningitis and Other Infections)

Refer to the manufacturer's manuals for specific instructions and precautions for performing a reservoir rinse, initial filling, refilling the reservoir, and programming.

Instructions for Use of PRIALT with Pump

1. Naïve Pump Priming (i.e., first time use with PRIALT)

Only the undiluted 25 mcg/mL formulation should be used for naïve pump priming. Rinse the internal surfaces of the pump with 2 mL of PRIALT at 25 mcg/mL. Repeat twice for a total of three rinses.

2. Initial Pump Fill

Only the undiluted 25 mcg/mL formulation should be used for initial pump fill. Fill the naïve pump after priming as above with the appropriate volume of

PRIALT at 25 mcg/mL. Begin dosing at a delivery rate no higher than 2.4 mcg/day (0.1 mcg/hr). In a naïve pump, PRIALT is lost due to two factors that do not occur upon subsequent refills: adsorption on internal device surfaces, such as the titanium, and by dilution in the residual space of the device. Consequently, the pump reservoir should be refilled with PRIALT within 14 days of the initial fill to ensure appropriate dose administration.

3. Pump Refills

For subsequent pump refills, fill the pump at least every 40 days if PRIALT is used diluted. For undiluted PRIALT, fill the pump at least every 60 days. To ensure aseptic transfer of PRIALT into the device, it is recommended that the Medtronic refill kit be used. The pump contents should be emptied prior to refill with PRIALT.

If the internal infusion system must be surgically replaced while the person is receiving PRIALT, the replacement pump should be rinsed with PRIALT (No. 1 above), and this initial fill solution must be replaced within 14 days (No. 2 above). Subsequent refills should be done at least every 60 days if PRIALT is used undiluted or at least every 40 days if PRIALT is used diluted.

PRIALT (ziconotide intrathecal infusion)	**Initial Fill** Expiry	**Refill** Expiry
25 mcg/mL, undiluted	14 Days	60 Days
100 mcg/mL, undiluted	N/A	60 Days
100 mcg/mL, diluted	N/A	40 Days

Cadd-Micro abulatory infusion pump (see PRECAUTIONS-Meningitis and Other Infections).

Refer to the manufacturer's manuals for specific instructions and precautions for performing the initial filling, refilling of the reservoir or replacement of the drug cartridge, and operation. The appropriate external microinfusion device is filled for the first time with PRIALT solution at a concentration of 5 mcg/mL. This solution is prepared by diluting PRIALT with 0.9% Sodium Chloride, USP (preservative free). The flow rate for the external microinfusion device usually starts at 0.02 mL/hr to deliver the initial dose rate of 2.4 mcg/day (0.1 mcg/hr) of PRIALT. Changes in dose rate are made by adjusting the flow rate of the infusion system and/or the concentration of PRIALT solution.

HOW SUPPLIED

PRIALT is supplied as a 25 mcg/mL solution in a single-use 20 mL glass vial and as a 100 mcg/mL solution in single-use glass vials containing 1 mL, 2 mL, or 5 mL of solution. One vial is packaged per carton.

Presentation (NDC)

25 mcg/mL: 20 mL vial (59075-723-10). Only the undiluted 25 mcg/mL formulation should be used for PRIALT naïve pump priming.

100 mcg/mL: 1 mL (59075-720-10)

2 mL (59075-721-10)

5 mL (59075-722-10)

STORAGE

- Refrigerate PRIALT during transit.
- Store PRIALT at 2°C–8°C (36°F–46°F).
- PRIALT, once diluted aseptically with saline, may be stored at 2°C–8°C for 24 hours
- Do NOT freeze PRIALT.
- Protect from light.

