1 SCIENTIFIC DISCUSSION

1.1 Introduction

Prialt is indicated for the treatment of severe, chronic pain in patients who require intrathecal (IT) analgesia. Dosing of ziconotide should be initiated at 2.4 μg/day and titrated on an individual patient basis with a minimal interval between dose increases of 24 hours and a recommended interval, for safety reasons of 48 hours or more, up to a maximum dose of 21.6 μg/day.

Treatment of protracted and resistant severe pain remains a difficult challenge for the physician. For example, the administration of strong opiates can lead to respiratory depression, in particular in patients with COPD or other respiratory diseases. Spinal/intrathecal (IT) opioid administration (neuraxial analgesia) has been used with the assumption that it was possible to dissociate the desirable analgesic effects of opioids from their adverse effects. Morphine is traditionally viewed as the gold standard neuraxial analgesic. It is the IT analgesic most frequently for the management of severe chronic pain. While there are no safety or efficacy data available from randomised, controlled clinical trials of IT morphine, numerous case reports, retrospective studies and a smaller number of prospective studies nonetheless suggest the potential for considerable pain relief with IT morphine. However, reported failure rates with IT morphine alone range from 23% to 80% and after long-term IT morphine injection, the incidence of side effects is relatively high (e.g. constipation, urinary retention, nausea, impotence, vomiting, nightmares, pruritus).

Ziconotide is a synthetic analogue of a 25-amino acid ω-conopeptide, MVIIA, found in the venom of the *Conus magus* marine snail. It is a N-type calcium channel blocker (NCCB). Voltage-sensitive calcium channel (VSCC) conduction plays a major role in the transmission of pain. The N-type VSCC's are found in high concentrations in the dorsal root ganglion cells responsible for the spinal processing of pain. Ziconotide selectively and reversibly binds to and blocks these channels without interacting with other ion channels or cholinergic, monoaminergic or μ- and δ-opioid receptors. Ziconotide thus inhibits the spinal signalling of pain.

Ziconitide has been developed for use as an intrathecal analgesic for the treatment of chronic pain in patients requiring IT analgesia. The product is formulated as a solution for infusion (100 μg/ml) and must be administered as a continuous infusion via an intrathecal catheter, using an external or internally implemented mechanical infusion pump.

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

Prialt was designated as an orphan medicinal product on 9 July 2001 in the following indication: treatment of chronic pain requiring intraspinal analgesia.

This is a stand alone application for a Marketing Authorisation (MA) according to Article 8.3 (i) of the Council Regulation EC No. 2309/93.

1.2 Quality aspects

Introduction

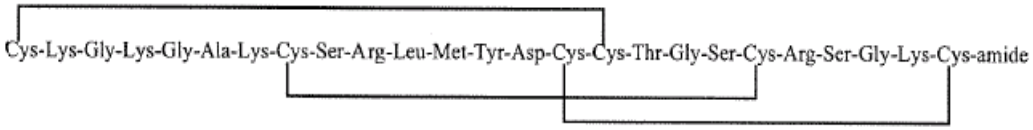
Prialt is a sterile, preservative-free and isotonic solution for intrathecal infusion, which is presented as 1ml, 2ml and 5 ml single dose vials containing 100 μg/ml of ziconotide (as acetate salt) corresponding to 100 μg, 200 μg and 500 μg of ziconotide (as acetate salt) per vial, which can be diluted prior to administration using normal saline infusion (0.9% sodium choride), if required.

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

The primary container consists in a single use Type I glass vials with butyl rubber stoppers coated with fluorinated polymer.
Prialt is intended for intrathecal delivery using either an external or an implanted pump.

Active Substance

Ziconotide is the synthetic analogue of an ω-conopeptide, MVIIA, found in the venom of the Conus magus marine snail. It consists of a 25-amino acid peptide with 3 cysteine disulphide bridges.



The soluble acetate form is used in the product of this application. Information on ziconotide acetate has been supplied in the form of an EDMF.

The peptide ziconotide is a single optical isomer of known absolute configuration. Ziconotide contains 21 chiral carbon atoms. The drug substance, however, is synthesised from protected amino acids with known Levo configurations and the synthetic methods are chosen to preserve the stereochemistry of the starting materials and intermediates.
Ziconotide is a highly hygroscopic, anhydrous material, which appears to pick up moisture continuously under increasing relative humidity conditions. It is a pH, heat and moisture sensitive and subject to oxidative degradation. The drug substance is therefore stored at –20°C in the presence of desiccant, and all manipulations during manufacturing are controlled under nitrogen atmosphere to help to minimise oxidative degradation. The stability of ziconotide in aqueous solution was found to be pH dependant.

- Manufacture

The substance is prepared by Solid Phase Peptide Synthesis (SPPS), followed by cleavage from the resin, conversion to the acetate salt and purification.

Adequate In-Process Controls are applied during the synthesis of ziconotide drug substance. Control methods for intermediate products, starting materials and reagents, have been presented.

Batch analysis data of three batches from the manufacturer are presented and confirm consistency and uniformity of the manufacturing process.

- Specification

The active substance specifications for ziconotide are relevant for a substance to be used in intrathecal as a route of administration and include tests for appearance, identification tests(specific rotation, solubility, amino acid analysis, molecular weight), purity (peptide purity, related substances, residual solvents, heavy metals, endotoxins), assay (peptide content, acetate, water, mass balance and binding assay).

Batch analysis data confirm satisfactory compliance and uniformity with the proposed specification.

- Stability

All the active substance stability studies were carried out on batches made at the proposed site of manufacture, using the proposed manufacturing process and stored in packs representative of the proposed marketing pack. The shelf-life specification is the same as at release and samples were tested for all parameters liable to change during storage.

Stability studies under long term and accelerate conditions were performed on a number of batches of ziconotide drug substance . Samples were filled under a nitrogen atmosphere and were stored for 36 months at -20°C, 3 months at 5±3°C and 3 months at 25°C/60%RH.

The results justify a retest period of 36 months when stored at –20°C in the proposed packaging.

Finished Product

- Pharmaceutical Development

The product development has taken into consideration the physicochemical properties of the formulation (active substance, excipients, tonicity), compatibility of product with infusion pumps and administration catheters, and suitability of shelf life.

The dosage form selected is justified by the properties of the peptide active substance. All components of the formulation have a justifiable pharmaceutical function and are used at concentrations that have been optimised for the dosage form (particularly with regard to the intrathecal route), its dilution if required and its method of administration.

The stability of ziconotide in aqueous solution was found to be pH dependant, as a consequence, formulation studies were carried out in the pH range of 3 - 5. Hydrochloric acid and sodium hydroxide have been used as pH adjusters.

The diluent of choice is normal saline infusion (0.9% sodium choride).

The choice of sterilisation by filtration was dictated by the peptidic nature of ziconotide, which is sensitive to heat.

The container (Type I glass vials) and closure system are standard for this kind of products and comply with the Ph Eur requirements. Clear glass was selected to facilitate inspection for visible particulate matter. Stability results demonstrate that the product has sufficient stability to light to allow this. The vials are treated with ammonium sulphate to minimise leaching from the glass and so facilitate pH stability in the formulation.

All formulation excipients and nitrogen processing aid comply with Ph. Eur. specifications.

Intrathecal delivery is by means of CE marked external or implantable delivery pumps. Compatibility studies of the product with pumps and catheters are performed and the compatibility is demonstrated.
The clinical formulation used in the clinical trials is identical with one proposed for marketing.

- Manufacture of the Product

Manufacturing consists of preparation of the bulk solution, followed by double sterile filtration and filling in the vials.

Validation studies have been carried out on the sterilisation/depyrogenation of the vials and steam sterilisation of stoppers, filters and aseptic equipment in three production-scale batches and is satisfactory**.** The in process controls are adequate for this pharmaceutical form.

- Product Specification

The drug product specifications include appropriatetests for appearance, assay of the drug substance, (RP-HPLC)and antioxidant, identity (RP-HPLC, UV), purity(RP-HPLC), pH, sterility (Eur Ph), bacterial endotoxins, particulate matter and fill volume.

Batch analysis results from 3 batchesconfirm consistency and uniformity of manufacture and indicate that the process is under control. Impurity limits in the specification are justified by toxicology studies

- Stability of the Product

Stability data are provided on 6 full-scale batches of product manufactured at the proposed manufacturing site. Samples were stored in the proposed marketing packs at 2-8°C, 25°C/160%RH, 30°C and 40°C/75%RH.

Samples were tested for all parameters liable to change during storage. Tests and assays methods used are satisfactorily described and validated.
The photostability of Prialt has also been investigated. The results show minimal degradation under light exposure conditions, and in practice will be adequately protected by the carton.

In use stability studies of the product are performed in the pump delivery system (either external or implantable pump) and catheters. Chemical and biological stability is established for the product during its use.

As a conclusion from the stability studies, the results indicate satisfactory stability and support the shelf life and conditions of used stated in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The intrathecal route poses restrictions on the formulation, which should be minimal, that is to say no extraneous excipients should be present. In this case, the presence of methionine as a stabilising agent is necessary, and since it is naturally-occurring amino acid this has no safety impact intrathecally.

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

1.3 Non-clinical aspects

Introduction

Calcium entry into presynaptic termini is a prerequisite for neurotransmitter release in vertebrate nervous systems. The ω-conotoxins have been found to selectively antagonise N-type voltage sensitive calcium channels (N-VSCCs), which are primarily found in neural tissue. N-VSCCs facilitate the calcium influx necessary for neurotransmitter release. The therapeutic potential of ziconotide is related to its ability to block N-type VSCCs. In the spinal cord, N-VSCC blockade inhibits the release of neurotransmitters involved in pain signalling.

Nonclinical studies with ziconotide were conducted inmultiple species. Long-term studies presented special technical difficulties related to the intrathrecal mode of delivery, the dog was found to be the best model for IT administration, and a 42-day study was the longest conducted by this proposed clinical route.

Most, but not all, of the toxicology studies contained in this application were performed in accordance with GLP (see below).

Pharmacology

- Primary pharmacodynamics (*in vitro/in vivo*)

The primary analgesic effects of spinally administered ziconotide involves blockade of depolarisation-induced calcium influx and consequent reduction of neurotransmitter release from nociceptive afferents terminating in the superficial lamina of the dorsal horn of the spinal cord.

Ziconotide has been shown to have a high specificity for N-type voltage sensitive calcium channels (VSCCs), which are distributed throughout the nervous system where, from ^{125}I-ziconotide visualisation studies, they are seen to be at highest density in the spinal cord (especially Rexed laminae I and II of the dorsal horn). N-type VSCCc are highly associated with primary afferent fibres that contain substance P, indicating that the major spinal nociceptive signaling pathway is involved. Ziconotide is a reversible blocker of neuronal N-type VSCCs.

Conventional rodent pain models have been used to demonstrate that ziconotide is an effective, non-tolerance forming analgesic when administered either intravenously (IV), intrathecally (IT) or epidurally. Continuous IT infusion doses in the range 0.003 to 0.6µg/kg/hr produced significant analgesia in models of acute, chronic, inflammatory, postoperative and neuropathic pain. The highest dose is above the proposed human maximum of 0.034µg/kg/hr for a 70kg adult.
Continuous IT infusion of ziconotide did not lead to tolerance nor did it alter opioid-induced analgesia.

- Secondary pharmacodynamics

Ziconotide reduces inflammation induced by a number of agents in rat models when administered i.v. or by local s.c. or intra-articular injection but not following IT administration.

- Safety pharmacology

Safety pharmacology studies were not performed according to GLP principles. Nevertheless, the safety pharmacology investigations not performed in accordance with GLP were incorporated into toxicological studies that were performed according to GLP and toxicity studies supported the findings of non-GLP safety pharmacology studies.

