PRIALT (ziconotide **intrathecal infusion**)

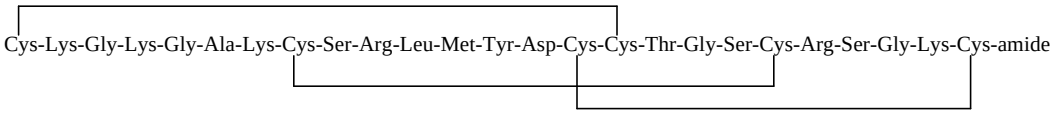
For use only in the Medtronic SynchroMed® EL, SynchroMed® II Infusion System and Simms Deltec Cadd Micro® External Microinfusion Device and Catheter

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 in 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 (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	30460 ± 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 0.1–7.0 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).

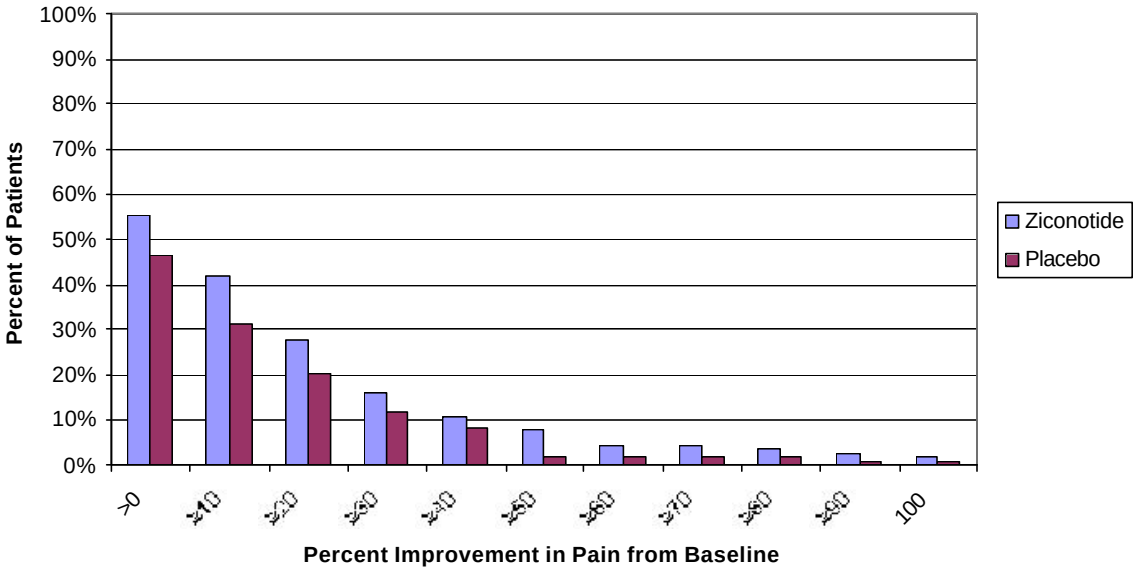
Using a 100 mm Visual Analog Scale of Pain Intensity (VASPI) where 100 mm = worst possible pain, mean baseline pain scores were 81 in both the PRIALT and placebo groups. The primary efficacy variable was the mean percent change in the VASPI score from baseline to day 21. In the intent-to-treat (ITT) 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 hyper-sensitivity 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 re-initiated, 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: creatinine 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

Simms Deltec Cadd Micro External Microinfusion Device and Catheter (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

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SynchroMed® EL and SynchroMed® II are registered trademarks of Medtronic, Inc.

Simms Deltec Cadd Micro® is a registered trademark of Ardus Medical, Inc.