Distributed by:
Elan Pharmaceuticals, Inc.
San Diego, CA 92121

(ELAN Logo)

6001451 Rev. 2/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-060 / S-001

MEDICAL REVIEW

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857
Tel:(301)827-7410

Medical Officer's Review

NDA # (serial):	**21-060**
Drug Name (generic):	**Prialt (Ziconotide Intrathecal Infusion)**
Sponsor:	**Elan Pharmaceuticals, Inc.**
Type of Submission:	**Request for waiver of pediatric studies**
Date of Submission:	**03March05**
Date of Review:	**26APR05**
Reviewer:	**Lex Schultheis, M.D., Ph.D.**
Project Manager:	**Sara Stradley, M.S., RPM**

BACKGROUND

Prialt (Ziconotide Intrathecal Infusion) was approved December 28, 2004 for the management of severe, chronic pain in patients for whom intrathecal therapy is warranted. A request for pediatric studies was made in the approval letter allowing for trials to be deferred:

> "Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required post marketing study commitments. The status of this post marketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.
>
> 1. Deferred pediatric study under PREA for the management of severe chronic pain in patients for whom intrathecal (IT) therapy is warranted and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies, or IT morphine in pediatric patients ages 0-16 years."

REVIEW OF SPONSOR'S SUBMISSION (2March05)

The sponsor requested that the requirement to study ziconotide in patients below that age of 16 years be waived. The rationale for the sponsor's position was based upon two points.

1. Only 130 implanted pumps were placed in pediatric patients from 1993 until 2005 as reported by the manufacturer of the Medtronic Synchromed pump, the infusion pump approved for use with ziconotide. The functional period before replacement of the implanted pump is approximately 5 years, so that the number of implanted pumps may overestimate the number of patients treated if patients received replacement pumps.

Reviewer's comment:

The small number of implanted pumps appears to be a strong argument that too few patients are likely to derive clinical benefit to enable the conduct of a practical clinical trial in this population.

2. A position statement prepared by Howard B. Gutstein, M.D., a pain physician at the University of Michigan, discounted the likely use of ziconotide in pediatric patients because:
    a. Nonmalignant neuropathic pain is very rare in children and it may be effectively treated less invasively than in adults.
    b. Implantation of a pump in children is avoided because of concerns over developmental issues regarding self-perception of a negative body image that could be associated with an implanted device.
    c. Treatment of cancer pain in children is qualitatively different in pediatric patients than in adults because pediatric patients are treated more aggressively with chemotherapy than adult patients because of a higher likelihood of cure in the pediatric population. Aggressive chemotherapy may increase risks of complication such as catheter infection and bleeding. The timing for study of ziconotide treatment in the course of the disease is uncertain because intrathecal treatment is instituted for severe pain usually occurs when survival to the end of an experimental protocol is unlikely and rapid escalation of analgesia is required. These features are expected to complicate analysis of efficacy.
    d. The number of patients that would benefit from ziconotide treatment is very small based upon the author's consultation with directors of pain management at several university practices. It was acknowledged that ziconotide may be an appropriate choice for a small number of pediatric patients as "humane use" exceptions. The number of patients that may be expected to be enrolled was estimated to be no more than about 15 annually so that two years would be needed to complete a clinical trial.

Reviewer's Comment:

a. Infrequent presentation of nonmalignant neuropathic pain in pediatric patients and the availability of other effective treatment will limit the potential population of patients who may benefit from ziconotide and impair the sponsor's ability to conduct a clinical trial.
b. The consultant's opinion is reinforced by the very small number of pumps placed in children for pain.
c. & d. There may be such significant qualitative differences in the management of pain resulting from malignancy in pediatric patients compared with adults that ziconotide would be an unlikely therapeutic option. The small number of patients estimated by the consultant and the potential for their wide geographic disparity support this point.

RECOMMENDATIONS:

The requirement for pediatric study of ziconotide may be waived at this time. The need to conduct clinical trials in pediatric patients may be reconsidered if there is evidence that indwelling intrathecal pumps become more frequently used for treatment or that ziconotide will offer an important and unique benefit in this population.

Lex Schultheis, M.D., Ph.D. Medical Officers	Date 4/26/05	Rigoberto Roca, MD Deputy Division Director	Date

CC: NDA #21,060
HFD-170: Division File

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lester Schultheis
5/17/05 08:21:50 AM
MEDICAL OFFICER

Rigoberto Roca
5/17/05 10:17:58 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-060 / S-001

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

Division of Anesthetic, Critical Care, and Addiction Drug Products

Regulatory Project Manager Review

Application Number: NDA 21-060/SLR 001

Name of Drug: Prialt (ziconotide intrathecal infusion)

Sponsor: Elan Pharmaceuticals

Material Reviewed

Submission Date(s): April 15, 2005

Receipt Date(s): April 18, 2005

Background and Summary Description: This supplement contains a package insert with minor revisions (i.e., addition or deletion of commas, dashes vs. hypens, subscripting or superscripting, capitalization vs. lower case).