Ziconotide had little or no adverse effect on the CNS or cardiovascular and respiratory systems or on the gastro-intestinal tract at the proposed clinical dosage.

Ziconotide elicits complex but mild and reversible motor disturbances, the most distinctive of which is dose-related shaking or tremor. However, when ziconotide is administered by IT infusion, the tremor abates as treatment progresses. Analgesia has been shown to occur in the absence of the tremorigenic effect associated with higher IT doses.

A continuous 24-hr i.v. infusion (toxicity) study of ziconotide in rats was performed that resulted in a significant decrease in mean arterial blood pressure. The blood pressure decrease was not prevented by pre-treatment with the H_1 and H_2 receptor antagonists, chlorpheniramine and famotidine, suggesting that ziconotide-induced mast cell degranulation was not the causative pharmacological mechanism inducing hypotension. In addition, concentrations of product required to stimulate histamine release and mast cell degranulation (as observed *in-vitro*) are in excess of what was used in the study.
Ziconotide probably reduces systemic blood pressure in rats by blocking sympathetic efferent activity. IT administration at supra-therapeutic levels has no appreciable effect on blood pressure or heart rate. Therapeutic IT administration of ziconotide is unlikely to elicit hypotension. Also, there is no clinical relevance of mast cell degranulation because the dose used in patients would be far lower.

The assessment of potential QT prolongation of ziconotide, has been evaluated in an *in vitro* electrophysiological study and *in vivo in non-rodents* (IV, IT and epidural) toxicology studies. Both bolus doses and continuous infusions were used and no significant effects on QT prolongation were noted, except in 1-2 animals at very high doses. Based on these non-clinical data and available clinical data, ziconotide is unlikely to cause QTc prolongation.

No animal studies on renal function have been conducted but no adverse effects were observed in the repeated dose toxicity studies at high dosage in relation to the clinical dose.

- Pharmacodynamic drug interactions

In drug interaction studies, concomitant administration of ziconotide and morphine had synergistic or additive effects depending on the pain model; no such effects occurred on cardiovascular and behavioural parameters. The clinical significance of the additive analgesic effects when ziconotide was co-administered with baclofen and clonidine is unclear.

Pharmacokinetics

A sensitive and specific RIA method has been used for quantification of ziconotide in plasma, CSF and brain.

The pharmacokinetics and metabolism of ziconotide in plasma and CSF have been determined after parenteral dosage in rats and non rodents,. In view of the proposed clinical use of the product by IT administration, the emphasis was on studies by this route and on the behaviour of the compound in the CSF.

- Absorption- Bioavailability

Ziconotide exhibits dose-proportional pharmacokinetics over the range of doses tested when administered by the i.v. route to rats and monkeys and by the IT and i.v. route to dogs. In the dog IT study, following bolus administration, ziconotide diffuses into the plasma at a slow rate with high CSF:plasma ratios (20,000:1 at 3 min, 600:1 at 8 hours). During the infusion study ziconotide was rapidly distributed through the CSF and plasma. After 48 hours the ratios of Lumbar CSF : Cisternal CSF : Plasma at steady state were1:0.01:0.001 at 1 ng/hr and 1:0.02:0.002 at 5 ng/hr. The low CSF bioavailability of i.v. administered ziconotide demonstrates the pharmacokinetic advantage of the IT route of administration.

- Distribution and metabolism

Ziconotide is rapidly distributed and/or metabolised in spinal CSF after IT administration, followed by relatively rapid mass transport of the product from the CSF into the plasma. The relative contributions of mass transport, within and outside the spinal cord, and metabolism within it, are unclear. There is certainly evidence for rapid transport into the blood and metabolism within the spinal cord is likely to have a significant role. Following entry into the blood, the compound is quickly metabolised by normal proteolytic mechanisms, eventually to its constituent amino acids; it can be assumed that these will be further metabolised or incorporated into proteins by normal processes.

In rats, dogs, monkeys and humans, the percentage of protein-bound ziconotide ranged from about 40–70% over the concentration range of 1–10,000 ng/ml. The extent of plasma protein binding of ziconotide was relatively low and not saturable over the concentration range likely to be encountered clinically. The partitioning of ziconotide into the cellular components of blood was found to be largely independent of drug concentration and was consistent among the species studied. The whole blood partitioning of ziconotide shows only marginal variation between rat, dog, monkey and humanwith Kd values ranging from 0.23–0.42.Excretion

No classical excretion data were provided. However, since after extensive proteolysis of ziconotide, the predominant products will be the free amino acids, these will be taken up by cellular carrier systems and will be subjected to normal intermediary metabolism or used as substrates for constitutive biosynthetic processes. Depending on the degree of resistance to proteolytic cleavage, one or more longer-lived fragments of the general structure could exist. These fragments would be expected to eventually be degraded to individual constituent amino acids that would be indistinguishable from other free amino acids in the amino acid pool.

Toxicology

The toxicity profile of ziconotide has been evaluated in single dose, repeated dose, reproduction toxicity, genotoxicity and immunogenicity studies. Investigations of local reactions at the IT injection

site and comparisons of effects of different formulations of the drug have also been conducted. Carcinogenic potential was initially based on a short-term *in vivo* cell transformation study.

Early studies indicated that the i.v. route did not deliver sufficient ziconotide to the CNS to be effective and thus the IT and epidural routes were explored in the majority of studies.

All the pivotal studies were stated to be performed in accordance with international standards and in compliance with GLP the main exceptions being dose-ranging studies and the majority of the pharmacokinetic analyses and the analyses of dose preparations. The assay methods themselves were satisfactorily validated.

The maximum human recommended dose (MHRD) of 0.034 µg/kg/hr (based on 2.4 µg/hr and 70 kg body weight) is used here for estimation of safety factors.

- Single dose toxicity

Acute toxicology studies in rats and non-rodents have shown that ziconotide is well tolerated at high i.v. doses and that adverse effects are attributable to exaggerated pharmacological actions of the compound (e.g. tremors and reduction in activity).

- Repeat dose toxicity (with toxicokinetics)

The toxicity profile of ziconotide was evaluated in studies by i.v. infusion of up to 14 days duration in the rat and monkey, by continuous IT infusion in the rat up to 28 days and in the dog up to 42 days duration, and by epidural infusion in the dog for up to 28 days. The proposed clinical usage of ziconotide as a chronic therapy would normally be supported by repeated dose studies of 6 months duration in a rodent and non-rodent. However, continuous IT dosage was not considered feasible by the applicant for such a duration because of the effects of inflammatory changes, consequent to the use of the indwelling spinal catheters.

High levels of systemic exposure were achieved in the i.v. studies compared with exposure in patients following IT infusion.

The principal finding in the repeated dose studies in all species was reversible CNS disturbances affecting the motor system and manifested mainly as tremors, incoordination and ataxia, which are expected from the pharmacological action of ziconotide. At the highest dose levels in studies by IT infusion in the dog, which were comparable - based upon the maximum therapeutic equivalent dose for dogs - to or up to 2.6-fold higher than the maximum human recommended dose (MHRD), these effects led to early sacrifice. The only other common finding in these studies was reduced plasma glucose; the effects were relatively minor and values generally remained within the physiological range. A similar pattern has not been observed in clinical use via the intended IT route of administration.

Whole-body fixation in the pivotal repeated dose studies has allowed good preservation of the brain and spinal cord in which there was no microscopic evidence of changes due to ziconotide. This observation supports the pharmacological basis for the clinical neurological effects.

Prolonged intraspinal catheter implantation was always associated with compression of the spinal cord and acute and chronic inflammatory changes within the spinal cord. Neurological effects produced by these lesions, in controls as well as treated animals, included altered gait in rats; decreased activity and occasional instances of mild motor effects were also observed in control animals. While the nature and extent of the catheter-induced pathological lesions and their neurological sequelae have not interfered with an accurate assessment of the toxicity potential of ziconotide, the practicality of conducting successful studies of longer duration is open to question.

- Genotoxicity *in vitro* and *in vivo*

Ziconotide was not mutagenic in bacterial reverse mutation assays (Ames test) with *S. typhimurium* strains and in mouse lymphoma forward mutation assays in the presence and absence of metabolic

activation. Ziconotide was negative in the *in vivo* mouse bone marrow micronucleus assay. These results sufficiently demonstrate ziconotide 's lack of genotoxic potential.

- Carcinogenicity

Standard carcinogenicity studies have not been performed with ziconotide. Ziconotide was tested in the Syrian Hamster Embryo (SHE) cell transformation assay in the absence of S9 for seven days. There were no statistically significant increases in transformation frequency at any ziconotide concentration.

Owing to the potential for long-term treatment of patients with Prialt, such standard carcinogenicity studies would be expected in accordance with the ICH S1A Guideline on the need for carcinogenicity studies of pharmaceuticals (CPMP/ICH/140/95). In addition, according to ICH S1B guideline on carcinogenicity (CPMP/ICH/299/95), whereas a short-term carcinogenicity assay can be taken into account as replacement assays for the 2-year mouse carcinogenicity assay, a 2-year rat carcinogenicity assay nevertheless needs to be performed as long as there is chronic systemic exposure at the clinical level.

Nevertheless, the absence of 2-year rat carcinogenicity study was accepted taking into account that:

- Ziconotide is a peptide containing amino acids that are naturally occurring in humans;
- Ziconotide was negative for genotoxic potential;
- Ziconotide was negative in the SHE cell transformation assay;
- Absence of carcinogenic potential in subchronic intrathecal exposure studies in dogs (no induction of apoptosis or cell proliferation, no potential pre-neoplasic lesions);
- It is not feasible to place and maintain IT catheters in rodents for sufficiently long periods of time;
- Clinical data show that there is almost no systemic exposure after IT administration due to fast metabolism.

Therefore, the risk of a carcinogenic potential for ziconotide is extremely low and classical carcinogenicity studies are not warranted.

- Reproductive and developmental studies

In rat fertility studies, there were no effects in males while reductions in corpora lutea, implantation sites and number of live embryos were observed in females. In a rat pre-and post-natal development study, slightly lower body weights in the F_1 offspring of dams were observed. No adverse effects on female reproduction and post-natal development in rats were seen at systemic exposures up to 2,300 times human exposures at the maximum recommended intrathecal dose.

Ziconotide was not teratogenic in rats and rabbits. Reduced foetal weights were associated with maternal toxicity at exposures > 100 times human plasma levels, with signs of transient, delayed ossification observed in rats at approximately 9,000 times human systemic exposures. Embryolethality due to post-implantation early resorptions was significantly increased in rats, but was not observed at exposures approximately 400 times human plasma levels.

- Local tolerance

In an exploratory study in rats, histopathological changes in spinal cord tissue were present in rats from all groups (vehicle control, 1, 3 and 10 µg) following daily IT bolus injections of ziconotide for 4 days. These changes, e.g., spinal cord compression, localised inflammation and periaxonal dilatation, appeared to be induced by the presence of the IT catheter. Ziconotide appeared to exert a slight effect on the inflammatory reaction, as suggested by the findings of modest differences in incidence and magnitude of histopathological changes occurring over the ten-fold dose range.

- Other toxicity studies

The antigenic potential of ziconotide for delayed type hypersensitivity and immediate hypersensitivity were assessed by skin reaction, systemic anaphylaxis (SA) and passive cutaneous anaphylactic (PCA) reaction in guinea pigs, mice or rats. Ziconotide has the potential to induce acute anaphylaxis in the guinea pig. No serum antibodies to ziconotide were detected in mice and rats injected with or without adjuvant, after repeated administration. A response in a single guinea pig in a PCA test is unlikely to indicate an antigenic potential in humans. In the guinea pig test using human serum samples, the negative result is of little relevance given the long period between analysis and the single IV dose. In addition, no elevations in ziconotide-specific IgE or IgG were observed in 58 patients following IV dosage of ziconotide for 72 hours and sampled 3 months later or in 41 patients who received IT doses for at least 3 months most of whom had an off-dose period before further challenge. The risk of immunological reactions in patients is likely to be very low.