(Rx Only Symbol) (ELAN Logo)

6000323 Rev. 12/04

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*BAR CODES ARE FOR POSITION ONLY

Elan Pharmaceutical Version 076A
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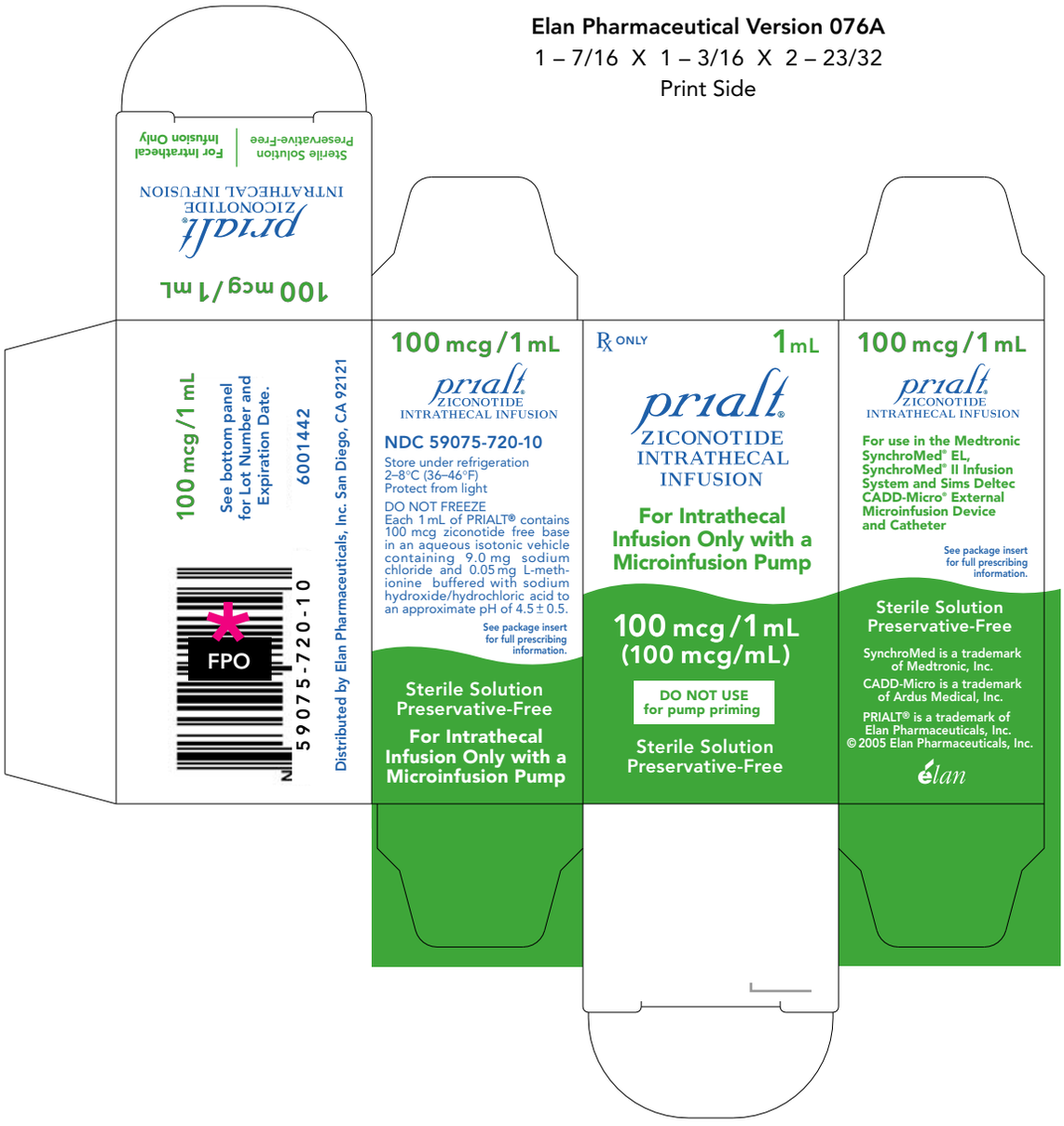
Print Side



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*BAR CODES ARE FOR POSITION ONLY

Vial Label 1.75" x .63"