This review compares the current submission with the final printed label acknowledged and retained on March 29, 2005

Note: The "Rx Only" symbol was removed from package insert.

Status Report

Reviews Completed: Sara E. Stradley, RPM, April 25, 2005

Concurrence: Parinda Jani, CPMS, April 27, 2005
Lex Schultheis, MD, April 29, 2005
Rigo Roca, MD, April 29, 2005

RPM Review

Please note that a strikethrough indicates deletion and an underline indicates addition to the approved label. The changes have also been highlighted in gray for easier viewing.

PRIALT (ziconotide **intrathecal infusion**)
~~For use only in the Medtronic SynchroMed® EL, SynchroMed® II Infusion System and Simms Deltec Cadd Micro® External Microinfusion Device and Catheter~~ For use only in the Medtronic SynchroMed ® EL, SynchroMed® II Infusion System and Cadd-Micro® ambulatory infusion pump

BOX WARNING: deleted an extra space in the box

DESCRIPTION: The following minor change was made.

PRIALT is formulated as a sterile, preservative-free, isotonic solution for intrathecal (IT) administration using an appropriate microinfusion device (~~See~~ see Dosage and Administration). Each 1, 2, or 5 mL vial of PRIALT (100 mcg/mL) respectively contains 100, 200, or 500 mcg of ziconotide acetate, and the 20 mL vial of PRIALT (25 mcg/mL) contains 500 mcg of ziconotide acetate, with L-methionine and sodium chloride as excipients at pH 4.0–5.0. Each vial is intended for single use only, either undiluted or after dilution to the appropriate concentration with 0.9% Sodium Chloride Injection, USP (preservative free).

CLINICAL PHARMACOLOGY: The following change was made.

Pharmacodynamics

Mechanism of Action

Ziconotide binds to N-type calcium channels located on the primary nociceptive (A-d and C) afferent nerves in the superficial layers (Rexed laminae I and II) of the dorsal horn in the spinal cord. Although the mechanism of action of ziconotide has not been established in humans, results in animals suggest that its binding blocks N-type calcium channels, which leads to a blockade of excitatory neurotransmitter release ~~in~~ from the primary afferent nerve terminals and antinociception.

Interaction with opioids

Ziconotide does not bind to opioid receptors and its pharmacological effects are not blocked by opioid antagonists. In animal models, IT ziconotide potentiated opioid-induced reduction in ~~gastro-intestinal~~ gastrointestinal (GI) motility, but did not potentiate morphine-induced respiratory depression. In rats receiving IT ziconotide, additive analgesic effects were observed with concurrent administration of morphine, baclofen, or clonidine. Concurrent administration of IT ziconotide and morphine did not prevent the development of morphine tolerance in rats.

PHARMACOKINETICS: The following minor changes were made.

The cerebrospinal fluid (CSF) pharmacokinetics (PK) of ziconotide have been studied after one-hour IT infusions of 1–10 mcg of PRIALT to patients with chronic pain. The plasma PK following intravenous (IV) infusion ~~(0.3–10 mcg/kg/day)~~ (0.3-10 mcg/kg/day) have also been studied. Both IT and IV data are shown below (Table 1).

Table 1: PRIALT PK Parameters
(Mean ± SD)

Route	Fluid	N	CL (mL/min)	Vd (mL)	T1/2 $_{elim}$ (hr)
IT	CSF	23	0.38±0.56	155 ± 263	4.6 ± 0.9
IV	Plasma	21	270 ± 44	30,460 ± 6366	1.3 ± 0.3