The physical dependence potential and abuse liability of ziconotide were evaluated in a battery of *in vitro* and *in vivo* studies, in mouse and monkey. In the *in vivo* studies, the compound (administered IV) did not attenuate the discrimination of morphine withdrawal and monkeys did not maintain IV self-administration.

Some impurities are present at a level > 0.1% in drug substance or drug product. A mixture of these impurities was prepared based on the highest amount of each impurity that appears in the drug substance or product and a definitive toxicity study was conducted in Beagle dogs to qualify the safety of ziconotide impurities when administered by continuous IT infusion for 28 days. The continuous IT infusion of total ziconotide impurities produced no test article-related clinical signs. There were no treatment-related adverse changes in body weight, food consumption or clinical pathology, nor were there any gross or microscopic alterations that were attributed to treatment with ziconotide or impurities. Total impurities were qualified at a safety factor 174 times the maximum predicted human dose, demonstrating the relative inactivity of ziconotide impurities.

Ecotoxicity/environmental risk assessment

Ziconotide, as recommended, will not pose a risk to the environment because, according to the applicant, the predicted annual usage of the product is very low, ziconotide is a peptide which is fully metabolised by normal proteolytic processes, there is negligible excretion of intact ziconotide, the crude predicted concentration of ziconotide in surface water is in the order of magnitude below the action limit of 0.01 µg/l and the product does not contain any excipients which may constitute an environmental risk.

Discussion on the non-clinical aspects

Ziconotide is a high-affinity, reversible blocker of neuronal N-type voltage sensitive calcium channels (N-VSCCs) which are found in high density in the brain and dorsal horn of the spinal cord in areas receiving pain signals from the periphery. In models of chronic pain, the proposed clinical indication, significant analgesia was produced by continuous IT infusion doses in the range of the proposed clinical dose. IT ziconotide was shown to be effective in neuropathic and nociceptive pain models. Continuous IT infusion of ziconotide did not lead to tolerance nor did it alter opioid-induced analgesia. Ziconotide elicits mild and reversible motor disturbances.. Ziconotide passes up the spinal cord and into the systemic circulation but only to a limited extent. Following entry into the blood, the compound is quickly metabolised by normal proteolytic mechanisms.

Ziconotide was well tolerated following i.v. administration at dose levels, based on body weight, at least 1750-fold higher than a maximum clinical IT infusion dose of 0.034 µg/kg/hr. In common with studies by the IT and epidural routes, ziconotide produced stimulation of motor activity in the CNS, as expected from the pharmacology of the compound. These effects occurred at dosages in the region of the maximum clinical dose and quickly regressed after cessation of dosing. There were no signs of target organ toxicity and the changes seen can be attributed to the pharmacological effects of the compound. A fairly consistent finding was a slight reduction in plasma glucose even at ziconotide plasma levels as low as 2 ng/ml; a likely reason is the stress associated with the neurological effects. Hypoglycaemia due to ziconotide has not been reported in clinical trials.

Due to the limited toxicity studies (with non GLP toxicokinetics), the absence of formal carcinogenicity study, the intended long-term use and clinical concerns with regard to safety (particularly lack of local safety data: neuronal function but also effects on more distant tissues), the applicant was requested to consider the feasibility of a new non-clinical stepwise strategy designed to perform subchronic toxicity studies in a relevant animal model using the intrathecal route with an as long as possible duration, including toxicokinetics and in compliance with GLP. The following aspects were to be given special consideration when designing the studies: local histopathology, apoptosis, cell proliferation markers, potential changes in CSF composition and consequences of long-term shutdown of N-channels on normal neuronal function. The Applicant provided the results of a new 28-day continuous intrathecal infusion study of ziconotide and ziconotide impurities in Beagle dogsT The study showed that there were no drug related microscopic changes in the brain, peripheral nervous system or non-nervous system tissues. No effects were seen on apoptosis or cell proliferation in the brain or spinal cord. CSF collected predose and just prior to necropsy showed no changes in cell count or clinical chemistry parameters.

Considering the possible difficulties in conducting IT studies with longer duration, the lack of evidence of a potential for target organ toxicity at very high multiples of the human dose and the lack of toxic effects on the CNS, again at high multiples of the CSF concentration of ziconotide in humans; additional information relevant to clinical safety conducting (sub-) chronic toxicity studies in animals according to GLP principles would probably limited.

Ziconotide was negative in a battery of genotoxicity assays.

Ziconotide is not teratogenic in rats or rabbits. Embryolethality observed in reproductive and developmental studies is directly attributable to parental toxicity brought on by the very high IV doses. Since there are no clinical data on exposed pregnancies and limited data on CNS long-term exposure, ziconotide should not be used during pregnancy unless clearly necessary.

1.4 Clinical aspects

Introduction

Prialt is indicated for the treatment of severe, chronic pain in patients who require intrathecal (IT) analgesia. Prialt is for intrathecal use only. Dosing should be initiated at 2.4 µg/day and titrated on an individual patient up to a maximum dose of 21.6 µg/day.

Ziconotide selectively blocks the neuronal N-type voltage sensitive calcium channels (N-VSCC), which are responsible for the spinal processing of pain.

Clinical studies with ziconotide are summarised in the following table, starting with IT studies. The three first studies are pivotal studies.

Intrathecal Studies

Study Number	**N** (treated)	**Study Design**		**Route**	**Dose**
Controlled Intrathecal Studies					
95-001	112	Phase II/III	Placebo-controlled, safety and efficacy (chronic malignant pain)	IT	0.1 - 21 µg/hr
96-002	257	Phase II/III	Placebo-controlled, safety and efficacy (chronic non-malignant pain)	IT	0.1 - 7.0 µg/hr
301	220	Phase II/III	Placebo-controlled, safety and efficacy (Adults with severe chronic pain)	IT	0.1– 0.9 µg/h
C96-003	30	Phase II	Pilot, placebo-controlled, (acute post-op pain)	IT	0.7 - 7.0 µg/hr

Uncontrolled Intrathecal Studies					
94-004	31	Phase I/II	Pilot, open-label (chronic pain)	IT	0.3 - 300 ng/kg/hr
95-002	155	Phase III	Long-term, open-label, safety (chronic pain)	IT	0.1 - 2.4 µg/hr
C96-010	1	Phase II	Open-label, safety and efficacy (chronic non-malignant pain)	IT	0.2 - 3.4 µg/hr
C97-013	22	Phase II	Open-label, PK (chronic pain)	IT	1, 5, 7.5, 10 µg single 1 hr infusion
C97-015	1	Phase III	Long-term, open-label, safety and efficacy (chronic non-malignant pain)	IT	0.04 - 0.1 µg/hr
C98-022	644	Phase III	Long-term, open-label, safety (chronic pain)	IT	0.1 µg/hr, titration to patient response
Intravenous Studies					
93-001	40	Phase I	Low dose, placebo-controlled safety (healthy male volunteers)	IV	0.3, 1, 3.3, 10 µg/kg/24hr
93-002	56	Phase I	High dose, placebo-controlled safety (healthy male volunteers)	IV	10, 30, 60, 125, 250, 500, 1000 µg/kg/24hr
93-003	8	Phase I	Haemodynamic, pilot (hypertensive and normotensive male volunteers)	IV	0, 1, 3.33, 10 µg/kg/24hr 6 dose levels as 1 hour ramped infusion for 6 hrs
94-001	68	Phase II	Pilot (severe head injury)	IV	62.5-250 or 250-1000 µg/kg/hr 70mg/d x 3d
94-002	16	Phase II	Placebo-controlled, safety (Coronary Artery Bypass surgery)	IV	Load/Maintenance 62.5/15, 125/30, 250/60, 500/0 µg/kg/24hr
95-004	15	Phase II	Placebo-controlled, safety (Coronary Artery Bypass surgery)	IV	Load/Maintenance 15/5, 30/10, 45/15 µg/kg/hr
1009-002/003	232	Phase II/III	Placebo-controlled, safety and efficacy (severe head injury)	IV	60 mg/24hrs
Epidural Studies					
96-012	25	Phase II	Placebo-controlled, pilot (acute, post-op pain)	EPI	0.7 or 7 µg/hr
98-021	42	Phase II	PK (chronic, severe pain patients and healthy volunteers)	EPI	2, 5, 10, 20 µg single 1hr infusion
98-023	180	Phase II/III	Placebo-controlled, dose response (surgical pain)	EPI	0, 2, 7 and 20 µg/hr
98-029	5	Phase II	Open-label safety (chronic, severe pain)	EPI	0.2 µg/hr titration to patient response

The primary objectives of the clinical development programme were:

- to evaluate the safety and efficacy of IT ziconotide in randomised, double-blind, placebo-controlled trials;
- to evaluate the safety and efficacy of long-term use of ziconotide in open-label studies.

It is stated that all studies performed were conducted in compliance with US GCP. This is assumed to reflect ICH GCP requirements. A number of trial sites have already been inspected by the FDAand problems relating to blinding were noted at one site.The analysis excluding this centre still demonstrated statistically significant efficacy of ziconotide.

The applicant also later provided some data:

- on ongoing combination and open label extension studies and an open-label compassionate use study.

Pharmacokinetics

Ziconotide pharmacokinetics (PK) have been studied after administration through the IV, IT, and epidural routes. The difficulties associated with doing studies in products for IT administration include a risk of infection. As insertion of two catheters would disturb kinetics and for ethical desire to limit dural puncture, only one catheter has been used in the PK studies and this has associated limitations.

Ziconotide has been measured in the cerebrospinal fluid (CSF) and in plasma in numerous studies during the development program. The most relevant to this application is study 97-013, where ziconotide was used intrathecally.

Ziconotide CSF and plasma concentrations were determined using a radioimmunoassay (RIA). The lower limit of quantification was 0.0391 ng/ml

- Absorption

The proposed route of administration is for intrathecal use and the product will therefore be delivered directly through a specified delivery system. The bioavailability of ziconotide in CSF following IT infusion was not assessed, but would be expected to be approaching 100%.

- Distribution, Metabolism and Elimination

In Study 97-013, CSF concentrations were measured after a single 1-hour IT infusion of ziconotide (1, 5, 7.5 or 10 µg) to 22 subjects. Cmax ranged from 16 to 130 ng/mL in the CSF, but plasma zicontide concentrationswere low and almost always undetectable . This means that the drug targeting index in the CSF is very high, although it is impossible to calculate with the current data since plasma AUC is not measurable. Vd (~100 mL) is close to the total volume of CSF. CSF clearance is around 0.3 ml/min, which is close to human CSF bulk flow (0.3 to 0.4 ml/min). Clearance was generally independent of dose. Spinal uptake contributes to clearance to some extent, and certainly is required for efficacy, but is not considered to be the dominant clearance pathway due to the size and charge of ziconotide. The mean half-life of zicotonide in CSF (monoexponential decline) is 4.6 hr, which is long for a 25-amino acid peptide. It appears to be independent of dose. Ultimately, ziconotide will be eliminated through ubiquitous proteolytic enzymes. The current stage of knowledge does not allow for the precise elucidation of the proteolytic pathways of ziconotide in humans, however, ziconotide is not expected to enter hepatocytes and be metabolised by enzyme systems.