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Package Colors

Blue PMS 285
Brown PMS 154
Barcode Imprint Black

*ALL BARCODES ARE FOR POSITION ONLY

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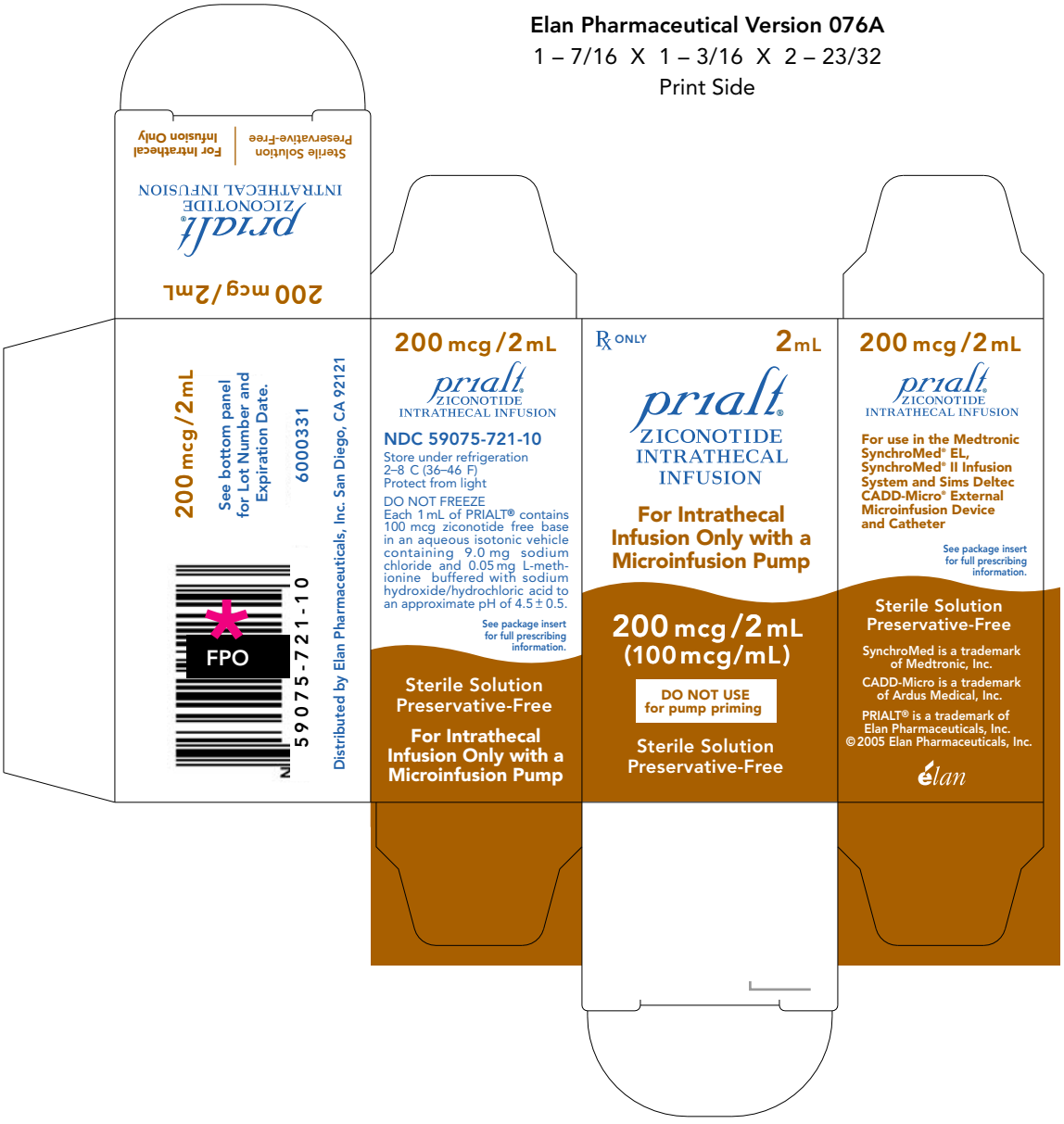

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*ALL BARCODES ARE FOR POSITION ONLY

Vial Label 1.75" x .63"