Following one-hour IT administration of ~~1 – 10 mcg~~ 1-10 mcg of PRIALT, both total exposure (AUC; range: ~~83.6 – 608 ng×h/mL~~ 83.6–608 ng×h/mL) and peak exposure (Cmax; range: ~~16.4 – 132 ng/mL~~ 16.4–132 ng/mL) values in the CSF were variable and dose-dependent, but appeared approximately dose-proportional. During 5 or 6 days of continuous IT infusions of PRIALT at infusion rates ranging from ~~0.1 – 7.0 mcg/hr~~ 0.1 to 7.0 mcg/hr in patients with chronic pain, plasma ziconotide levels could not be quantified in 56% of patients using an assay with a lower limit of detection of approximately 0.04 ng/mL. Predictably, patients requiring higher IT infusion dose rates were more likely to have quantifiable ziconotide levels in plasma. Plasma ziconotide levels, when detectable, remain constant after many months of IT PRIALT infusion in patients followed for up to 9 months.

Metabolism
Ziconotide is cleaved by endopeptidases and exopeptidases at multiple sites on the peptide. Following passage from the CSF into the systemic circulation during continuous IT administration, ziconotide is expected to be susceptible to proteolytic cleavage by various ubiquitous peptidases/proteases present in most organs (e.g., kidney, liver, ~~lung muscle~~, lung, muscle, etc.), and thus readily degraded to peptide fragments and their individual constituent free amino acids. Human and animal CSF and blood exhibit minimal hydrolytic activity toward ziconotide *in vitro*. The biological activity of the various expected proteolytic degradation products of ziconotide has not been assessed.

Elimination
Minimal amounts of ziconotide (<1%) were recovered in human urine following IV infusion. The terminal half-life of ziconotide in CSF after an IT administration was around 4.6 hours (~~range 2.9-6.5~~ range 2.9-6.5 hours). Mean CSF clearance (CL) of ziconotide approximates adult human CSF turnover rate (0.3–0.4 mL/min).

CLINICAL TRIALS: The following minor changes were made

The safety and efficacy of IT PRIALT in the management of severe chronic pain were studied in three double-blind, placebo-controlled, multicenter studies in a total of 457 patients (268 PRIALT, 189 placebo) using two different titration schedules. The slow titration schedule tested dose increases ~~2-3~~ 2-3 times per week with a maximum dose of 19.2 mcg/day (0.8 mcg/hr) at 21 days. The fast titration schedule used daily increases up to a maximum dose of 57.6 mcg/day (2.4 mcg/hr) in ~~5-6~~ 5-6 days. The safety in chronic use was studied in four additional open-label, ~~long-term~~ long-term studies in 977 patients.

A randomized, double-blind, placebo-controlled study was conducted at 39 centers to evaluate the efficacy of IT PRIALT administered using a slow titration schedule in 220 patients with severe chronic pain. Patients were randomized 1:1 between PRIALT (112 patients) and placebo (108 patients). At baseline, 97% of these patients reported that their pain was refractory to treatment including IT morphine, IT bupivacaine (an off-label use for this drug), and/or IT clonidine (an off-label use for this drug) in addition to their systemic analgesics and adjunctive therapy. All IT medications were discontinued over a one to three week period, and patients were maintained on a stable regimen of non-IT analgesics, including opiates, for at least 7 days prior to randomization. This period was successfully completed by 93% of the patients screened. Dosing with PRIALT was started at 2.4 mcg/day (0.1 mcg/hr) and the dose could be increased by 2.4 mcg/day (0.1 mcg/hr) two to three times/week (minimum titration interval 24 hours) to a maximum dose of 19.2 mcg/day (0.8 mcg/hr). The final mean dose at the end of the trial at 21 days was 6.9 mcg/day (0.29 mcg/hr).

Using a 100 mm Visual Analog Scale of Pain Intensity (VASPI) where ~~100 mm = worst~~ 100 mm=worst possible pain, mean baseline pain scores were 81 in both the PRIALT and placebo groups. The primary efficacy variable was the mean percent change in the VASPI score from baseline to day 21. In the intent-to-treat (ITT) efficacy analysis, there was a statistically significant difference between groups in the mean percent change in VASPI score from baseline with the PRIALT group having a 12% mean improvement at Week 3 compared to a 5% mean improvement in the placebo group (p=0.04). The 95% confidence interval for the treatment difference (~~PRIALT – placebo~~ PRIALT–placebo) was 0.4%, 13%.