The other PK studies following IT administration used various protocols. Overall, there were only minimal plasma concentrations measured after IT administration of ziconotide, i.e. little or no plasma exposure at recommended infusion rates (0.1 – 0.9 µg/h).

- Dose proportionality and time dependencies

After 1-hour IT infusions (study 97-013), the PK of ziconotide is roughly linear over the 1- to 10-µg dose range. However in study 97-013 saturation in AUC and Cmax seemed to have occurred at doses >7.5 µg. Nevertheless, the recommended dosage is much lower (0.1 to maximum 0.9 µg/hr). Therefore the highest dosages tested in this study will generally not be used.

The interindividual variability in intrathecal concentrations appears quite high. Noting also the large inter-individual variability in CSF volume (Hogan, Anesthesiology, 1996) and the lack of a well-defined dose-concentration-response relationship, ziconotide should be titrated on an individual basis to a desired level of response to ensure efficacy and safety.

- Special populations

Patients with liver or renal impairment were not studied in a specific way and this isstated in the summary of product characteristics due to very limited experience in such population, even if, based on its metabolism, it is not expected that liver or renal impairment will influence plasma ziconotide concentrations.

The PK parameters in elderly patients and females did not appear to differ from those of young and male controls, respectively.

The data were also examined to see if there were any changes associated with weight. Based on limited data, there did not appear to be any effect of weight on CSF parameters following either epidural or IT dosing. In any case, ziconotide is to be individually titrated.

- Pharmacokinetic interaction studies

No PK interaction studies have been submitted. Nevertheless, clinical interaction studies between IT ziconotide and IT morphine or baclofenare ongoing or planned (see pharmacodynamic and clinical safety sections).

- Pharmacokinetics using human biomaterials

Ziconotide was modestly bound (53%) to human plasma proteins and the binding was independent of concentration.

- Other routes of administration

Following *IV administration* reaching steady-state plasma concentrations of 0.6 to 1.9 ng/mL, there were unacceptably high rates of hypotension, somnolence, dizziness, dry mouth and rhinitis. This pattern was explained by a strong sympathicolytic effect of ziconotide. Plasma half-life of ziconotide (1.3–1.5 h) was much shorter than in the CSF. Less than 1% of ziconotide is recovered intact in human urine following IV infusion.

Epidural administration sometimes gave high plasma levels of ziconotide; furthermore, epidural injections were clinically ineffective and this form of administration is not sought.

Pharmacodynamics

- Mechanism of action

Ziconotide is a N-type of Voltage Sensitive Calcium Channel blocker. It inhibits the voltage sensitive calcium current into primary nociceptive afferents terminating in the superficial layers of the dorsal horn of the spinal cord. In turn this inhibits their release of neurotransmitters (including Substance P) and hence the spinal signalling of pain.

- Primary and Secondary pharmacology

In Study 97-013 (IT), ziconotide exhibited a dose-response effect in analgesic terms, although the analgesic response was lower in the 10 µg dose group than in the 7.5 µg dose group, as were also the AUC and Cmax. CSF concentrations of ziconotide were moderately correlated with efficacy with IT administration. CSF pharmacokinetic parameters, AUC∞ and Cmax, were moderately well correlated with a number of analgesic parameters and overall an increasing strength of correlation was noted over the 48 hour study period. The occurrence of adverse effects also tended to show a dose-response relationship, with 3 severe adverse effects being reported in the 10 µg dose group. CSF ziconotide concentrations were highly correlated with the incidence of nervous system adverse effects. Dizziness, nausea and abnormal gait demonstrated the strongest relationships with CSF exposure.

In Study 98-021 (EPI), minimal efficacy was observed, presumably related to a median CSF bioavailability of less than 1% with a bolus dose of 2-20 µg administered epidurally over 1 hour.

In Studies 93-001 and 93-002, in which ziconotide was administered intravenously, correlations were observed between plasma ziconotide concentrations and non-nervous system adverse effects, all adverse effects, cardiovascular system adverse effects and reductions in blood pressure. Postural hypotension was consistently observed in Study 93-001 at a mean plasma concentration of ziconotide of 0.64 ng/ml, a relatively high plasma level that is nearly never reached by an IT injection.

Nervous system adverse effects were not correlated with plasma exposure following any route of administration.

Pharmacodynamic interactions

It is noted that potential interactions with morphine, fentanyl and buprenorphine have not been examined, whereas these drugs are quite likely to be co-administered with ziconotide to control intractable pain. Almost all patients involved in the clinical trials received concomitant treatment with IT ziconotide and non-IT opioids. No major respiratory or cardiovascular adverse events occurred.

IT interaction studies with morphine and baclofen are either planned or ongoing.

Clinical efficacy

- **Dose response study**

A rising dose, open label study, 94-004, to determine safety and effectiveness in chronic pain, was performed in 20 patients with chronic malignant and 11 with non malignant pain. Dosing was started at 0.3 ng/kg/hr and could be tripled at intervals of 24 to 48 hrs for up to 7 days depending on analgesic or adverse effects. The maximum dose was 300ng/kg/hr.. Whilst the mean maximal analgesic effect was a 42.7% decrease in the Visual Analogue Scale of Pain Intensity (VASPI), 94% patients experienced at least one adverse event and 32% discontinued due to an adverse event. 10 of 26 samples had detectable drug plasma levels and 7 of the 10 patients with detectable levels were experiencing adverse events when the samples were obtained. Three patients experienced postural hypotension. Some of the levels attained following the higher intrathecal doses corresponded to levels seen following intravenous administration and found to be associated with postural hypotension. Dose response analyses did not suggest that greater doses were asssociated with greater efficacy. The starting dose, dose increments and titration rate in the pilot dose finding study mean that the lowest effective dose would not have been identified. Onset of adverse effects or neurological effects such as nystagmus was used to determine attainment of maximal dose and could be considered to represent overdose rather than adequate dose.

Dose response was also considered in the main clinical studies 95-001 and 96-002. Nevertheless, it is unclear how the starting dose, dose range and up-titration interval were chosen.

See discussion on clinical efficacy.

- **Main studies**

Three pivotal placebo-controlled clinical trials were performed:
- Study 95-001: patients with chronic malignant pain (associated with cancer or AIDS) – 112 patients (72 ziconotide and 40 placebo).
- Study 96-002: patients with chronic non-malignant pain, especially neuropathic pain – 257 patients (170 ziconotide and 87 placebo).
- Another randomised, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain was submitted during the evaluation process (study 301).

The first two studies were prolonged into a long-term open-label study (95-002).

- **Analysis of studies 95-001 and 96-002**

METHODS

Study Participants

For both studies, the following key eligibility criteria were required:
- necessity of an intrathecal administration as the next pain management step;
- average pain score > 50 mm on a Visual Analogue Scale of Pain Intensity (VASPI).

Patients who demonstrated an unsatisfactory response to systemic opioid therapy or suffered from intolerable side effects induced by morphine were eligible.

Patients were randomised in a 2:1 ratio to ziconotide or placebo and received 5 or 6 days of treatment in an initial titration phase. At the end of initial titration phase, some patients crossed over according to the following pattern: in study 95-001 non-responders crossed-over to the alternate blinded treatment. In study 96-002 non-responders to ziconotide terminated from the study, while placebo non-responders crossed over to open-label ziconotide.

Treatments

In study 95-001, overall hourly infusion doses of ziconotide ranged from 0.1-21μg/hr. A number of amendments to the titration regimen were made during the study. Initially, the dose range was 5-300 ng/kg/hr with a forced up-titration until intolerable related adverse events and a 12 hourly up-titration interval. Because of PK data, the body weight-dependent dosing was first discontinued and dose range converted to 0.4-21 μg/hr. Then, upper dose limit was reduced and up-titration interval extended to 24 hours. Finally, dose range was reduced to 0.1 – 2.4 μg/hr with an up-titration until satisfactory analgesia or change in lateral gaze nystagmus or related adverse event, with possibility to extend the up-titration interval of an additional 24 hours in case onset of analgesia.

In study 96-002, overall hourly infusion doses of ziconotide ranged from 0.1-7.0 μg/hr. A number of amendments to the titration were made during the study. Initially, the dose range was 0.4-7 μg/hr with up-titration until intolerable related adverse events or satisfactory analgesia and a 24 hourly up-titration interval. The upper dose limit was then reduced to 0.4 – 3.9 μg/hr. Finally, dose range was reduced to 0.1 – 2.4 μg/hr with an up-titration until satisfactory analgesia or change in lateral gaze nystagmus or related adverse event, with possibility to extend the up-titration interval of an additional 24 hours in case onset of analgesia.

Ziconotide was formulated in an aqueous isotonic vehicle containing 100 micrograms/mL of ziconotide free base with L methionine, sodium chloride, and water USP as excipents. Placebo was identical to the active drug product except for the absence of the active substance.

Intrathecal catheters were placed in a clinically indicated position. If placement of a catheter was necessary it was placed between the intravertebral spaces L1-2, L2-3 or L3-4 and the tip was advanced to the area below the conus medullaris but was not to be advanced beyond vertebral T10 level.

Objectives

The objectives of the studies were to compare the effect of increasing intrathecally administered dose levels of ziconotide to those of placebo on chronic malignant (95-001) and non-malignant (96-002) pain and to assess the safety of increasing dose levels of ziconotide in this patient population.

Outcomes/endpoints

The primary efficacy endpoint was the percent change in VASPI (Visual Analogue Scale of Pain Intensity) score from baseline to the end of the titration phase. The VASPI scores can range from 0 to 100 mm along a horizontal line representing the intensity of pain.

Secondary endpoints were:

- Percent change in VASPI score from baseline to the end of crossover phase.
- Categorical Pain Relief Scale (CPRS) score at the end of initial titration phase.
- Change in Wisconsin Brief Pain Inventory (WBPI) subsets from baseline to the end of the initial titration phase.
- Change in opioid use from baseline to the end of the initial titration phase.
- Proportion of responders at the end of the initial titration phase.
- Incidence of adverse events.

The response rate was defined as a ≥ 30 % reduction in VASPI without an increase in dose or change in type of concomitant opioid therapy.

Randomisation

Patients were randomised in a 2:1 ratio to ziconotide or placebo.

Statistical methods

In the original protocols, the primary efficacy patient cohort was defined as the evaluable population (having received at least 4 days of treatment). However primary analysis was then amended from evaluable patients to a modified intention to treat population. A modified ITT (mITT) population was defined as randomised patients who had received any amount of study medication, had a baseline VASPI score and had at least one follow up VASPI during the initial titration phase.

RESULTS

Study 95-001 (Chronic malignant pain)

Participant flow

At randomisation, 71 patients received ziconotide and 40 received placebo. One additional patient enrolled after randomisation and was included in the safety evaluation.

Of the 72 patients initially treated with ziconitide, 11 discontinued during initial titration, 9 during maintenance phase receiving ziconotide and 5 during crossover to placebo.

Of the 40 patients initially treated with placebo, 3 discontinued during initial titration, none during maintenance phase and 8 during crossover to ziconotide.

Baseline data

Baseline and demographic variables were comparable between treatment groups: mean age was 55.5 years, 87% of patients had cancer and 13% AIDS. Mean baseline VASPI was 75 mm. Mean baseline

opioid use was very high at 5.4 g/day oral morphine equivalents and 32% of patients had received prior IT morphine.

Outcomes and estimation

The table below provide results of the primary efficacy criterion (change in VASPI at the end of the initial titration phase) and the proportions of responders in both the "Evaluable" and the mITT population.

