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EN3231, AN NMDA-ENHANCED ANALGESIC, IS SAFE AND WELL TOLERATED AFTER 1 YEAR OF TREATMENT IN CHRONIC PAIN PATIENTS

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The objective of this study was to demonstrate that EN3231, a combination of morphine sulfate (MS) and dextromethorphan (DM), is safe for treatment of chronic pain for 1 year.

Patients from 3 clinical trials enrolled in long-term, open-label extensions. Study designs prior to open-label phase were: Study 1: EN3231 vs. MS for 4 weeks; Study 2: 2-week crossover between EN3231 and MS; Study 3: opioid conversion to EN3231. Patients completing 1 year of treatment were analyzed. Safety was assessed by incidence and severity of treatment-related adverse events (AEs).

Two hundred thirty-one chronic pain patients were treated with EN3231 for 1 year. Adverse events were collected over the extension period. The most prevalent treatment-related AEs were: constipation (n = 45; 19.5%); somnolence (n = 39; 16.9%); nausea (n = 35; 15.2%); asthenia (n = 25; 10.8%); and sweating (n = 16; 6.9%). Eighty-one serious AEs occurred; only 4 were possibly related to treatment.

For this cohort of chronic pain patients who were treated with daily doses of EN3231 for 1 year, the incidence and type of treatment-related adverse events were not different compared to those reported with currently available opioid analgesics. The severity of these adverse events was generally mild-to-moderate. These data suggest that EN3231 is both safe and well tolerated in patients with chronic cancer pain or nonmalignant pain. It is recognized that these data are limited to only those patients completing 1 year of exposure and do not represent the safety profiles of patients who discontinued prior to 1 year of exposure.

1. Trujillo KA and Akil H. Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801. *Science* (1991) 251:85-87. 2. Marke P, Ben-Eliyahu S, Vaccarino AL, Liebeskind JC. Delayed application of MK-801 attenuates development of morphine tolerance in rats. *Brain Res* (1991a) 558:163-165. 3. Marek P, Ben-Eliyahu S, Gold M, Liebeskind JC. Excitatory amino acid antagonists (kynurenic acid and MK-801) attenuate the development of morphine tolerance in the rat. *Brain Res* (1991b) 548:77-81. 4. Tiseo PJ and Inturrisi CE. Attenuation and reversal of morphine tolerance by the competitive N-Methyl-D-aspartate receptor antagonist, LY274614. *J Pharmacol Exp Ther* (1993) 264:1090-1096. 5. Elliott K, Hynansky A, Inturrisi CE. Dextromethorphan attenuates and reverses analgesic tolerance to morphine. *Pain* (1994) 59:361-368.