The effect of IT PRIALT on pain was variable over the time period of treatment for some patients. Some patients had a reduction in VASPI in the first or second week, but did not maintain pain relief by the end of the third week. Other patients, who did not exhibit a reduction in VASPI early in treatment, did have a reduction in VASPI by the third week.

Patients exhibited various degrees of improvement in pain after three weeks of treatment compared with baseline pain assessment. Figure 1 depicts the fraction of patients by their degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 30%, are also included at

every level of improvement below 30%. Patients who did not have a VASPI score recorded at Week 3 (Study days 17-23, inclusive) were assigned 0% improvement. The improvement in the proportion of "responders," defined as having a ≥30% improvement from baseline in VASPI, was 16% in the PRIALT group compared to 12% in the placebo group, for a net difference of 4%. The use of non-IT opioids decreased by 24% in the PRIALT group and by 17% in the placebo group.

Figure 1: Patients Achieving Various Levels of Pain Relief ~~From~~ from Baseline to Week 3

INDICATIONS AND USAGE: The following minor change was made.

PRIALT (ziconotide intrathecal infusion) is indicated for the management of severe chronic pain in patients for whom intrathecal (IT) therapy is warranted, and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies, or IT morphine.

CONTRAINDICATIONS: The following minor change was made.

PRIALT is contraindicated in patients with a known ~~hyper-sensitivity~~ hypersensitivity to ziconotide or any of its formulation components and in patients with any other concomitant treatment or medical condition that would render IT administration hazardous.

WARNINGS: No changes noted.

WITHDRAWAL FROM OPIATES: No changes noted.

PRECAUTIONS: The following minor changes were made.

COGNITIVE AND NEUROPSYCHIATRIC ADVERSE EVENTS
Use of PRIALT has been associated with CNS-related adverse events, including psychiatric symptoms, cognitive impairment, and decreased alertness/unresponsiveness. For the 1254 patients treated, the following cognitive adverse event rates were reported: confusion (33%), memory impairment (22%), speech disorder (14%), aphasia (12%), thinking abnormal (8%), and amnesia (1%). Cognitive impairment may appear gradually after several weeks of treatment. The PRIALT dose should be reduced or discontinued if signs or symptoms of cognitive impairment develop, but other contributing causes should also be considered. The various cognitive effects of PRIALT are generally reversible within 2 weeks after drug discontinuation. The medians for time to reversal of the individual cognitive effects ranged from 3 to 15 days. The elderly – 65 years of age) are at higher risk for confusion. (~~See~~ see GERIATRIC USE.)

In placebo-controlled trials, there was a higher incidence of suicide, suicide attempts, and suicide ideations in PRIALT-treated patients (N=3) than in the placebo group (N=1). The incidence was 0.10/patient year for placebo patients and 0.27/patient year for PRIALT patients.

Events of acute psychiatric disturbances such as hallucinations (12%), paranoid reactions (3%), hostility (2%), delirium (2%), psychosis (1%), and manic reactions (0.4%) have been reported in patients treated with PRIALT. Patients with pretreatment psychiatric disorders may be at an increased risk. PRIALT may cause or worsen depression with the risk of suicide in susceptible patients. If appropriate, management of psychiatric complications should include discontinuation of PRIALT, treatment with psychotherapeutic agents if appropriate, and/or short-term hospitalization. Before drug is ~~re-initiated~~ reinitiated, careful evaluation must be performed on an individual basis.

REDUCED LEVEL OF CONSCIOUSNESS
Patients have become unresponsive or stuporous while receiving PRIALT. The incidence of unresponsiveness or stupor in clinical trials was 2%. During these episodes, the patient sometimes appears to be conscious and breathing is not depressed. If reduced levels of consciousness occur, PRIALT should be discontinued until the event resolves, and other etiologies (e.g., meningitis) should be considered. There is no known pharmacologic antagonist for this effect. Patients taking concomitant antiepileptics, neuroleptics, sedatives, or diuretics may be at higher risk of depressed levels of consciousness. If altered consciousness occurs, other ~~CNS depressant~~ CNS-depressant drugs should also be discontinued as clinically appropriate.