Endpoint	Population	Ziconotide	Placebo	p-value
Mean % change (SE) from baseline VASPI at the end of the initial titration phase	Evaluable (n)	53.1% (4.63) (68)	18.1% (6.77) (40)	<0.001
	mITT (n)	51.4% (4.59) (71)	18.1% (6.77) (40)	<0.001
Treatment responders at the end of the initial titration phase	Evaluable (n)	50.0% (68)	17.5% (40)	<0.001
	mITT (n)	47.9% (71)	17.5% (40)	0.001

The treatment effect remained statistically significant with the use of an ANCOVA model including percent change in opioid use (p=0.0001).

The table below provide mean VASPI scores at baseline and at the end of the titration, as well as the mean dose at the end of titration (mITT population).

Parameter	Ziconotide (n = 71)	Placebo (n = 40)
Mean VASPI score at baseline in mm (SD)	74.1 (± 13.82)	77.9 (± 13.60)
Mean VASPI score at end of initial titration in mm (SD)	35.7 (± 33.27)	61.0 (± 22.91)
Dose at end of titration (µg/hr)		
Mean	0.91	
Median	0.60	
Range	0.074 – 9.36	

Secondary efficacy analyses:

CPRS results (Categorical Pain Relief Scale): the response rate was 47.9% in the ziconotide group and 17.5% in the placebo group (p=0.001).

WBPI subsets (Wisconsin Brief Pain Inventory): there were no statistically significant differences between ziconotide and placebo in terms of WBPI subsets.

No significant linear correlation was observed between the percent change in VASPI and percent change in opioid use at the end of the initial titration period.

Non-responders to initial therapy were crossed over to the alternate blinded treatment at the end of the initial titration phase. Amongst these "initial non-responders", the mean percent improvement in VASPI from baseline at the end of the crossover phase was 44.9% and 4.2% in ziconotide and placebo treated patients respectively (p=0.005).

Post-hoc analyses performed by the applicant

Subgroup analysis of the primary efficacy parameter revealed similar mean VASPI improvements in ziconotide-treated patients who were IT morphine-naïve and experienced.

Using a more stringent responder definition of ≥ 50% decrease in VASPI, an exploratory posthoc response rate analysis demonstrated a 42.3% response in rate in the ziconotide group compared to 17.5% in the placebo group (p=0.008).

Study 96-002 (Chronic non-malignant pain)

Participant flow

At randomisation, 169 patients received ziconotide and 86 received placebo.

Of the 169 receiving initial ziconotide, 40 patients discontinued during initial titration and 8 withdrew during the maintenance phase with ziconotide. 48 patients (28.2%) completed initial titration and did not enter second phase and 82 patients (48.2%) entered the second phase. In the placebo group, 7 patients discontinued during initial titration and none discontinued during maintenance phase; 18 patients discontinued during the crossover phase with ziconotide.

Baseline data

The two groups were comparable with regard to demographic and baseline characteristics. However, the mean baseline VASPI score was higher for the ziconotide group (80.2 mm) than for the placebo group (76.9 mm). Mean age was 52 years. Mean baseline opioid use was 528 mg/day oral morphine equivalents.

58% of the patients had previously been treated with IT morphine.
76 % of the patients suffered from neuropathic pain.
98% of the patients had pain of greater than one year's duration.

Outcomes and estimation

The table below provides results of the primary efficacy criterion (change in VASPI at the end of the initial titration phase) and the proportions of responders, for both in the "Evaluable" and modified ITT (mITT) populations.

Endpoint	Population	Ziconotide	Placebo	p-value
Mean % change (SE) from baseline VASPI at the end of the Initial titration phase	Evaluable (n)	30.7% (3.47) (159)	6.2% (3.24) (79)	<0.001
	mITT (n)	31.2% (3.41) (164)	6.0% (3.05) (86)	<0.001
Treatment responders at the end of the initial titration phase	Evaluable (n)	33.3% (162)	13.9% (79)	0.002
	mITT (n)	33.7% (169)	12.8% (86)	<0.001

The treatment effect remained statistically significant with the use of an ANCOVA model including baseline VASPI score and percent change in opioid use (p=0.0005).

The table below provide mean VASPI scores at baseline and at the end of the titration, as well as the mean dose at the end of titration (mITT population).

Parameter	Ziconotide (n = 169)	Placebo (n = 86)
Mean VASPI score at baseline in mm (SE)	80.1 (± 15.10	76.9 (± 14.58)
Mean VASPI score at end of initial titration in mm (SE)	54.4 (± 29.30)	71.9 (± 30.93)
Dose at end of titration (µg/hr)		
Mean	1.02	
Median	0.50	
Range	0.019 - 9.60	

Secondary efficacy analyses:

CPRS results: the response rate was 33.7% in the ziconotide group and 12.8% in the placebo group ($p < 0.001$).

WBPI subset scores: there were statistically significant differences between treatment groups in favour of ziconotide in mood, walking ability, sleep and enjoyement of life WBPI subset scores at the end of the initial titration period.

Global Mc Gill Pain Score: the mean percent reduction in this score from baseline to the end of the initial titration phase was 23.6% in the ziconotide group compared to 9.2% in the placebo group ($p=0.028$).

In terms of change in opioid use, there were no statistically significant differences between ziconotide and placebo. No significant linear correlation was observed between the percent change in VASPI and percent change in opioid use at the end of the initial titration period.

Post-hoc efficacy analyses performed by the applicant

The mean VASPI improvements in ziconotide-treated patients were similar in the IT-morphine naïve and experienced patients, 29.6% and 33.2%, respectively.

Using a response rate analysis with a ≥ 50% decrease in VASPI, an exploratory posthoc analysis demonstrated a 28.4% response rate in the ziconotide group compared to 7.0% in the placebo group ($p<0.001$).

Analysis performed across trials (pooled analyses and meta-analysis)

As the two pivotal studies 95-001 and 96-002 were similar in design and conduct, a pooled analysis was provided.

For the pooled mITT (all dosing regimens) population, the mean VASPI score at the end of the initial titration period was 48.8 mm for the ziconotide group and 68.4 mm for the placebo group. The mean percent improvement of 37.3% in VASPI score for ziconotide patients was significantly greater than the 9.8% for placebo patients ($p < 0.001$, ANOVA). The 95% confidence interval for the treatment difference was 19.4 to 35.6.

The difference in the mean percent improvement in VASPI score between ziconotide patients and placebo-treated patients was somewhat greater for malignant pain patients in Study 95-001 compared to non-malignant pain patients in Study 96-002 (33.3% vs. 25.2%).

For the pooled ITT (all dosing regimens) population, the cumulative proportion of responders by dose level at end of initial titration period shows that 92% of patients, who responded to treatment, did so by a dose of 1.2 µg/hr of ziconotide.

For the pooled ITT (0.1-2.4 µg/hr dosing regimen) population, the cumulative proportion of responders by dose level at end of initial titration period for the pooled population suggests that 90% of patients, who responded to treatment, did so with a dose of 1.2 µg/hr of ziconotide.

Study 301

301 was the third randomised, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain.

The primary objective was to confirm the efficacy results observed in the two pivotal short-term clinical trials (five to six days – studies 95-001 and 96-002) on a longer period (three weeks), and with a slower dose titration schedule.

220 patients with severe chronic pain (VASPI score >50 mm) that was not adequately controlled by and/or who were intolerant to systemic opioids were included. Neuropathic pain was the most common pain mechanism and accounted for 75.9% and 71.3 % of patients in the ziconotide and placebo groups, respectively. Failed back surgery was the most common pain aetiology, reported for 60.7% of patients in the ziconotide group and 55.6% of patients in the placebo group. In both treatment groups, the mean VASPI score was 80.7 mm at baseline.

This additional controlled study was designed to assess a slower titration schedule at a lower ziconotide dose with a longer blinded observation (3 weeks, which was sometimes extended up to 9 months under open conditions):

Starting dose (per day)	Maximum dose (per day)	Titration interval
0.1 µg/h (2.4 µg)	0.9 µg/h (21.6 µg)	24 hours

Efficacy results from study 301

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

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

Secondary endpoints:

- Mean weekly opioid use: There was a 23.7% mean decrease in weekly opioid use from the pre-treatment stabilization period at week 3 for the ziconotide group compared to a 17.3% decrease in the placebo group (p = 0.4371). Therefore, the improvement in VASPI score was not due to an increase in opioid use.
- For both "satisfaction with therapy" and "overall pain control", the CGI evaluation showed a statistically significant improvement in patients treated with ziconotide compared with placebo.
- The mean change in the Global McGill Pain Total Score from baseline to termination was 3.2 in the ziconotide group and 0.6 in the placebo group, showing a statistically significant improvement in the ziconotide group over the placebo group (p = 0.0259; two-sample t-test).

- Brief Pain Inventory (BPI): Patients in the ziconotide group in comparison to the placebo group experienced an improvement in all BPI subset scores; however, the changes from baseline to termination did not reach statistical significance.
- Sleep pattern and quality of sleep: At termination, there were statistically significant improvements in the number of hours of uninterrupted sleep and overall sleep quality in the ziconotide group, and evidence of fewer awakenings due to pain in the ziconotide group.
- Categorical Pain Relief Scale (CPRS): The difference between the two treatment groups approached statistical difference (p=0.0596; Mantel-Haenszel chi-square test).

- **Clinical studies in special populations**

None

- **Supportive studies : Open-label studies**

Study 95-002 was an extension study enrolling patients who had demonstrated an analgesic response to ziconotide in the controlled studies (Studies 95-001 and 96-002). After an initial 30-day fixed-dose period, dose increases were limited to a maximal two-fold increase 12 hourly. Safety and efficacy (VASPI) assessments were performed monthly. One hundred and fifty-five patients were enrolled; 48 with malignant pain and 107 with non-malignant pain. The mean and median number of days in the study was 288 and 86 respectively. 34 patients were treated for at least 360 days. The mean percentage improvement in VASPI score compared to the pre-treatment baseline was 37.2% (N=139), 32.5% (N=57), 40.6% (N=37), 45.8% (N=31) and 36.9% (N=144) at Week 4, Months 3, 6, 12 and the last available observation, respectively. The apparent increase in efficacy is considered to reflect selection bias as the number of patients decreased with time.

Study 98-022 was designed to assess long-term safety and tolerability of ziconotide administered zicotide intrathecally to patients with chronic pain. Titration began at 0.1 μg/hr and could increase by ≤0.1 μg/hr every 24 hours. After the titration/stabilisation period safety assessments were performed monthly. Six hundred and forty four patients, with chronic nociceptive and/or neuropathic pain requiring intraspinal analgesia received treatment. Unlike the pivotal studies, there was no minimum baseline VASPI eligibility criterion. 97% of patients had pain of non-malignant origin, and 79% of patients had a neuropathic component to their pain. Patients were treated as outpatients but were seen monthly for filling of infusion pump. The mean and median number of days on ziconotide was 199 and 67 respectively. One hundred and nineteen patients were treated for at least 360 days. The mean % VASPI change at 1 month for all patients (N = 453) was a reduction of only 7.2% ($p<0.0104$). A post hoc subgroup analysis revealed that the mean % VASPI change at 1 Month for patients (N=394/453) with VASPI scores ≥50 mm (i.e., a comparable population to the pivotal trials) was a reduction of 18.3% ($p<0.0001$). Thirty-one percent (138/453) of patients fulfilled the protocol definition of response defined as: ≥ 30% reduction in VASPI at 1 month.