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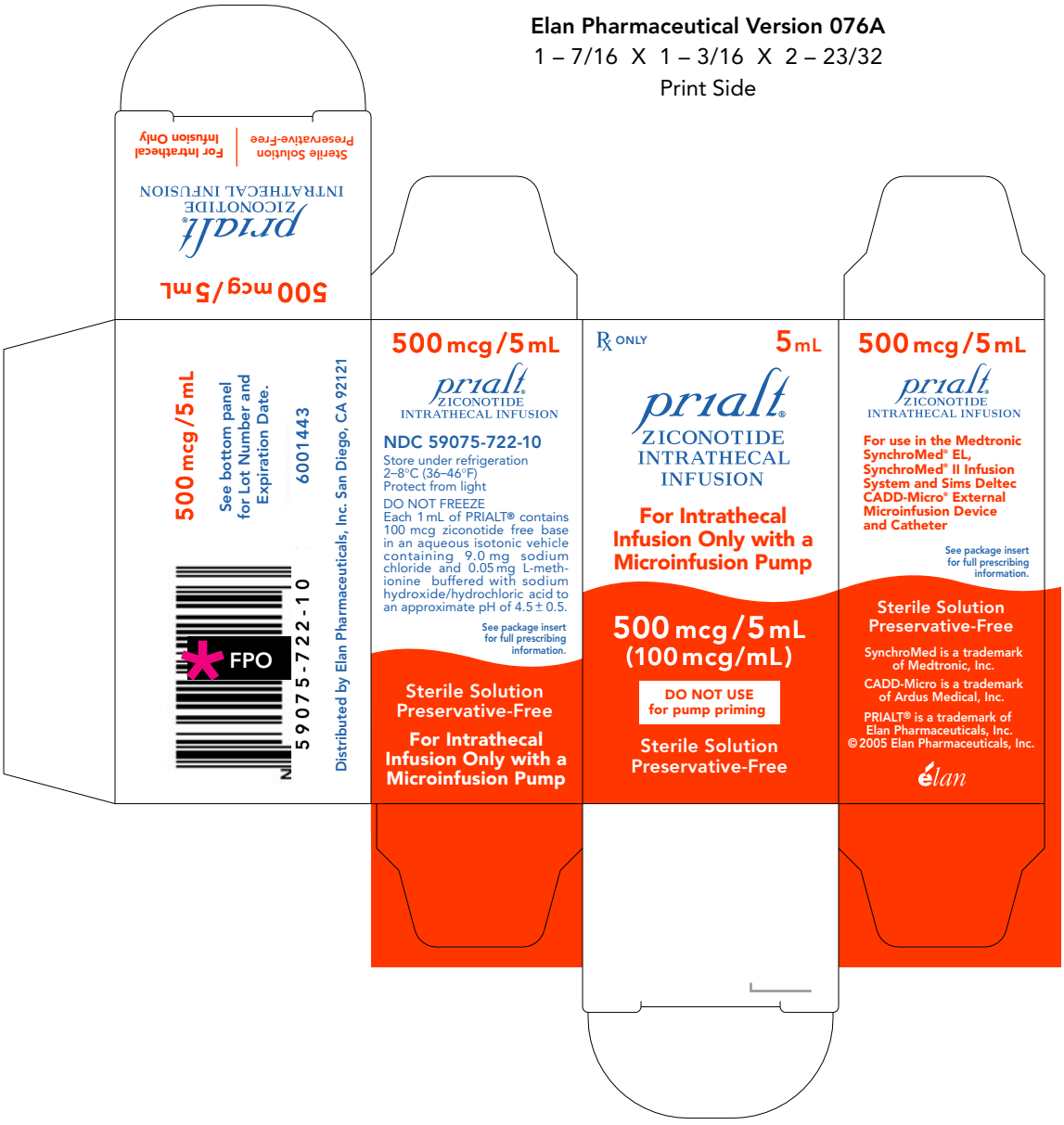

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*BAR CODES ARE FOR POSITION ONLY

Vial Label 2.25" x .75"

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*BAR CODES ARE FOR POSITION ONLY