INFORMATION FOR PATIENTS: No changes noted

LABORATORY TESTS: The following minor change was made.

In clinical studies (mostly open label), up to 40% of patients had serum creatine kinase (CK) levels above the upper limit of normal, and 11% had CK levels that were ~~≥3 times~~ 3 times the upper limit of normal (see Elevation of Serum Creatine Kinase). Most cases of CK elevation were not associated with muscle weakness, however one case of myopathy with EMG findings, and two cases of acute renal failure associated with rhabdomyolysis and extreme CK elevations (17,000–27,000 IU/L) were reported.

DRUG INTERACTIONS: The following change was made.

Formal PK drug-drug interaction studies have not been performed with PRIALT. As ziconotide is a peptide, it is expected to be completely degraded by endopeptidases and exopeptidases (Phase I hydrolytic enzymes) widely located throughout the body, and not by other Phase I biotransformation processes (including the cytochrome P450 system) or by Phase II conjugation reactions. Thus, IT administration, low plasma ziconotide concentrations, and metabolism by

ubiquitous peptidases make metabolic interactions of other drugs with ziconotide unlikely. Further, as ziconotide is not highly bound in plasma (approximately 50%) and has low plasma exposure following IT administration, clinically relevant plasma protein displacement reactions involving ziconotide and co-administered medications are unlikely.

Interaction with CNS Depressants
Almost all patients in the PRIALT clinical trials received concomitant non-IT medication. Of the 1254 patients treated, most received several concomitant drugs, including antidepressants (66%), anxiolytics (52%), antiepileptics (47%), neuroleptics (46%), and sedatives (34%). The use of drugs with ~~CNS depressant~~ CNS-depressant activities may be associated with an increased incidence of CNS adverse events such as dizziness and confusion (see PRECAUTIONS).

Pregnancy
Pregnancy Category C:
Ziconotide was embryolethal in rats when given as a continuous IV infusion during the major period of organogenesis as evidenced by significant increases in post-implantation loss because of an absence or a reduced number of live fetuses. Estimated exposure for embryolethality in the rat was approximately 700-fold above the expected exposure resulting from the maximum recommended human daily intrathecal (IT) dose of 0.8 mcg/hr (19.2 mcg/day). Ziconotide was not teratogenic in female rats when given as a continuous IV infusion at doses up to 30 mg/kg/day or in female rabbits up to 5 mg/kg/day during the major period of organ development. Estimated exposures in the female rat and rabbit were approximately 26,000-fold and 940-fold higher than the expected exposure resulting from the maximum recommended human daily intrathecal (IT) dose of 0.8 mcg/hr (19.2 mcg/day) based on plasma exposure. Maternal toxicity in the rat and rabbit, as evidenced by decreased body weight gain and food consumption, was present at all dose levels. Maternal toxicity in the rat led to reduced fetal weights and transient, delayed ossification of the pubic bones at doses ≥15 mg/kg/day, which is approximately 8900-fold higher than the expected exposure resulting from the maximum recommended human daily IT dose of 0.8 mcg/hr (19.2 mcg/day) based on plasma exposure. The no observable adverse effect level (NOAEL) for embryo-fetal development in rats was 0.5 mg/kg/day and in rabbits was 5 mg/kg/day. Estimated NOAEL exposures in the rat and rabbit were approximately 400-fold and 940-fold higher than the expected exposure resulting from the maximum recommended human daily IT dose of 0.8 mcg/hr (19.2 mcg/day) based on plasma exposure.

In a pre- and post-natal study in rats, ziconotide given as a continuous IV infusion did not affect pup development or reproductive performance up to a dose of 10 mg/kg/day, which is approximately 3800-fold higher than the expected exposure resulting from the maximum recommended human daily intrathecal (IT) dose of 0.8 mcg/hr (19.2 mcg/day) based on plasma exposure. Maternal toxicity, as evidenced by clinical observations, and decreases in body weight gain and food consumption were observed at all doses.

ADVERSE REACTIONS: The following minor changes were made.