Data on other ongoing open-label studies were also provided:

- Study 302 – Open-label, 3-week, with optional long-term extension phase, multicenter outpatient study to enrol 150 IT naïve patients with chronic, severe pain of either malignant or non-malignant origin and with a baseline VASPI score of ≥40 mm. The study includes a treatment phase when Prialt (external pump) is uptitrated at dose increments of ≤ 0.1 μg/hr no more than once in every 24 hours over a 3-week period. Patients with pain of malignant origin may be eligible to continue with the external system for a further 6 months of treatment with Prialt. Patients with pain of non-malignant origin and suitable for an implanted pump should terminate this study and be enrolled in 352, a long-term follow-up study.
- Study 352 - Open-label, long-term extension study of 301 or 302. Safety assessments and VASPI pain measurements are performed once every 60 days.
- Study 351 - Open-label, long-term extension study of patients who had completed the open-label, long-term studies 95-002 and 98-022. Patients in this study have had the longest exposure to ziconotide and approximately 50 patients have been treated for over 3 years.
- Study 501 – The ZEST study is an open-label, long-term, compassionate multicentric study started in January 2004 in the US under a treatment IND. The dosing regimen is as follows:

starting dose is 0.1 µg/hr with dose changes every 48 hours. Dose increment is ≤0.1 µg/hr with a maximum dose of 0.9 µg/hr.

- **Discussion on clinical efficacy**

Two placebo-controlled trials, similar in design and conduct, were performed involving 366 patients: 111 with malignant pain mainly due to cancer (with 13% due to AIDS) and 255 with a non-malignant pain with a demonstrable neurological basis, 76% of whom had neuropathic pain The use of placebo rather than a comparator such as IT morphine is considered appropriate as IT morphine lacks controlled clinical trial data to justify its use as a gold standard and also because patients would be likely to have been treated with morphine previously. The reasons for keeping the duration of the pivotal trials brief (the primary endpoint was set at the end of a 5- to 6-day titration period) can be accepted in view of the proposed severe chronic pain indication (mean baseline VASPI score ~80 mm) and in an attempt to minimise the incidence of meningitis.

The efficacy of IT ziconotide during 5 to 6 days in patients with severe, chronic pain of malignant and non-malignant origin was demonstrated. In the pooled analysis, the mean percent improvement of 37.3% in VASPI score for ziconotide patients was significantly greater than the 9.8% for placebo patients ($p < 0.001$). Secondary endpoints (verbal Category Pain Relief Scale, Global McGill Pain scores and responder analyses also support the efficacy.

The studies were characterised by a very high withdrawal rate: in Study 95-001, 20/72 patients on ziconotide withdrew before the end of the titration phase and 8/29 patients on placebo crossed over to ziconotide; in Study 96-002, 88/170 ziconotide patients did not enter the second phase and 18/80 patients on placebo crossed to ziconotide. In response, the applicant showed that the effect of early dropouts and the use of the last observed carried forward (LOCF) approach during the initial titration phase did not confound the efficacy data from the two placebo-controlled studies.

It was questioned whether the high rate of confusion and other related adverse events in the ziconotide patients may have obscured the interpretation of the pain scales. Post-hoc analyses conducted by the Applicant revealed a consistently greater reduction in mean VASPI in the confusion-affected cohort treated with ziconotide compared to the unaffected cohort across the three studies. On the other hand, a treatment difference between unaffected ziconotide- and unaffected placebo-treated patients was consistently observed in favour of ziconotide in all three studies. So the VASPI scores appear suitable despite a possible influence of confusion or related adverse events on the evaluation of efficacy.

Long-term data from 31 patients who remained in the study 95-002 shows that sustained analgesic effect in these patients was accompanied by relatively stable mean doses (0.4–0.6 µg/h) over a 12-month period: median dose (0.3 µg/h) requirements were also constant over this period. No increment in mean dose was noted between 5 and 12 months of treatment.
The lack of tolerance has been demonstrated in only 31 patients of the long-term study 95-002 needs confirmation in further studies.

The main topic for discussion were the following:
- The optimal dosage and dose increment strategy for the safe and efficient use of ziconotide have not been clearly established, especially in view of the narrow therapeutic index of the product.
- The benefit of the product on the different types of pain.
- The long-term maintenance of efficacy.

Dose recommendation

The Applicant provided a detailed explanation of the rationale underlying the dosing regimen mainly based on analyses of the results of studies study 98-022 and study 301in which dose increments were smaller in those studies than the two key studies 95-001 and 96-002, and suggested an amendment to the original dosing recommendation.

In study 98-022, therapeutic doses in responders ranged from 0.02 – 0.83 µg/h. Only 1.5% of the total population required a dose ≤0.1 µg/h and only 2.0% of the total population required a dose ≥0.9 µg/h. In study 301, the range of therapeutic doses (0.05 – 0.60 µg/h) is not far from that in Study 98-022.

As a consequence, 0.1 µg/hour was considered a safe initial dose as only 1% of patients had serious adverse events at this dose or at a lesser dose and approximately 30% of patients experienced related adverse events at doses ≤ 0.1 µg/hour.

The estimated median time to CSF steady state following infusion is 22.5 hours (based of a median CSF half-life of 4.5 hours). The Applicant has analysed the time interval between dose changes for the three placebo-controlled trials as well as for the long-term open-label safety trial, to support that a dosing interval of 48 hours or more. In the first two placebo-controlled trials (95-001, 96-002), patients were hospitalized for the initial titration, and rapid titration over 5 or 6 days was thought to be necessary. The dose was increased at 24-hour intervals until analgesia was obtained or adverse events were encountered. The third placebo-controlled trial (301) used a 21-day titration period and specified that the dose could not be increased more than once in a 24-hour period. Longer time intervals between dose increases were permitted by the protocol. The long-term open-label safety trial 98-022 also specified a 24-hour minimum titration time interval and titrated the dose over a 4-week period. The table below summarises the statistics for all dose interval by trial.

Summary Statistics for Dose Interval by Trial[1]

Statistic	95-001	96-002	301	98-022 (long-term)
N[2]	346	780	285	2300
Mean	22.2 hrs	27.6 hrs	3.9 days	94.9 hrs
Median	21.9 hrs	24.0 hrs	4.0 days	74.3 hrs

[1]All dose increases (any dose decrease is ignored).
[2]N = the total number of dose increases in the ziconotide group

The Applicant also provided analysis showing that in the first two trials (95-001 and 96-002), only 5% and 20% of the dose increases were "safe", i.e. not associated with a subsequent dose decrease, whereas in the later trials (301 and 98-022), 59% and 46% of dose increases were not associated with subsequent dose decreases.

Although a correlation of the individual dose intervals with outcome variables such as VASPI and adverse events were not provided, a dose interval of at least 48 hours is recommended to optimise safety.

In summary, because of the narrow therapeutic index, it is prudent to start with a relatively low dose (2.4 µg/day), to limit the dose increments to 2.4 µg/day, and to uptitrate with a minimal interval between dose increases of 24 hours and a recommended interval, for safety reasons of 48 hours or more.

Efficacy depending on the type of pain

The efficacy appeared somewhat greater for malignant pain patients in Study 95-001 compared to non-malignant pain patients in Study 96-002 (improvement in VASPI score: 51.4% versus 31.2%; response rate: 47.9% versus 33.7%) and in Study 301 (see below).

On the other hand, subgroup analysis of the primary efficacy parameter revealed similar mean VASPI improvements in ziconotide-treated patients who were IT morphine-naïve and in those who had previously received IT morphine. These results, and the limited benefit of intraspinal morphine when pain is unresponsive to other routes of morphine administration, provide a strong argument against the mandatory use of morphine as first line IT therapy in all situations.

In study (301), neuropathic pain was the most common pain mechanism and accounted for more than 70 % of the patients. Failed back surgery was the most common pain aetiology. The primary and secondary results of Study 301 support the analgesic activity of ziconotide in patients suffering from severe chronic pain of neurological origin necessitating intrathecal administration of analgesics. However, the overall efficacy was limited: the primary endpoint, i.e. the mean percent change in VASPI score from baseline to week 3 (LOCF), was 14.7% in the ziconotide group vs 7.2% for the placebo group (p=0.0360). In addition, the number of responders was rather low and not significantly different: only 16.1% in the ziconotide group vs 12% in the placebo group. One should note that the selection of patients in study 301 was more stringent, and that it is also possible that the efficacy of ziconotide is lower in patients who do not respond to, or are intolerant to, systemic morphine.. In Study 301, incidences of adverse effects, namely neurological adverse reactions, in particular confusion, and rate of discontinuation due to adverse effects were lower than in the previous two controlled studies. This seems to confirm that a better control of the posology, from the initial starting dose to the dose increments to the interval between doses, allows a better tolerance of ziconotide.

The recruitment of malignant pain patients for long-term treatment via intrathecal route appears very difficult and only 20 % of patients in the clinical studies had exclusively non-neuropathic pain

There are differences in the therapeutic effect (i.e. ziconotide – placebo efficacy) observed in the three placebo-controlled studies (95-001, 96-002, and 301), with the malignant pain study (95-001) having the greatest effect and 301 having the smallest effectIt is likely that the differences in therapeutic effect are due to differences in patient populations, dose regimens, and study design.

- The cancer patients in 95-001 suffered from severe pain for a shorter duration and were exposed to less therapeutic procedures than nonmalignant patients in 96-002; perhaps they were more responsive to analgesia. This is reflected by the difference in placebo response between the two populations (6% in the non-malignant patients in 96-002 compared to the 18% in the malignant pain patients in 95-001).
- The patients enrolled in the 301 study were the most refractory population of patients studied in the ziconotide program; all already had implanted pumps and most had failed IT therapy with combination analgesics. The treating physicians considered that 97% of the patients were refractory to currently available treatments.
- Studies 95-001 and 96-002 were of short duration and used a more rapid dose escalation using higher doses compared to study 301.

In addition, a meta-analysis of the efficacy data from the three controlled trials (95-001, 96-002, and 301) by pain mechanism shows that ziconotide has a therapeutic effect in both neuropathic and non-neuropathic pain subgroups.

Percent change in VASPI score by pain mechanism

Pain Mechanism Classification	Ziconotide N=268	Placebo N=189
Neuropathic		
N	185	129
Mean	23.6	6.8
Median	14.9	1.4
Non-neuropathic		
N	42	40
Mean	15.5	7.6
Median	6.8	3.0

Long-term efficacy

The long-term effects of ziconotide (beyond 3 weeks) has been insufficiently demonstrated in controlled studies, especially in patients with malignant pain where these malignant pain patients were end of stage or terminal and so the high death rate precluded determination of long-term experience with ziconotide.

Data from these two ongoing long-term, open-label studies have been provided to show that a total of 172 patients have been treated for one year or longer. Almost all patients have non-malignant pain. The mean and median dosage in both long-term studies is within the maximum recommended dose (21.6 μg/day).

Long-term efficacy of ziconotide needs further demonstration despite anecdotal evidence and accruing safety data. Furthermore, there is little experience with long-term ziconotide treatment in patients with malignant pain. This concern is reflected in the Warning/Precautions section 4.4 of the SmPC

Clinical safety

- Patient exposure

At the time of the submission of the application, ziconotide had been administered to 1048 patients by the IT route, including 353 treated for at least three months and 153 treated for at least 360 days. The total exposure to IT ziconotide was 477 patient-years. A number of safety populations were identified including the Controlled Study Population (patients from placebo-controlled Studies 95-001and 96-002) and the Combined IT Study Population (patients from all IT studies; 94-004, 95-001, 95-002, 96-002, 96-003, 96-010, 97-013, 97-015 and 98-022). Patients received IT doses of ziconotide in the range of 0.05 to 38 μg/hr.
Safety data of study 301, which dose titration was close to the one recommended in the SPC were provided at a later stage and are described after the above mentioned initial populations.

- Adverse events

The analyses of the Combined IT Study Population presented below compare the ziconotide-treated and placebo-treated populations. It is important to point out that there is a large imbalance in ziconotide versus placebo exposure with 477 versus 2.5 patient-years exposure in these respective populations.