Elan Pharmaceutical Version 076A
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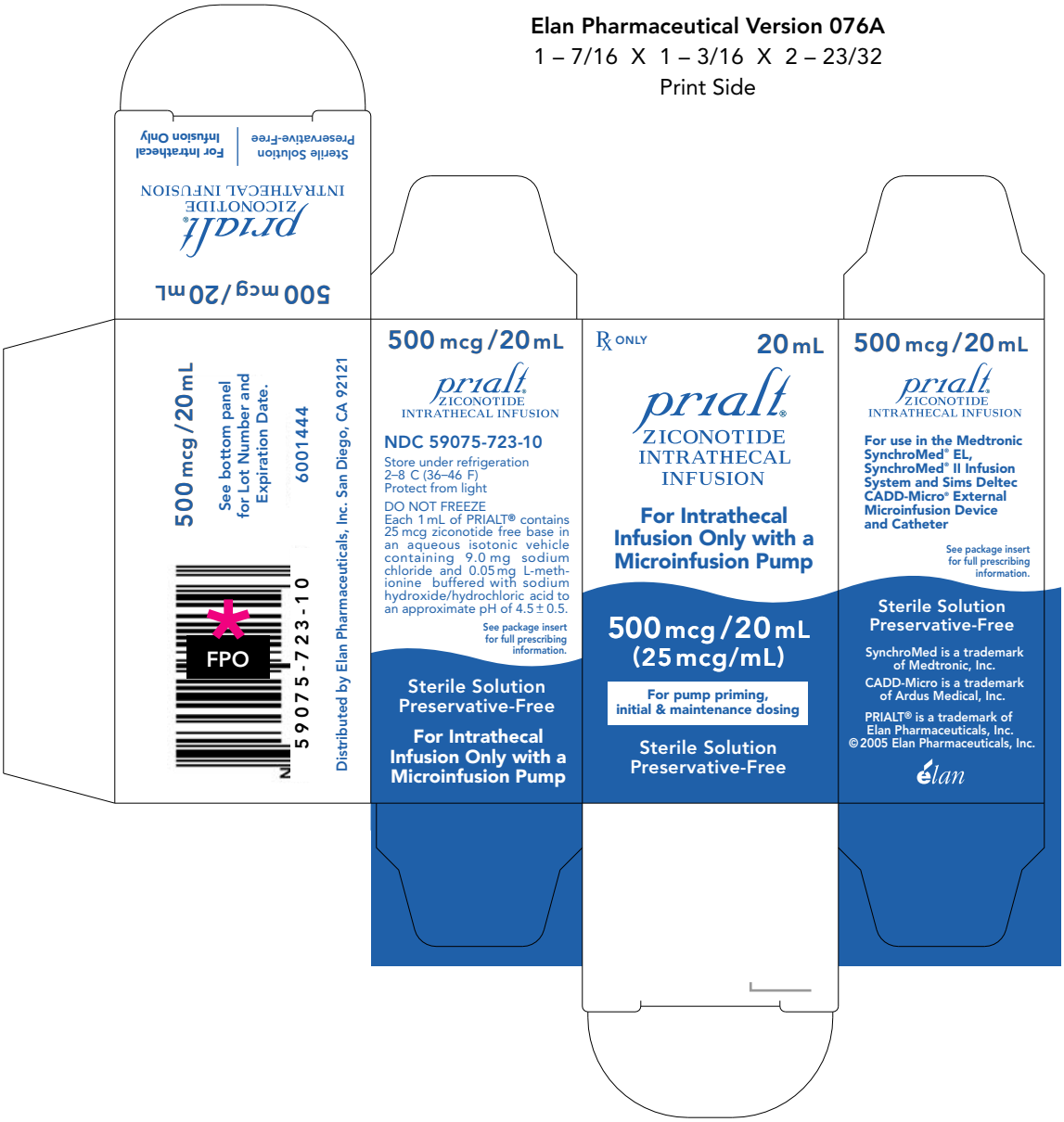

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*BAR CODES ARE FOR POSITION ONLY

Vial Label 3.25" x1.18"

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