EDITORIAL

A Consensus Statement Regarding the Present Suggested Titration for Prialt (Ziconotide)

Ziconotide IT Infusion (previously known as SNX-111), a neuron specific N-type calcium-channel antagonist marketed by Elan Pharmaceuticals as Prialt®, has been approved for long-term intrathecal use by the FDA. This marks the first time an intrathecal drug for pain control has met the high standards of clinical investigation required by the FDA. Morphine was approved more than a decade ago, but was "grandfathered" in by the FDA. Baclofen is approved by the FDA for the intrathecal treatment of uncontrolled spasticity.

The process of bringing this drug to the market place was begun in 1994, over a decade ago. This decade-long process was required because of the multiple drug studies required by the FDA, the thoroughness of Elan Pharma, the owner of the drug, and the unexpected extreme potency of the drug discovered in the early clinical trials.

Because of the side-effect profile of this drug, the recommended **maximum** titration rate approved by the FDA on December 28, 2004 and stated in the package insert is considered, unanimously, by the undersigned authors of this editorial and the vast majority of Prialt clinical investigators, to be two and one-half to five times too rapid.

The titration protocol of the final study of this drug called for a starting dose of 0.1 μg/24 hr (2.4 μg/24 hr) to be increased by 2.4 μg/24 hr, no more often than 2 to 3 times per week. Although no permanent sequelae were reported, the incidence and severity of the adverse events associated with this titration rate prompted many investigators to terminate patient trials of this drug, abruptly and permanently.

Many of us who have followed the clinical investigations of this exceptionally potent medication remember the results of the early clinical studies in the early to mid-1990s. Excessive starting doses consistently produced severe dizziness, memory loss, nystagmus, confusion, loss of the ability to word find, and even frank psychosis. There were even rumors, erroneous though they were, that SNX-111 had been responsible for permanent cognitive impairment and even death in some patients.

It should be emphatically stated here that 12 separate multicenter studies of ziconotide, involving over 1200 patients, spanning more than 10 years, have demonstrated no permanent sequelae of the drug, despite several known instances of inadvertent and profound overdosing. Additionally, no abstinence syndromes, following sudden cessation of the drug has ever occurred, in any patient, receiving ziconotide. The FDA has therefore released this drug with dosing recommendations at which it was studied at the end.

Given the severity of the side-effects of this drug, it is recommended by a consensus of the most experienced clinical investigators (signatures below), that the "mantra" regarding the initiation of intrathecal Prialt for pain control should be to "Start Low and Go Slow." We, the undersigned consensus group, based on our own experience with this drug, suggest a starting dose of not more than 0.5 μg/24 hr with increases of not more than 0.5 μg/24 hr, no more often than once **weekly**. This rate of titration (although not formally studied or reported) seems to significantly limit the incidence, severity, and duration of side-effects associated with Prialt.

It should also be noted, as an important side, that this lower, suggested slower titration rate makes the Elan Pharma's recommended "rinse" process much more important for reasons that go beyond the scope of this editorial. However, it must be

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noted that due to adsorption of ziconotide to the titanium of the implanted pump and the dilution errors that occur with residual pump volume, despite reservoir evacuation, the rinse process helps to insure the concentration of the anticipated final pump solution. Therefore it is very important that you do not initiate Prialt without the appropriate rinse process as suggested by the manufacturer.

A much more rapid titration schedule is FDA approved, and therefore may be utilized in specific cases trying to establish pain control more rapidly. In such cases it must be recognized that the side-effects which may occur will delay the eventual pain relief we seek for our patients. It must be recognized that when this occurs these difficulties result from our impatience as physicians and not with this newly approve drug, which holds so much promise for so many patients with chronic pain.

Respectfully submitted,

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