Adverse Events Occurring in ≥ 5% of Patients – Combined IT Studies

Adverse Events	While Receiving Ziconotide (n = 1048)	While Receiving Placebo (n = 151)
	% Patients	% Patients
Any Adverse Event	98.4	76.2
Dizziness	53.2	13.2
Nausea	51.2	20.5
Headache	34.6	20.5
Confusion	33.8	6.6
Nystagmus	30.1	11.3
Somnolence	27.4	6.6
Pain	26.4	4.0
Memory Impairment	21.7	0
Abnormal Gait	21.3	2.0
Fever	20.0	6.0
Vomiting	19.3	7.3
Constipation	18.9	10.6
Asthenia	17.4	3.3
Myasthenia	15.6	2.0
Diarrhoea	15.5	4.0
Urinary Retention	14.7	1.3
Peripheral Oedema	14.0	1.3
Anxiety	13.9	5.3
Blurred Vision	13.9	2.0
Insomnia	13.5	2.0
Depression	13.0	0.7
Accidental Injury	12.5	2.0
Hypertonia	12.5	2.0
Speech Disorder	12.1	2.0
Hallucinations	11.9	0
Ataxia	11.7	1.3
Nervousness	11.3	3.3
Back Pain	11.1	0.7
Dysaesthesia	10.8	0
Urination Impaired	10.8	1.3
Anorexia	10.5	0.7
Hypaesthesia	10.5	2.0
Infection	10.5	1.3
Postural Hypotension	9.7	7.9
Pruritos	9.7	6.6
Paraesthesia	9.6	2.0
Tremor	9.3	2.6
Arthralgia	9.0	0

Impaired Verbal Expression	9.0	0
Abdominal Pain	8.9	2.0
Creatine Kinase Increased	8.9	0
Sweating	8.9	3.3
Catheter Complication	8.7	0
Chest Pain	8.6	1.3
Dyspnoea	8.6	2.6
Taste Perversion	8.5	0
Dry Mouth	8.4	1.3
Mental Slowing	8.3	0.7
Agitation	7.5	0.7
Cerebrospinal Fluid Abnormal	7.4	0
Abnormal Vision	7.3	0
Myalgia	6.9	0
Chills	6.7	2.0
Nausea And Vomiting	6.1	2.0
Pump Complication	5.8	0
Vertigo	5.8	0.7
Diplopia	5.4	0
Hypotension	5.2	7.3
Pump Site Oedema	5.2	0
Reflexes Decreased	5.0	1.3

Studies include: 94-004, 95-001, 95-002, 96-002, 96-003, 96-010, 97-013, 97-015, 98-022

A comparison of the AE profiles for ziconotide (all dosing regimens), ziconotide (0.1-2.4 μg/hr regimen) and all placebo patients for the initial titration period is shown in the following table which suggests that there may be a reduced number of adverse events with the lower doses.

Incidence of Adverse Events in Ziconotide and Placebo-Treated Patients During the Initial Titration Period - Controlled Studies.

	Ziconotide Patients All Dosing Regimens (0.1-21 μg/hr) (n=242)	Ziconotide Patients Final Dosing Regimen (0.1-2.4 μg/hr) (n=170)	All Placebo Patients (n=126)
Adverse events	% patients	% patients	% patients
All Aes	95.5	94.1	72.2
Severe Aes	23.6	19.4	9.5
Serious Aes	20.2	15.9	4.8

The commonest individual AEs in the ziconotide-treated population that were statistically significantly more frequent than in the placebo group are presented in the following table.

Incidence Individual Adverse Events Occurring in ≥ 10% of Ziconotide-Treated Patients Statistically Significantly More Frequent Than in Placebo-Treated Patients During The Initial Titration Period - Controlled Studies

Adverse Events	Ziconotide Patients		All Placebo Patients (n=126) % Patients	p-value[a]
	All Dosing Regimens (0.1–21 μg/hr) (n=242) % Patients	Final Dosing Regimen (0.1–2.4 μg/hr) (n=170) % Patients		
Dizziness	52.5	50.6	13.5	<0.0001
Nausea	43.0	42.4	19.0	<0.0001
Nystagmus	41.7	41.2	11.9	<0.0001
Abnormal gait	22.7	22.4	2.4	<0.0001
Urinary retention	16.1	13.5	1.6	<0.0001
Somnolence	15.7	12.9	5.6	0.0042
Postural hypotension	15.3	13.5	5.6	0.0063
Vomiting	15.3	13.5	5.6	0.0063
Confusion	14.5	11.8	5.6	0.0097
Fever	13.2	9.4	4.0	0.0055
Pain	11.2	12.4	3.2	0.0092

[a] comparison between ziconotide (all dosing regimens) and all placebo patients is presented.

Regarding study 301, the incidence of adverse events is summarised in the following table.

Summary of treatment-emergent adverse events and serious adverse events (Study 301)

	Ziconotide (N=112)	Placebo (N=108)
Adverse events		
Any AE	104 (92.9%)	89 (82.4%)
Nervous system AE	91 (81.3%)	55 (50.9%)
Serious adverse events		
Any SAE	13 (11.6%)	10 (9.3%)
Nervous system SAE	5 (4.5%)	2 (1.9%)
Drug-related serious adverse events		
Any drug-related SAE	2 (1.8%)	2 (1.9%)
Nervous system drug-related SAE	2 (1.8%)	1 (0.9%)

The following adverse events are more frequently reported in patients treated with ziconotide than in patients treated with placebo:
- dizziness : 47.3% versus 13.0%
- nystagmus : 8.0% versus 0.0%
- abnormal gait : 15.2% versus 1.9%
- confusion : 17.9% versus 4.6%
- ataxia : 16.1% versus 1.9%
- hallucinations : 7.1% versus 0.0%
- memory impairment : 11.6% versus 0.9%
- vertigo : 7.1 % versus 0.0%

Most of these adverse events occurred for the first time during the first treatment week.

Adverse events considered to be severe were reported for 42.0% of patients in the ziconotide group and 26.9% of patients in the placebo group. In the ziconotide group, severe adverse events were

dizziness (10.7% of patients), diarrhoea (5.4%), nausea (10.7%), abnormal gait (3.6%) and confusion (2.7%). In the placebo group, no serious case of dizziness or abnormal gait occurred, and one case of confusion was reported.

- Serious adverse event/deaths/other significant events

SAE and deaths

In the initial safety database, serious adverse events were reported in 38.1% of all patients although many of these were associated with the comorbid disease. Serious adverse events considered related to treatment occurred in 14% of all patients, with confusion (3.5%) and dizziness (1.1%) the commonest individual related events. Among IT ziconotide-treated patients there have been 76 deaths. The great majority of these patients had cancer and death was clearly attributed do the underlying disease. In 3 cases (all patients with malignant pain), investigators could not exclude a contribution of ziconotide to the events leading to death. For two of these patients aspiration pneumonia was the cause of death and the investigators could not rule out an effect of ziconotide (oropharyngeal dyskinesia and altered mental status with delirium, respectively) as a contributory/causative factor. The third patient committed suicide a day after completing Study 95-001. Five further patients have committed suicide, during or within a month of discontinuing ziconotide therapy. The rate of suicide in the ziconotide trials is lower than that reported in a cohort of chronic pain patients treated with IT opiates and/or bupivacaine (3.3%).

In study 301, serious adverse events were reported in 11.6% of the patients in the ziconotide group and in 9.3 % in the placebo group. Serious nervous system adverse events were not common and their incidence was similar in the ziconotide and placebo groups. There was one death reported in a patient randomised to placebo.

Other significant AEs
CNS events

Dizziness occurred in 53.3% of patients in the combined IT group (versus 13.3% in the placebo group), but caused serious adverse events in only 1.2% of patients in this group and was the reason for discontinuation in 6.7% of patients. Nystagmus (30.1% of patients versus 11.3% in the placebo group) as well as speech and gait disorders also occurred more frequently in the ziconotide population.

Confusion is a particular cause for concern. It occurred in 33.8% of patients in the combined IT group (versus 6.6% in the placebo group) and caused serious AE's in 4.1% of patients. Confusion was the reason for discontinuation in 11.7% patients. Mean duration of confusion was 15.3 days with a range of 1 to 292 days. Also notable were memory impairment (8.3% in the IT group), hallucination (11.9%), mental slowing (33.8%), and somnolence (27.4%). Confusion is certainly the "most undesirable" AE for patients suffering from severe chronic pain, because they can loose the control of their pain and because the need for hospitalisation is mandatory. This issue was part of the Applicant's decision to recommend a dose interval of 48 h in order to minimise all adverse events.

The cognitive AE's (median time to onset 22–31 days) raised the fear that some persistent or even irreversible injury to the CNS may have occurred. However, pre-clinical data did not support such a toxic phenomenon.

In the combined IT group the neurological AE's of particular interest occurred at a median dose at onset ranging from 0.2 – 0.3 μg/hr.

Meningitis: In the initial total safety population, 42 events of meningitis occurred (ziconotide 40, placebo 2). Compared with placebo, the ziconotide group had a much larger number of patients (1048 versus 151) and a substantially higher mean number of days on treatment (177.4 versus 6.6 days). The number of events per patient-year was lower in the ziconotide group than in the placebo group (0.0839 versus 0.8 events per patient-year). In the literature, the rates for meningitis following IT administered morphine either alone or in combination with other analgesics by externalised catheter were similar: 4/90 patients (4%) in Nitescu et al., (Clin J Pain, 1998) and between 0/15 patients and 3/33 patients

(9%) in a review of studies (Du Pen, Techniques in regional anaesthesia and pain management, 1998). Thirty eight events involved an external pump system and 4 events involved an internal system. The risk of meningitis is thought to be greater with external infusion systems (Dahm, Clin J Pain, 1998). This is reflected in the recommendation in the SPC to use internal pump systems rather than external pumps over prolonged periods.

Urinary impairment/retention occurred in 10.8% of patients in the Combined IT group (versus 1.36% in the placebo group), caused serious adverse events in 2.9% of patients in the controlled group and 1.2% of patients in the combined IT group. Mean duration was 15.3 days with a range of 1 to 292 days.

Greater incidence of pain reported as an adverse event ("pain exacerbation") in the ziconotide group compared with placebo in Studies 95-001 and 96-002. In Study 301, the incidence of pain as an adverse event during the 3-week placebo-controlled phase was not significantly different in the ziconotide group. It is unlikely that ziconotide directly induces pain. However, the development of a paradoxical hyperalgesia is not excluded and should be further evaluated.

- Laboratory findings

Drug-related elevations in creatine kinase (CK) have been observed amongst patients on IT ziconotide. Isoenzyme analysis revealed the origin to be almost entirely skeletal muscle (MM fraction). Elevations are typically modest and CK elevations were asymptomatic.

Three cases of rhabdomyolysis in conjunction with acute renal injury were reported in patients receiving IT ziconotide but in all 3 cases other significant medical factors were present which may have been implicated in the muscle injury.

- Safety in special populations

No specific studies were performed in special populations.

- Safety related to drug-drug interactions and other interactions

Formal interaction studies between ziconotide and other analgesic drugs have not been performed. For morphine, this may be acceptable as most patients used systemic morphine concomitantly in the clinical studies and clinical IT morphine and ziconotide studies are ongoing.

An increased incidence of somnolence has been observed when ziconotide is administered concomitantly with systemic baclofen, clonidine, bupivacaine or propofol. Nevertheless, there is no indication that the incidence of more serious CNS adverse effects such as stupor and coma is increased by with these products. The increased incidence of somnolence will be stated in the SPC.