The most frequently reported adverse events (≥25%) in the 1254 patients (662 patient years) in clinical trials were dizziness, nausea, confusion, headache, somnolence, nystagmus, asthenia, and pain. Serious adverse events and discontinuation of PRIALT for adverse events are less frequent when the drug is slowly titrated over 21 days~~,~~ than with a faster titration schedule. (~~See~~ see CLINICAL TRIALS and DOSAGE and ADMINISTRATION.)

~~Table 2. Incidence of Treatment-Emergent Adverse Events in Slow Titration Placebo-Controlled Trial by Percent (Events That Occurred in ≥5% of patients and more commonly with PRIALT than with placebo)~~
Table 2. Incidence of Treatment-Emergent Adverse Events in Slow Titration Placebo-Controlled Trial by Percent (Events That Occurred in ≥5% of Patients and More Commonly with PRIALT than with Placebo)

BODY AS A WHOLE: abdominal pain, accidental injury, asthenia, back pain, catheter complication, catheter site pain, cellulitis, chest pain, chills, fever, flu syndrome, headache, infection, malaise, neck pain, neck rigidity, pain, pump site complication, pump site mass, pump site pain, viral infection. CARDIOVASCULAR SYSTEM: hypertension, hypotension, postural hypotension, syncope, tachycardia, vasodilation. DIGESTIVE SYSTEM: anorexia, constipation, diarrhea, dyspepsia, gastrointestinal disorder, nausea, nausea and vomiting, vomiting. HEMIC AND LYMPHATIC SYSTEM: anemia, ecchymosis. METABOLIC AND NUTRITIONAL DISORDER: ~~creatinine~~ creatine phosphokinase increased, dehydration, edema, hypokalemia, peripheral edema, weight loss. MUSCULOSKELETAL SYSTEM: arthralgia, arthritis, leg cramps, myalgia, myasthenia. NERVOUS SYSTEM: abnormal dreams, abnormal gait, agitation, anxiety, aphasia, ataxia, cerebrospinal fluid abnormal, confusion, depression, difficulty concentrating, dizziness, dry mouth, dysesthesia, emotional lability, hostility, hyperesthesia, hypertonia, incoordination, insomnia, memory impairment, mental slowing, meningitis, nervousness, neuralgia, nystagmus, paranoid reaction, paresthesia, reflexes decreased, somnolence, speech disorder, stupor, thinking abnormal, tremor, twitching, vertigo. RESPIRATORY SYSTEM: bronchitis, cough increased, dyspnea, lung disorder, pharyngitis, pneumonia, rhinitis, sinusitis. SKIN AND APPENDAGES: cutaneous surgical complication, dry skin, pruritus, rash, skin disorder, sweating. SPECIAL SENSES: abnormal vision, diplopia, photophobia, taste perversion, tinnitus. UROGENITAL SYSTEM: dysuria, urinary incontinence, urinary retention, urinary tract infection, urination impaired.

OVERDOSAGE: The following minor changes were made.

The maximum recommended IT PRIALT dose is 19.2 mcg/day. The maximum IT dose of PRIALT in clinical trials was 912 mcg/day. In some patients who received IT doses greater than the maximum recommended dose, exaggerated pharmacological effects (e.g., ataxia, nystagmus, dizziness, stupor, unresponsiveness, spinal myoclonus, confusion, sedation, hypotension, word-finding difficulties, garbled speech, nausea, and vomiting) were observed. There was no indication of respiratory depression. Overdoses may occur due to pump programming errors or incorrect drug concentration preparations. In these cases, patients were observed and ziconotide was either temporarily discontinued or permanently withdrawn. Most patients recovered within 24 hours after withdrawal of drug. In the event of an IT overdose, elimination of ziconotide from CSF would be expected to remain constant ~~(CSF $t_{½}$ = 4.6 hours)~~ (CSF $t_{½}$ = 4.6 hours). Therefore, within 24 hours of stopping therapy, the ziconotide CSF concentration should be less than 5% of peak levels.

There is no known antidote to ziconotide. General medical supportive measures should be administered to patients who receive an overdose until the exaggerated pharmacological effects of the drug have resolved. Treatment for an overdose is hospitalization, when needed, and ~~symptom related~~ symptom-related supportive care. Ziconotide does not bind to opiate receptors and its pharmacological effects are not blocked by opioid antagonists.

DOSAGE AND ADMINISTRATION: The following minor changes were made.

IT PRIALT should be initiated at no more than 2.4 mcg/day (0.1 mcg/hr) and titrated to patient response. Doses may be titrated upward by up to 2.4 mcg/day (0.1 mcg/hr) at intervals of no more than ~~2-3 times~~ 2-3 times per week, up to a recommended maximum of 19.2 mcg/day (0.8 mcg/hr) by Day 21. Dose increases in increments of less than 2.4 mcg/day (0.1 mcg/hr) and increases in dose less frequently than ~~2-3 times~~ 2-3 times per week may be used. For each dose titration, assess the dosing requirements and adjust the pump infusion flow rate as required to achieve the new dosing. Controlled studies of pain relief have not been conducted for longer than 3 weeks duration, although 977 patients have been treated with IT PRIALT in long-term open-label trials.

The dose of IT PRIALT should be adjusted according to the patient's severity of pain, their response to therapy, and the occurrence of adverse events. The effective dose of PRIALT for analgesia is variable. The average dose level at the end of the 21-day titration used in the slow titration clinical trial (~~SEE~~ see CLINICAL TRIALS) was 6.9 mcg/day (0.29 mcg/hr) and the maximum dose was 19.2 mcg/day (0.8 mcg/hr) on Day 21. Due to the frequency of adverse events, 19.2 mcg/day (0.8 mcg/hr) is the maximum recommended dose.

Administration
PRIALT is used for therapy undiluted (25 mcg/mL in 20mL vial) or diluted (100 mcg/mL in 1, 2, or 5 mL vials). Diluted PRIALT is prepared with 0.9% Sodium Chloride Injection, USP (preservative free) using aseptic procedures to the desired concentration prior to placement in the microinfusion pump. The 100 mcg/mL formulation may be administered undiluted once an appropriate dose has been established. SALINE SOLUTIONS CONTAINING PRESERVATIVES ARE NOT APPROPRIATE FOR IT DRUG ADMINISTRATION AND SHOULD NOT BE USED. Refrigerate but do not freeze all PRIALT solutions after preparation and begin infusion within 24 hours. Discard any PRIALT solution with observed particulate matter or discoloration and any unused portion left in the vial.

Medtronic SynchroMed EL or SynchroMed II Infusion System (~~SEE~~ see PRECAUTIONS-Meningitis and Other Infections)
Refer to the manufacturer's manuals for specific instructions and precautions for performing a reservoir rinse, initial filling, refilling the reservoir, and programming.

Cadd Micro (~~See~~ see PRECAUTIONS-Meningitis and Other Infections).

HOW SUPPLIED: No changes noted.

STORAGE: The following minor changes were made.

Distributed by:
Elan Pharmaceuticals, Inc.
San Diego, CA 92121

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~~(Rx Only Symbol)~~ (ELAN Logo)
~~6000323~~ 6001451 ~~Rev. 12/04~~ Rev. 2/05

RECOMMENDATIONS

An approval letter should be sent to the Sponsor.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sara Stradley
5/26/05 11:48:36 AM
CSO

Lester Schultheis
5/26/05 11:59:32 AM
MEDICAL OFFICER
I concurr with the review by Ms. Stradley

Parinda Jani
5/26/05 03:57:19 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-060/S-001

CBE-30/CBE-0 SUPPLEMENT

Elan Pharmaceuticals, Inc.
7475 Lusk Blvd.
San Diego, CA 92121

Attention: Mark Brunswick, PhD
Interim Head, US Regulatory Affairs

Dear Dr. Brunswick:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Prialt (ziconotide intrathecal infusion)

NDA Number: 21-060

Supplement number: S-001

Date of supplement: April 15, 2005

Date of receipt: April 18, 2005

This supplemental application, submitted as "Supplement - Changes Being Effected" proposes minor editorial changes to the package insert.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 17, 2005 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 18, 2005.

Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170
Attention: Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7430

Sincerely,

{See appended electronic signature page}

Sara E. Stradley
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sara Stradley
4/22/05 09:39:07 AM