There was no increased incidence of confusion and other CNS AE in ziconotide patients taking anticonvulsants. The risk of additive CNS adverse effects when CNS-active products are co-administered with IT ziconotide cannot be excluded and will be further assessed post-marketing.

The potential interaction between ziconotide and diuretics was assessed as diuretics have been reported to reduce CSF turnover. No consistent evidence was observed to suggest an increase in the incidence of adverse events amongst patients receiving diuretics in conjunction with ziconotide.

Ziconotide is contraindicated in combination with IT chemotherapy because multiple instrumentation of the subarachnoid space to administer IT ziconotide and IT chemotherapy increases the potential risk of infectious complications and co-administration of chemotherapy with an indwelling intrathecal catheter is likely to alter the dynamics of CSF flow, so rendering the spread and response to ziconotide unpredictable.

- Discontinuation due to adverse events

The following table depicts the adverse events most commonly resulting in temporary or permanent discontinuation of ziconotide. As expected, neurological adverse events are predominant and complications commonly associated with IT infusion systems are also noted.

Incidence of adverse effects (%) leading to temporary or permanent drug discontinuation in ≥ 2% ziconotide-treated patients – Combined IT studies

Adverse events	Ziconotide patients (n=1048)	All placebo patients (n=151)
	% PATIENTS EXPERIENCING EVENT	% PATIENTS EXPERIENCING EVENT
Any adverse event	50.6	6.6
Confusion	11.7	0.7
Dizziness	6.7	0
Nausea	5.3	0
Abnormal gait	3.5	0
Headache	3.3	0.7
Memory impairment	3.3	0
Catheter complication	3.1	0
Somnolence	2.9	0
Hallucinations	2.9	0
Nystagmus	2.9	0
Mental slowing	2.8	0
Pain	2.6	1.3
Fever	2.3	0.7
Cerebrospinal fluid abnormal	2.1	0
Vomiting	2.0	0

The median time to recovery for adverse events usually ranged from 3-15 days.

In study 301, the most commonly reported primary adverse event leading to study drug discontinuation was dizziness (2/112). Nausea, agitation and tremor led to withdrawal for one patient each.

- Post marketing experience

Not applicable.

- Discussion on clinical safety

Adverse events (AE's), particularly affecting the nervous system, were much more common in ziconotide-treated than placebo-treated patients during the initial titration period in studies using the higher doses. Some non-nervous system AE's that were more common in ziconotide-treated patients, such as nausea and urinary retention, are probably also neurologically mediated. Although most AE's to ziconotide were mild to moderate, ziconotide administration seemed to be associated with a range of AE's that were frequent, severe, persistent and often leading to patient withdrawal or discontinuation. Ziconotide-related AE's were one of the main reasons for temporary or permanent patient withdrawal from studies (50.6% of patients). Serious AE's occurred in 38.1% of patients versus 11.9% for placebo. Some of the adverse events such as confusion, memory impairment, somnolence, dizziness were not only severe, but in some cases also persistent.

Dizziness, nystagmus and gait abnormalities are considered to reflect vestibular effects as N-type channels are abundant in the granule cell layers of the cerebellum, the site of vestibular afferent input, and also influence pathways between brainstem vestibular nuclei and the cerebellum. Ataxia and abnormal gait may be associated with blockade in the spinocerebellar tracts and/or basal ganglia, and nausea, vomiting, urinary impairment/retention (10.8% of patients versus 1.4% in the placebo group), amblyopia and hypotension may be associated with blockage in central autonomic pathways.

The more recent study (301) confirmed that ziconotide administered at a lower dose or with slower titration provided a better safety profile. In that study, the mean initial dose level was 0.1 µg/h and the mean dose level at termination was 0.26 µg/h. The mean duration of days on study drug was 29.4 days for the 112 patients who received ziconotide. The withdrawal rate in study 301 was low. The adverse events that were more frequent on ziconotide than on placebo included abnormal gait, ataxia, confusion, dizziness, hallucinations, memory impairment, nystagmus and vertigo. Most of these adverse events occurred for the first time during the first treatment week. This study showed that with a better control of posology, the frequency of confusion decreases dramatically. For confusion, the median dose of onset and the median cumulative dose at onset are higher than for the other neurological adverse events.

Non-neurological AE's were less of concern. The changes in CPK are unexplained and of unknown consequence. It should be stressed that ziconotide induces no respiratory depression and few vomiting, which are important advantages over morphine derivatives. The absence of cardiac toxicity and of endocrine long-term effects, which would be another advantage of ziconotide over opioids, remains to be confirmed in longer term studies.

1.5 Overall conclusions, benefit/risk assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

Non-clinical pharmacology and toxicology

The mechanism of the analgesic action of ziconotide has been well characterised. Ziconotide is a blocker of the N-type voltage-sensitive calcium channel; it inhibits the voltage-sensitive calcium current into primary nociceptive afferents terminating in the superficial layers of the dorsal horn of the spinal cord. In turn this inhibits the release of neurotransmitters (including Substance P) and hence the spinal signalling of pain. Efficacy has been shown in appropriate animal pain model.

Toxicology studies showed that there were no signs of target organ toxicity and the changes seen can be attributed to the pharmacological effects of the compound. Ziconotide was negative in a battery of genotoxicity assays.

The lack of carcinogenicity study and the limited data on chronic toxicity are acceptable in view of the difficulties in conducting IT studies with long duration, the lack of evidence of a potential for target organ toxicity at very high multiples of the human dose and the lack of toxic effects on the CNS at high multiples of the CSF concentration of ziconotide in humans.

Ziconotide is not teratogenic in rats or rabbits. Embryolethality observed in reproductive and developmental studies is directly attributable to parental toxicity.

Efficacy

Prialt is for intrathecal use only and must be administered as a continuous infusion. Low plasma exposure occurs during IT infusion due to the low recommended IT infusion rates and relatively rapid plasma clearance.

In three placebo-controlled studies in patients with severe and chronic pain requiring intrathecal analgesia, IT ziconotide produced a clinically significant efficacy, as measured by improvements in Visual Analog Scale of Pain Intensity (VASPI) scores and supported by the secondary endpoints. The requirement for IT analgesic therapy relies on a clinical decision after all other available resources have been exhausted. The available data shows efficacy in patients with severe and chronic malignant and non-malignant pain, both in the short-term studies 95-001 and 96-002 and in the middle-term study 301, although the effect size appeared samller in this latter study which included patients refractory to other IT therapies. The indication "*Ziconotide is indicated for the treatment of severe, chronic pain in patients who require intrathecal analgesia*" reflects the representative ziconotide study population. However, the definitions of neuropathic pain used in the three placebo-controlled studies may not be accurate enough to ensure distinction between pain mechanisms. Therefore, in order to gain a better insight into this issue, a specifically designed post-marketing study is suggested.

Ziconotide should be titrated on an individual patient basis according to the patient's analgesic response and adverse reactions. The median dose at response is approximately 6.0 μg/day and approximately 75% of responsive patients require ≤ 9.6 μg/day.

Long-term efficacy data (beyond 3 weeks) are limited especially in patients with malignant pain and should be expanded post-marketing.

Data on IT combination studies with morphine and baclofen will be provided post-marketing

Safety

All results suggest that ziconotide has a narrow therapeutic window.

Dizziness, nystagmus, gait abnormalities, ataxia, nausea, vomiting, urinary impairment/retention, amblyopia and hypotension were common and may be associated with the pharmacological mechanism of the product.

Adverse reactions, particularly affecting the nervous system were more common in ziconotide-treated during the initial titration period in studies using the higher doses.

Dose increments should be of ≤2.4 μg/day and the recommended interval between dose increases is 48 hours or more, for safety reasons. To limit the occurrence of serious adverse drug reactions, a maximum dose of 21.6 μg/day is recommended.

The most commonly reported adverse drug reaction reported in long-term clinical trials were dizziness (45%), nausea (35%), nystagmus (27%), confusional state (25%), gait abnormal (18%), memory impairment (13%), vision blurred (14%) headache (13%), asthenia (13%), and vomiting (13%). Most ADRs were mild to moderate in severity and resolved over time.

Cognitive and neuropsychiatric adverse reactions, particularly confusion, are common in patients treated with ziconotide. Cognitive impairment typically appears after several weeks of treatment. The ziconotide dose should be reduced or discontinued if signs or symptoms of cognitive impairment or neuropsychiatric adverse reactions develop, but other contributing causes should also be considered.

The administration of medicinal products by the intrathecal (IT) route carries the risk of meningitis.

Potential interaction with other product, in particular CNS products will be futher investigated post-marketing.

Benefit/risk assessment

The benefit/risk ratio of Prialt in the treatment of severe, chronic pain in patients who require intrathecal (IT) analgesia is considered positive based on the following elements:

- IT ziconotide is a novel and interesting alternative to IT morphine for patients who need intrathecal therapy.
- Although no carcinogenic study has been performed and elements of some of the long-term toxicological studies were not GLP compliant, a well-designed, GLP-compliant, 1-month toxico-kinetic study with IT administrations of ziconotide in Beagle dogs showed no sign of histo-pathological lesions.
- In three placebo-controlled studies involving patients with severe, chronic pain of malignant and non-malignant (including neuropathic pain) origin, ziconotide produced a clinically significant efficacy, as measured by improvements in VASPI scores.
- The requirement for intrathecal analgesic therapy, whether in cancer or non-cancer pain, is a clinically valid parameter to define the target population.
- Follow-up long-term studies and ongoing studies have allowed to delineate the optimal dosage and dose increment strategy for the safe and efficient use of ziconotide. Because of the narrow therapeutic index, it is prudent to start with a relatively low dose (2.4 μg/day), to limit the dose increments to 2.4 μg/day, and to uptitrate after a minimum of 24, but preferably 48 hours or more.
- The safety profile and safety database of IT ziconotide are acceptable. Neurological adverse events were frequent and often led to treatment discontinuation in the earlier studies, but when lower doses and safer uptitration procedures were used, the adverse events were acceptable and included mostly dizziness and nausea, then diarrhea, abnormal gait, and confusion.
- As ziconotide does not induce respiratory depression, it could be used first line in patients presenting a risk for acute respiratory depression.
- Ziconotide could potentially be used in association with other IT drugs, such as morphine, clonidine, fentanyl, baclofen, and bupivacaine, which are often needed in patients with intractable pain. However, the benefits, and especially the risks of potential associations (respiratory depression, sedation, other CNS adverse events) are still unclear and require planned follow-up studies, two of which (morphine and baclofen) are ongoing or planned.
- The long-term maintenance of efficacy is not currently proven, especially in patients with pain of malignant origin, although preliminary data are available.

Treatment with ziconotide should only be undertaken by physicians experienced in intrathecal (IT) administration of medicinal products (See Annex I: Summary of Product Characteristics, 4.2.). In line with the SOP on “Legal status on the supply to the patients of centrally approved medicinal products”, it should be emphasised that any kind of restriction envisaged by the CHMP will be translated into the legal status in Annex II of the CHMP Opinion by the introduction of the word "restricted". In such case a cross-reference will be made to the section 4.2 of the SPC where the restriction will be reflected.

This would guide national authorities when using any subcategory at national level.
Nevertheless, the CHMP considers that the marketing authorisation should be granted under exceptional circumstances since the indication for which ziconotide is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence/data on the safety and efficacy of the medicinal product. In particular, the Applicant should perform a Post-Marketing Observational study designed to evaluate the long-term efficacy and safety of ziconotide given for malignant and non-malignant severe, chronic pain.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk ratio of Prialt in the treatment of severe, chronic pain in patients who require intrathecal (IT) analgesia was favourable and therefore recommended the granting of the marketing authorisation under exceptional circumstances.